Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende nivolumab til behandling af planocellulært karcinom i spiserøret med fremskreden sygdom efter tidligere behandling med kemoterapi

Vers. 1.0

Bilagsoversigt

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2. Forhandlingsnotat fra Amgros vedr. nivolumab
3. Høringssvar fra ansøger, inkl. eventuel efterfølgende dialog vedr. den sundhedsøkonomiske afrapportering
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Medicinrådet

Udkast: Medicinrådets sundhedsøkonomiske afrapportering

Nivolumab

Planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske analyse er udarbejdet efter Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren.

Dokumentoplysninger	
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Indholdsfortegnelse

1. Begreber og forkortelser

AIC	*Akaike information criterion*
AIP	Apotekernes indkøbspris
BIC	*Bayesian information criterion*
DKK	Danske kroner
DoT	*Duration of treatment (*behandlingsvarighed)
DRG	Diagnose Relaterede Grupper
SAIP	Sygehusapotekernes indkøbspriser
PFS	Progressionsfri overlevelse
OS	Samlet overlevelse

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for nivolumab ca. [redacted] DKK pr. patient sammenlignet med taxaner. Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. 288.000 DKK pr. patient.

De inkrementelle omkostninger er næsten udelukkende drevet af prisen på nivolumab. Derfor har behandlingslængden og dosis af nivolumab stor indflydelse på resultatet af analysen. Hvis en vægtbaseret dosis anvendes for nivolumab bliver de inkrementelle omkostninger i stedet [redacted] DKK.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af nivolumab som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 9,2 mio. DKK i år 5.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af nivolumab som mulig standardbehandling på danske hospitaler til planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Bristol Myers Squibb (BMS). Vi modtog ansøgningen den 16. marts 2021.

3.1 Patientpopulation

I 2019 blev der i Danmark registreret 1.167 nye tilfælde af patienter med kræft i spiserør, mavesæk eller mavemund ifølge Dansk EsophagoGastrisk Cancer Gruppe (DEGC) database [1]. Af disse var der 626 tilfælde af adenokarcinom i mavemunden, 221 tilfælde af adenokarcinom i mavesækken og 320 tilfælde af planocellulær spiserørskræft. Behandlingen med nivolumab vil være relevant for de af disse 320 patienter med planocellulær spiserørskræft, der er kandidater til 2. linjebehandling.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af nivolumab på baggrund af følgende kliniske spørgsmål:

Hvilken værdi har nivolumab sammenlignet med paclitaxel, docetaxel eller irinotecan for patienter med planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for nivolumab sammenlignet med docetaxel og paclitaxel (taxaner). Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for model

Sammenligningen med taxaner er lavet ved en direkte sammenligning på baggrund af data fra et randomiseret, internationalt, multicenter, open-label fase-III studie ATTRACTION-3. Studiet inkluderede 419 voksne patienter der var refraktære eller intolerante overfor mindst et fluoropyrimidin- og platinbaseret kombinationsregime.

4.1.1 Modelbeskrivelse

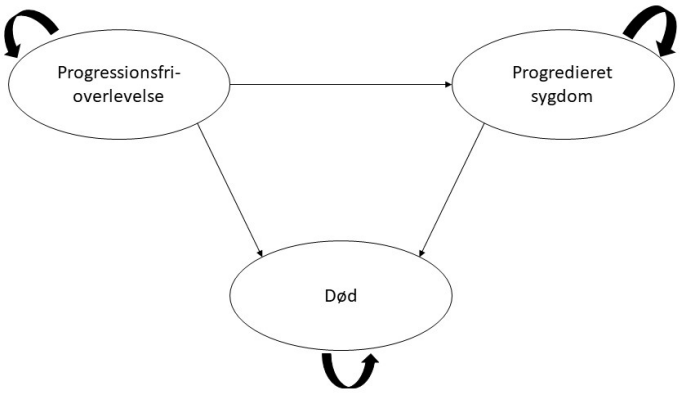
Ansøger har indsendt en *partitioned survival* analyse til at estimere omkostningerne forbundet med behandlingen med nivolumab.

Modellen indeholder en række sygdomsstadier, som patienterne skifter mellem i takt med sygdomsprogression. Ansøgers model består af tre stadier: progressionsfri overlevelse (PFS), progredieret sygdom og stadiet død. Se Figur 1 for de forskellige sygdomsstadier, og hvordan patienten kan bevæge sig mellem dem.

Alle patienter starter i sygdomsstadiet progressionsfri-overlevelse, hvorfra deres bevægelse gennem modellen bestemmes ud fra ekstrapoleret *time-to-event* data. Patientens tid i stadiet progressionsfri-overlevelse bestemmes ud fra PFS-data fra studiet ATTRACTION-3, mens længden på den aktive behandling med nivolumab og taxaner bestemmes ud fra data vedr. behandlingsvarighed (*duration of therapy*, DoT) fra ATTRACTION-3. Fra progressionsfri-overlevelse kan patienten bevæge sig videre til stadiet progredieret sygdom og til stadiet død.

Patienter, der er progredieret, men ikke døde, vil befinde sig i stadiet progredieret sygdom. Tiden, patienterne befinder sig i dette stadie, estimeres ud fra PFS- og samlet overlevelse (OS)-data fra ATTRACTION-3 som den andel af patienter, der hverken er i progressionsfri-overlevelse eller død. Fra progredieret sygdom kan patienten udelukkende bevæge sig til det absorberende stadie død.
Andelen af patienter i stadiet død bliver estimeret ud fra OS-data fra ATTRACTION-3.

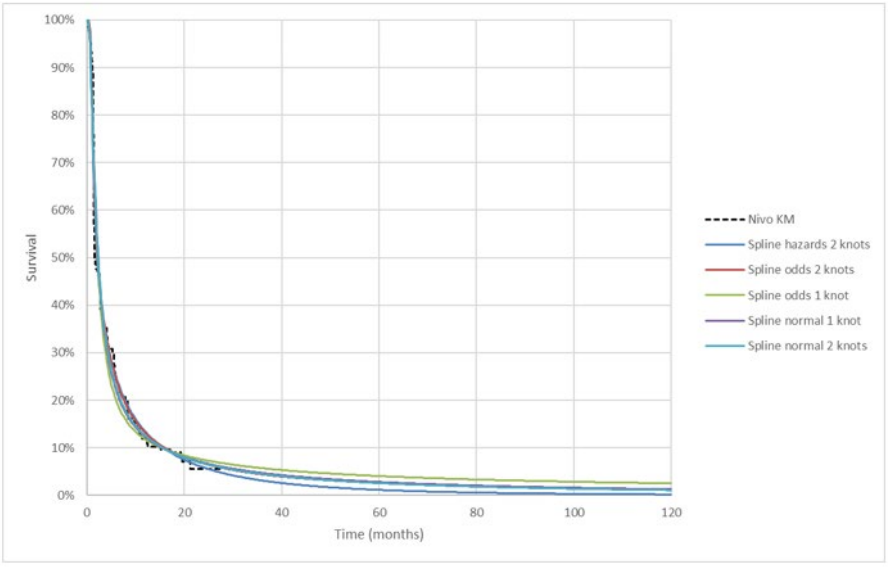
Modellen har en cykluslængde på en uge.



Figur 1: Beskrivelse af modelstrukturen i omkostningsanalysen.

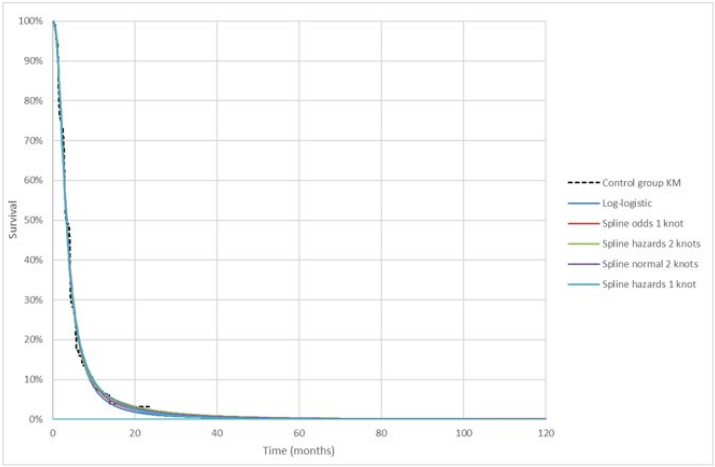
Ansøger modellerer tiden i de forskellige stadier ved at anvende ekstrapolerede Kaplan-Meier (KM)-data for PFS, OS og DoT. Dette er nødvendigt, da opfølgningen i ATTRACTION-3-studiet er kortere end den anvendte tidshorisont.

Ansøger har anvendt en *2-knot spline hazard* funktion til at ekstrapolere PFS for nivolumab, se kurverne i Figur 2. For taxan-baseret kemoterapi har ansøger valgt at anvende en log-logistisk fordeling, se Figur 3. For OS har ansøger valgt at ekstrapolere data for nivolumab med en *spline normal 1 knot* fordeling mens de for taxanerne anvender en log-normal fordeling, se Figur 4 og Figur 5. Til at ekstrapolere DoT anvender ansøger for nivolumab *spline normal 1 knot* fordeling mens *spline odds 1 knot* anvendes for taxanerne, se Figur 6 og Figur 7. Disse parametriske funktioner er valgt, da, de jf. AIC- og BIC-værdierne, har det bedste statistiske fit.



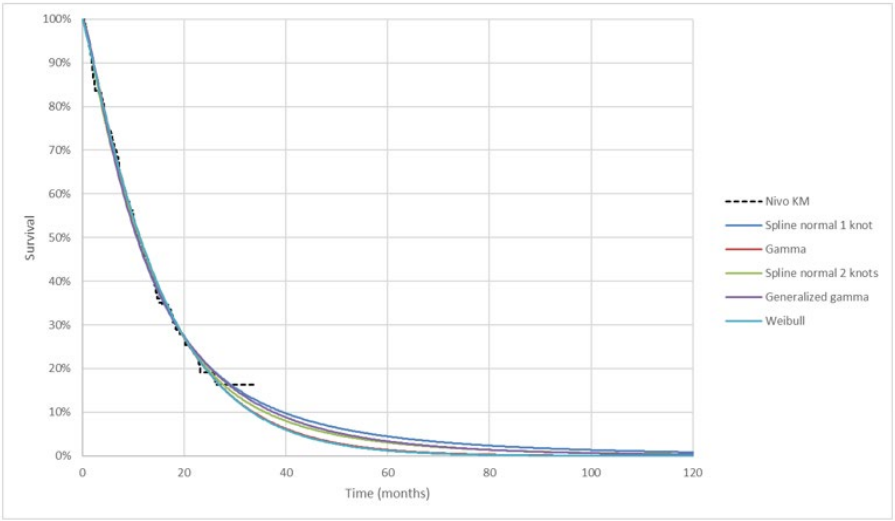
Abbreviations: KM, Kaplan Meier; Nivo, Nivolumab; PFS, Progression-free survival

Figur 2. Ekstrapolering af PFS for nivolumab



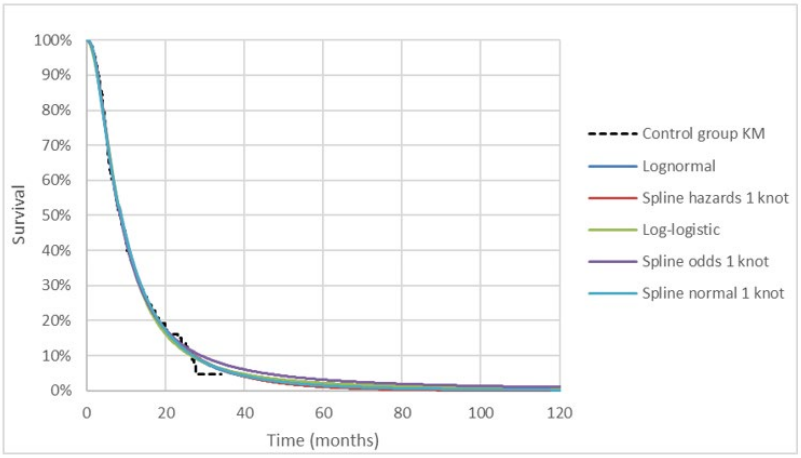
Abbreviations: KM, Kaplan Meier; PFS, Progression-free survival

Figur 3. Ekstrapolering af PFS for taxaner



Abbreviations: KM, Kaplan Meier; Nivo, nivolumab; OS, Overall survival

Figur 4. Ekstrapoleringer af OS for nivolumab



Abbreviations: KM, Kaplan Meier; OS, Overall survival

Figur 5. Ekstrapoleringer af OS for taxaner

[redacted]

Figur 6. Ekstrapolering af *duration of therapy* (DoT) for nivolumab

Figur 7. Ekstrapolering af *duration of therapy* (DoT) for taxaner

Medicinrådets vurdering af ansøgers modelantagelser

Ansøger har valgt at ekstrapolere forløbsdata for nivolumab og taxanerne med forskellige funktioner for både PFS, OS og DoT. Medicinrådet ændrer dette, så forløbsdata ekstrapoleres med samme funktion for begge behandlingsarme og der vælges de kurver der for både nivolumab og taxan-baseret kemoterapi har bedste statistiske fit. For OS vælges *spline normal 1 knot.* For PFS vælges *spline hazard 2 knot.* For DoT vælges *spline normal 1 knot.* Estimaterne er præsenteret i Tabel 1.

Tabel 1. Gennemsnitlig tid i behandling og i stadierne PFS og PD

Behandling	DoT [måneder]	PFS [måneder]	OS [måneder]
Nivolumab	[redacted]	[redacted]	[redacted]
Taxaner	[redacted]	[redacted]	[redacted]

Behandlingsvarighed (DoT), progressionsfri overlevelse (PFS), samlet overlevelse (OS)

Fagudvalget er blevet præsenteret for kurverne med ekstrapoleringerne, for at validere den kliniske plausibilitet. Fagudvalget mener, at ekstrapoleringerne for taxanerne stemmer godt overens med det forløb de vil forvente. Kurverne for nivolumab mener fagudvalget kan overestimere effekten af nivolumab, da de vil forvente en kortere PFS, hvis der var tale om median værdier. Kurverne estimeret gennemsnitsværdier og kan derfor godt være længere end medianværdier.

Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser, men vælger dog at ekstrapolere overlevelsesdata for nivolumab og taxaner med samme parametriske funktioner.

4.1.2 Analyseperspektiv

I overensstemmelse med metoderne har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 10 år.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 3,5 % pr. år.

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv.

4.2 Omkostninger

I det følgende er ansøgers antagelser vedrørende omkostningerne i den sundhedsøkonomiske analyse af nivolumab sammenlignet med taxan-baseret kemoterapi (paclitaxel og docetaxel) præsenteret. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger, omkostninger til efterfølgende behandling og patientomkostninger.

4.2.1 Lægemiddelomkostninger

Ansøger har jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren* estimeret lægemiddelomkostninger på baggrund af apotekets indkøbspris (AIP).

I ATTRACTION-3-studiet modtog patienterne 240 mg nivolumab hver anden uge, mens de der blev behandlet med paclitaxel modtog 100 mg/m^2 hver uge. Ansøger antager, at patienter modtager behandling med docetaxcel af 75 mg/m^2 hver tredje uge.

I kontrolarmen modtog 31 % af patienterne docetaxel og 69 % paclitaxel. Ansøger har anvendt den relative dosisintensitet fra ATTRACTION-3-studiet. Den relative dosisintensitet i studiet var [redacted] % for nivolumab, [redacted] % for docetaxel og [redacted] % for paclitaxel.

Ansøger har antaget i deres hovedanalyse, at der vil være deling af hætteglas.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekets indkøbspris (SAIP), se Tabel 2.

Tabel 2. Anvendte lægemiddelpriser, SAIP, (april 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Nivolumab	240 mg	1 stk.	[redacted]	Amgros
	100 mg	1 stk.	[redacted]	Amgros
	40 mg	1 stk.	[redacted]	Amgros
Paclitaxel	60 mg	1 stk.	[redacted]	Amgros
	100 mg	1 stk.	[redacted]	Amgros
	300 mg	1 stk.	[redacted]	Amgros
	500 mg	1 stk.	[redacted]	Amgros
Docetaxel	20	1 ml	[redacted]	Amgros

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
	80	4 ml	[redacted]	Amgros
	160	8 ml	[redacted]	Amgros

Fagudvalget er blevet konsulteret i forhold til ansøgers anvendte doseringer i analysen. De bemærker at paclitaxel gives i høj dosis i forhold til hvad man ville gøre i dansk klinisk praksis, hvor der vil blive anvendt 80 mg/m^2. Ansøger anvender en dosisintensitet på [redacted] for nivolumab, hvilket fagudvalget ikke finder realistisk, da de ikke mener at patienter i behandling med en immunterapi vil blive dosisjusteret, men altid vil modtage den fulde dosis. Den laver dosisintensitet kan dog skyldes pausering af behandling, hvorfor et scenarie hvor dosisintensiteten for nivolumab er [redacted] også præsenteres.

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger, men ændrer dosis for paclitaxel og nivolumab så det afspejler fagudvalgets forventninger til dosis i dansk klinisk praksis.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Ansøger anvender den samme DRG-takst til at estimere omkostninger forbundet med administrering af nivolumab og taxan-baseret kemoterapi. DRG-taksten 06MA11 på 5.297 DKK anvendes i ansøgers analyse.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Den valgte DRG-takst, som ansøger anvender til at estimere omkostninger til administration af lægemidlerne, er en 2020 DRG-takst. Medicinrådet udskifter alle 2020 DRG-takster med 2021 DRG-takster i denne analyse. Denne ændring vurderes at have minimal betydning for analysens resultat. Se anvendte enhedsomkostning i Tabel 3.

Tabel 3. Omkostninger til lægemiddeladministration

	Enhedsomkostning [DKK]	Kode	Kilde
Intravenøs infusion	5.130	06MA11, BWAA60	DRG-2021

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger, men opdaterer DRG-takster til takster for 2021.

Monitoreringsomkostning

Ansøger estimerer frekvenserne for monitoreringsbesøg på baggrund af udsagn fra en dansk klinisk ekspert.

Ansøger antager, at patienter i behandling med nivolumab vil have et monitoreringsbesøg hver fjerde uge, mens patienter der behandles med taxan-baseret kemoterapi vil have et monitoreringsbesøg hver tredje uge. Ansøger estimerer omkostninger til disse monitoreringsbesøg ved at anvende enhedsomkostninger fra kommunernes og regionernes løndatakontor og anvender bruttolønnen for en overlæge.

Både patienterne i behandling med intervention og komparator vil ifølge ansøger blive CT-scannet hver anden måned. Til at estimerer omkostningerne ved en CT-scanning anvender ansøger DRG-2020-taksten 30PR06 (CT-scanning, kompliceret).

Ansøger antager, at patienter i behandling med nivolumab skal have kontrolleret deres lever- og nyrefunktion samt have foretaget komplet blodtælling hver fjerde uge, mens de patienter der i behandling med taxan-baseret kemoterapi vil modtage disse prøver hver tredje uge. Til at estimere omkostningerne ved test af lever- og nyrefunktion og komplet blodtælling, anvender ansøger enhedsomkostninger fra Rigshospitalets labportal.

Udover monitoreringsomkostninger har ansøger også inkluderet omkostninger til sygdomskontrol. Her estimerer ansøger omkostningerne forbundet med sygdomskontrol, i stadierne progressionsfri-overlevelse og progredieret sygdom, baseret på inputs fra en dansk kliniker. Ansøger antager at patienter i progressionsfri-overlevelse hver fjerde uge vil have et ambulant besøg, modtage en CT-scanning og få en komplet blodtælling. Ansøger estimerer at patienter med progredieret sygdomsstadiet vil have de samme procedurer og omkostninger.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger
Ansøger anvender kommunernes og regionernes løndatakontor opgørelse over lønninger til at estimere omkostninger til en læge. For at øge konsistensen i anvendte metode til at estimere omkostninger, vælger Medicinrådet at anvende DRG-takster til at estimere omkostninger ved hospitalsbesøg.

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger, men udskifter alle enhedsomkostninger på DRG-takster.

Bivirkningsomkostninger

Ansøgers model benytter frekvenser for uønskede hændelser (AE) af grad 3-4 som mål for bivirkningerne. For nivolumab og begge taxan-baserede kemoterapier har ansøger benyttet de rapporterede bivirkningsrater fra ATTRACTION-3-studiet. til at estimere omkostninger forbundet med behandling af bivirkninger anvender ansøger DRG 2020, kommunernes og regionernes løndatakontor og Rigshospitalets labportal.

Ansøger antager, at anæmi vil være forbundet med blodtransfusion. Ansøger antager ikke, at nedsat appetit og leukopeni vil være forbundet med nogle omkostninger. Ansøger antager, at febril neutropeni, neutropeni og nedsat leukocyttal vil være forbundet med konsultation ved en læge.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger
Fagudvalget estimerer ikke, at nedsat lymfocyttal og neutropeni vil være forbundet med behandling. Ansøger har anvendt Kommunernes og Regionernes løndatakontor 2021 til

at estimere omkostninger til lægekonsultation. Medicinrådet vælger for at øge konsistensen i analysen at udskifte dette med DRG-takster.

Bivirkningsfrekvenser og anvendte takster kan ses i Tabel 4.

Tabel 4. Rapporterede bivirkningsfrekvenser ved behandling med nivolumab og taxsanbaseret kemoterapi samt enhedsomkostninger for bivirkningerne

	Nivolumab [%]	Taxan-baseret kemoterapi [%]	DRG-kode	Takst
Anæmi	1,9	9,1	16PR02	4.628,00
Nedsat appetit	1,0	4,8	Ingen behandling	0 DKK
Febril neutropeni	0,0	10,6	16MA98	3.114,00
Leukopeni	0,0	6,7	Ingen behandling	0 DKK
Nedsat lymfocyttal	1,0	5,8	Ingen behandling	0 DKK
Neutropeni/ nedsat neutrofiltal	0,5	42,3	Ingen behandling	0 DKK
Nedsat leukocyttal	0,5	22,1	Inge behandling	0 DKK

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men ekskluderer omkostninger ved nedsat lymfocyttal og neutropeni samt anvender DRG-takster til at estimere øvrige bivirkningsomkostninger.

4.2.3 Efterfølgende behandling

Ansøger inkluderer omkostninger til efterfølgende behandling, da OS forventes at afspejle både effekten af 1. linjebehandling og effekten af de efterfølgende behandlinger. Som efterfølgende behandling har ansøger antaget, at patienter, som progredierer på nivolumab, vil modtage enten docetaxel eller paclitaxel som efterfølgende behandling. Det samme vil patienter, som progredierer efter behandling med docetaxel eller paclitaxel i 2. linje.

Ansøger antager, at 53,3 % af patienterne vil modtage en efterfølgende behandling efter nivolumab, mens 47,4 % af patienterne vil modtage en efterfølgende behandling efter taxan-behandling, hvilket svarer til andelen af patienter der modtog efterfølgende behandling i ATTRACTION-3-studiet. Ansøger antager på baggrund af DoT data fra CheckMate 473-studiet at varigheden af docetaxel i efterfølgende linje vil være 2,92 måneder, og at varigheden efter paclitaxel vil være 3,51 måneder.

Ansøger har inkluderet terminale omkostninger i modellen. Da alle patienter dør i modellen, er forskelle i terminale omkostninger udelukkende drevet af forskelle i diskontering, der afhænger af tidspunktet for død.

Medicinrådets vurdering af ansøgers antagelser vedr. efterfølgende behandling
Medicinrådet har udskriftet AIP for lægemiddelpriser til efterfølgende behandling med SAIP, se Tabel 5.

Tabel 5. Anvendte lægemiddelpriser for efterfølgende behandling, SAIP (april 2021)

Lægemiddel	Styrke	Mg/dosis	Pakningsstørrelse	Kilde
Paclitaxel	60 mg	1 stk.	[redacted]	Amgros
	100 mg	1 stk.	[redacted]	Amgros
	300 mg	1 stk.	[redacted]	Amgros
	500 mg	1 stk.	[redacted]	Amgros
Docetaxel	20 mg/ml	1 ml	[redacted]	Amgros
	80 mg/4 ml	4 ml	[redacted]	Amgros
	160 mg/8 ml	8 ml	[redacted]	Amgros
Irinotecan	20 mg/ml	5 ml	[redacted]	Amgros
	20 mg/ml	25 ml	[redacted]	Amgros

Fagudvalget mener ikke, at patienter der har modtaget en taxan-baseret kemoterapi i 2. linje også vil modtage samme type behandling efterfølgende, og finder derfor ikke ansøgeres estimering af efterfølgende behandling for paclitaxel og docetaxel, i overensstemmelse med dansk klinisk praksis. Fagudvalget mener, at patienter efterfølgende taxan-baseret kemoterapi i stedet vil modtage palliativ behandling og en lille andel (ca. 10 %) vil modtage behandling med irinotecan.

Medicinrådet vælger at ekskludere terminale omkostninger, da disse omkostninger udgør en andel af DRG-taksterne, som er anvendt til at estimere monitoreringsomkostninger og administrationsomkostninger i denne analyse.

Medicinrådet accepterer ikke ansøgers tilgang til estimering af efterfølgende behandling efter taxan-baseret kemoterapi, men ændre denne behandling til at være tilsvarende fagudvalgets forventning til efterfølgende behandling.

4.2.4 Patientomkostninger

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 100 DKK pr. besøg, jf. Medicinrådets værdisætning af enhedsomkostninger.

Patientomkostninger og transportomkostninger baserer sig på det estimerede antal besøg patienten har i forbindelse med administration og monitorering.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet accepterer ansøgers tilgang vedr. patientomkostninger.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre.

Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Følgende følsomhedsanalyser er udført:

Tabel 6. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Tidshorisont 5 år	Det antages at tidshorisonten for analysen er 5 år
Diskonteringsrente 0 %	Det antages at omkostninger ikke diskonteres
Vægtbaseret dosis	Det antages at dosis for nivolumab vil være vægtbaseret og patienterne vil modtage 3 mg/kg hver anden uge
Ingen deling af hætteglas	Det antages at hætteglas ikke deles, og ubrugt lægemiddel vil være spildt
DoT ikke ekstrapoleret	DoT ekstrapoleres ikke, men baseres udelukkende på Kaplan-Meier-data
Sygdomsmonitoreringsomkostninger ekskluderet	Omkostninger til monitorering af sygdom ekskluderes fra analysen
Patientomkostninger ekskluderes	Omkostninger ved patientens tid på hospitalet samt transport til og fra hospitalet ekskluderes.

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Ud af de følsomhedsanalyse ansøger har udført, vurderes analysen der undersøger omkostninger ved anvendelse af vægtbaseret dosis at være den mest relevante. Flere af de øvrige analyser modstrider Medicinrådets metoder for de sundhedsøkonomiske analyser og bliver derfor ikke præsenteret.

Medicinrådet vælger at præsentere ansøgers følsomhedsanalyse der undersøger omkostningerne for nivolumab ved vægtbaseret dosis, dog justeres analysen så de øvrige ændringer Medicinrådet har lavet i hovedanalysen også gør sig gældende.

4.4 Opsummering af basisantagelser

I Tabel 7 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 7. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	10 år	10 år
Diskonteringsrate	3,5 %	3,5 %
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Efterfølgende behandling Patient- og transportomkostninger	Lægemiddelomkostninger Hospitalsomkostninger Efterfølgende behandling Patient- og transportomkostninger
Dosering	Nivolumab [redacted] mg hver anden uge Paclitaxcel 100 mg/m^2	Nivolumab 240 hver anden uge Paclitaxcel 80 mg/m^2
Parametriske funktioner for PFS Nivolumab: Taxaner:	 *Spline hazard 2 knot* *Log-logistisk*	 *Spline hazard 2 knot* *Spline hazard 2 knot*
Parametriske funktioner for OS Nivolumab: Taxaner:	 *Spline normal 1 knot* *Log-normal*	 *Spline normal 1 knot* *Spline normal 1 knot*
Parametriske funktioner for DoT Nivolumab: Taxaner:	 *Spline normal 1 knot* *Spline odds 1 knot*	 *Spline normal 1 knot* *Spline normal 1 knot*

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de ændringer, der fremgår af Tabel 7.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i Medicinrådets hovedanalyse.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 288.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 8.

Tabel 8. Resultatet af Medicinrådets hovedanalyse ved sammenligning med taxaner, DKK, diskonterede tal

	Nivolumab	Taxaner	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	112.411	99.661	12.750
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	4.880	5.203	-323
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 9.

Tabel 9. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Vægtbaseret dosis for nivolumab	[redacted]
Nivolumab dosisintensitet på [redacted]	[redacted]
Vægtebaseret dosis og dosisintensitet på [redacted] for nivolumab	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at nivolumab vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Nivolumab bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Nivolumab bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Ansøgers estimat af patientantal og markedsandel

Ansøger har antaget, at der årligt vil være 30 patienter der er kandidater til nivolumab. Et år efter anbefaling af nivolumab antager ansøger at 66,6 % af de patienter der er kandidater, vil være i behandling med nivolumab, mens det fortsat vil være 33,3 % af patienterne der, vil modtage behandling med taxaner.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget er blevet konsulteret i forhold til patientantal, hvis nivolumab anbefales som mulig standardbehandling, og hvis ikke nivolumab anbefales. Fagudvalget estimerer, at under 50 patienter pr. år forventes at være kandidater til behandling med nivolumab til den pågældende indikation. Fagudvalget vurderer yderligere, at hvis nivolumab anbefales som mulig standardbehandling, så vil 95 % af patienterne modtage denne behandling fra år 2, se Tabel 10.

Tabel 10. Medicinrådets estimat af antal nye patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Nivolumab	36	43	43	43	43
Taxaner	9	2	2	2	2
			Anbefales ikke		
Nivolumab	0	0	0	0	0
Taxaner	45	45	45	45	45

Medicinrådet har udført sin egen budgetkonsekvensanalyse, hvor patientantallet er ændret til 45 patienter pr. år.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet har korrigeret følgende estimater i sin budgetkonsekvensanalyse i forhold til ansøgers budgetkonsekvensanalyse:

- 45 patienter kandiderer til behandling med nivolumab om året

- Markedsoptag på 95 % for nivolumab fra det andet år efter en anbefaling

Medicinrådet estimerer, at anvendelse af nivolumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 11.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 9,2 mio. DKK i år 5.

Tabel 11. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7. Diskussion

Behandling med nivolumab er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med taxaner. De inkrementelle omkostninger er næsten udelukkende drevet af prisen for nivolumab. Derfor har behandlingslængden og dosis for nivolumab stor indflydelse på resultatet af analysen. Hvis en vægtbaseret dosis i stedet anvendes for nivolumab bliver de inkrementelle omkostninger i stedet ca. [redacted] DKK.

8. Referencer

1. Multidisciplinære Cancer Grupper (DMCG). Onkologisk behandling af non-kurabel cancer i esophagus , GEJ og ventrikel. 2020;2020(september):1–17.

9. Bilag

9.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 10 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 12.

Tabel 12. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Nivolumab	Taxaner	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	113.045	100.224	12.821
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	4.880	5.203	-323
Totale omkostninger	[redacted]	[redacted]	[redacted]

9.2 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Med de ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af nivolumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 13.

Tabel 13. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Forhandlingsnotat

Dato for behandling i Medicinrådet	29.09.2021
Leverandør	Bristol-Myers Scuibb (BMS)
Lægemiddel	Nivolumab (opdivo)
EMA-indikation	Nivolumab til behandling af planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere kemoterapi

Forhandlingsresultat

Amgros har følgende pris på nivolumab:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	SAIP (DKK)	Rabatprocent ift. AIP
Nivolumab	240 mg/24 ml	1 stk.	22.567,94	[redacted]	[redacted]
Nivolumab	100 mg/10 ml	1 stk.	9.403,31	[redacted]	[redacted]
Nivolumab	40 mg/4 ml	1 stk.	3.785,32	[redacted]	[redacted]

Leverandøren har valgt at fastholde prisen på nivolumab til denne patientpopulation og tilbyder derfor ikke en yderligere rabat.

Amgros gennemførte et udbud på de 3 immunterapilægemidler, med aftalestart d. 1.1.2020. [redacted].

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at vi på nuværende tidspunkt har den bedst mulige pris på nivolumab. Denne vurdering baserer vi på følgende punkter:

- Leverandøren er ikke interesseret i at justere prisen til denne relativt lille patientpopulation.
- Nivolumab er den første immunterapi til denne indikation. [redacted]

Konklusion

Amgros vurderer at den nuværende pris er rimelig til denne patientpopulation. [redacted]

Relation til markedet

Følgende tabel viser de rene lægemiddelpriser for et års behandling med nivolumab. Årspriserne for behandling med paclitaxel er 6100 DKK og 3800 DKK for docetaxel for, hvilket er meget lavt sammenlignet med nivolumab.

Lægemiddel	Dosis	Frekvens	SAIP (DKK) pr. behandling	Antal årlige behandlinger	Et års behandling SAIP (DKK)
Nivolumab	240 mg	Hver 2. uge	[redacted]	[redacted]	[redacted]

Status i andre lande

Norge: Beslutningsforum for nye metoder valgte i april 2021 ikke at anbefale nivolumab. Grundlaget for afslaget var en for høj pris i forhold til den dokumenterede kliniske effekt af behandlingen.[1]

Sverige: NT-rådet valgte i maj 2021 at anbefale nivolumab til behandling af tilbagevendende eller metastatisk planocellulært karcinom i spiserøret.[2]

UK: NICE valgte i maj 2021 at anbefale nivolumab som mulig standardbehandling.[3]

[1] Nivolumab (Opdivo) - Indikasjon XIII (nyemetoder.no)
[2] Opdivo (nivolumab) för behandling av avancerad esofaguscancer i andra linjen (janusinfo.se)
[3] 1 (nice.org.uk)

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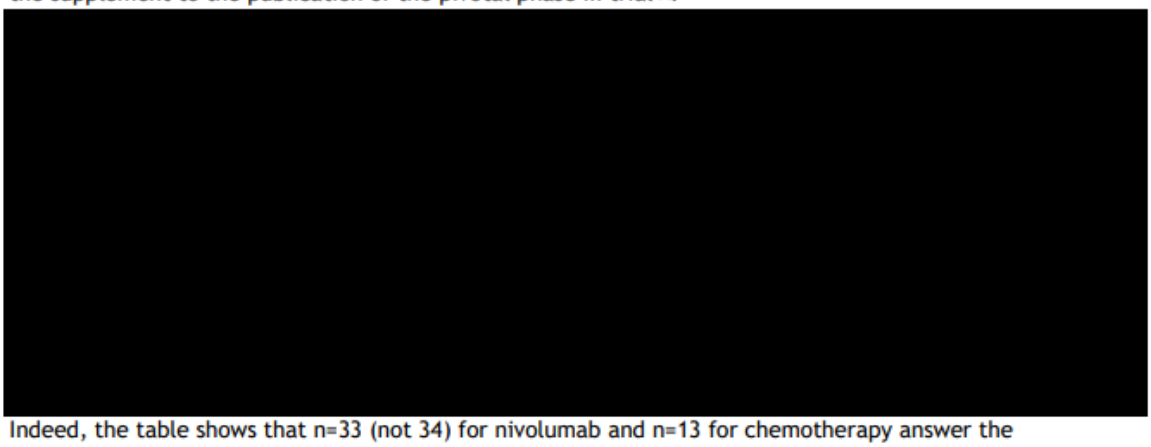
To the Medicines Council,

Consultation reply from Bristol Myers Squibb (BMS) regarding the draft clinical and economic assessment of nivolumab (Opdivo) for the 2L treatment of esophageal squamous cell carcinoma

BMS generally agree to the assessment of nivolumab for the treatment of 2L ESCC, but we have a few remarks with respect to some of the specifics in the clinical and economic assessment reports:

Firstly, the assessment applies a very stringent interpretation of the statistically significant health-related quality of life benefit (HRQoL), and of the data provided regarding HRQoL.

BMS suspects that there is a misunderstanding surrounding the quality of our HRQoL data. The Medicines Council critiques the number of responses and Table 7, page 31, of the assessment report mentions n=34 for nivolumab and n=13 for chemotherapy. The misunderstanding seems to originate from the following table in the supplement to the publication of the pivotal phase III trial [1]:



Indeed, the table shows that n=33 (not 34) for nivolumab and n=13 for chemotherapy answer the questionnaire at week 42; however, at baseline 96/97% of the randomized 210/209 patients answered the questionnaire and at response rate remained stable at a high level (never below 86%). As such, the absolute number of responses must be interpreted with caution given the average survival and progression rates in this patient population.

The study measured HRQoL using the three level EQ-5D utility index (EQ-5D-UI) score and the EQ 100-point visual analog scale (EQ-VAS) tool. In both measurements, the difference was statistically significant and would have been considered clinical meaningful by the Medicines Council if one less decimal had been provided; EQ-5D-3L VAS of 6.9 (95% CI 3.0-10.9; p=0·00069) and EQ-5D-UI 0.076, (95% CI: 0.011-0·142; p=0·02). The nature of the HRQoL measurements is such, that the relative and absolute measurements are one and the same (as opposed to e.g. overall survival where the relative difference is assessment on the confidence interval of the hazard ratio and the absolute difference is at the median or at 12 months).

The data provided by BMS clearly proves the benefit of nivolumab on the quality of life versus chemotherapy.

Secondly, BMS recognizes the scientific committee's concern regarding the efficacy of nivolumab across race. In addition to the arguments made in the dossier, BMS has since reported that two additional pivotal phase III trials within the esophageal cancer have meet the primary endpoint: CM-648 within 1L esophageal squamous cell carcinoma and CM-577 within adjuvant treatment of resected esophageal or gastroesophageal junction cancer. The effect of nivolumab across race in patients with esophageal cancer is supported by the recent CM-577 publication[2]:

Thirdly, the relative dose intensity in the nivolumab arm was changed by the Medicines Council from the observed 95% to 100%. No changes were made to the relative dose intensity of the chemotherapy arm.

However, the relative dose intensity does not only relate to dose reductions as claimed in the Medicines Council assessment report, but also to *dose delays*. The Phase III manuscript[1] explains that "*Dose delays due to treatment-related adverse events were more common with chemotherapy (any grade, 104 [50%];grade 3-4, 81 [39%]) than with nivolumab (any grade, 34 [16%]; grade 3-4, 15 [7%])*", i.e. dose delays did occur in the nivolumab arm.

BMS requests that the Medicines Council reinstall the 95% relative dose intensity for nivolumab in their analyses as this may well occur in routines care when it was seen in the ATTRACTION 3 trial.

Sincerely,

Anders Thelborg

Anders Thelborg
General Manager
Bristol Myers Squibb, Denmark

1. Kato, K. *et al*. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* **20**, 1506–1517 (2019).

2. Kelly, R. J. *et al*. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N. Engl. J. Med.* **384**, 1191–1203 (2021).

Medicinrådet

Medicinrådets vurdering vedrørende nivolumab til behandling af planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Dokumentoplysninger	
Godkendelsesdato	26. maj 2021
Dokumentnummer	107468
Versionsnummer	1.0

Indholdsfortegnelse

1. Medicinrådets konklusion

Medicinrådet vurderer, at nivolumab til patienter med planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi giver en **merværdi af ukendt størrelse** sammenlignet med kemoterapi (paclitaxel eller docetaxel).

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (f.eks. på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 26. maj 2021

MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET), I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2. Begreber og forkortelser

5FU: 5-Fluoropyrimidin

CI: Konfidensinterval

CPS: *Combined Positive Score*

EMA: Det Europæiske Lægemiddelagentur (*European Medicines Agency*)

EORTC: *European Organisation for Research and Treatment of Cancer*

EPAR: *European Public Assessment Report*

ESMO: *European Society for Medical Oncology*

FDA: *The Food and Drug Administration*

GRADE: System til at vurdere evidens *(Grading of Recommendations, Assessment, Development and Evaluation)*

ITT: *Intention-to-treat*

I.V. Intravenøst

MKRF: Mindste klinisk relevante forskel

OS: *Overall survival*

PD-1: *Programmed cell death-1*

TPS: *Tumor Proportion Score*

S1: *Dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine (DIF) based on a biochemical modulation of 5-fluorouracil (5FU); S-1 contains tegafur (FF) and two types of enzyme inhibitor, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) in a molar ratio of 1:0.4:1.*

3. Introduktion

Formålet med Medicinrådets vurdering af nivolumab til planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Bristol Myers Squibb (BMS). Medicinrådet modtog ansøgningen den 16. marts 2021.

De(t) kliniske spørgsmål er:

Hvilken værdi har nivolumab sammenlignet med paclitaxel, docetaxel eller irinotecan for patienter med planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi?

3.1 Spiserørskræft

Kræft i esophagus (spiserør), ventrikel (mavesæk) og gastroesophageal overgang (mavemund) hører samlet til den 8. hyppigste kræftform i Danmark. Medianalderen for diagnosetidspunktet er for alle tre kræftformer omkring 70 år. En stor del af patienterne kan ikke tilbydes helbredende behandling, da de på diagnosetidspunktet enten har spredt sygdom eller er i for dårlig almen tilstand til at gennemgå behandling.

I Danmark håndteres patientgruppen samlet via et multidisciplinært esophagus- og ventrikelcancerteam på fire afdelinger (Rigshospitalet, Odense Universitetshospital, Aalborg Universitetshospital og Aarhus Universitetshospital).

Spiserørskræft forekommer dobbelt så hyppigt hos mænd som hos kvinder. Rygning og alkohol øger risikoen for kræft i spiserøret. Den hyppigste form for kræft i spiserøret er planocellulært karcinom, som overvejende er lokaliseret højt og/eller midt i spiserøret. Planocellulære karcinomer, der involverer mavemunden, betragtes også som spiserørskræft. En lille andel af karcinomerne i spiserøret udgøres af adenokarcinomer. Forekomsten af adenokarcinom i mavemunden er steget i de senere år og er nu hyppigere end både planocellulære karcinomer i spiserøret og adenokarcinomer i den distale del af mavesækken.

Symptomer
Det første symptom på kræft i spiserøret eller mavemunden er som regel synkebesvær og eventuelt opkastninger. Ofte ses ledsagende betydende vægttab og kvalme. Der kan være trykken eller en brændende fornemmelse bag brystbenet eller højt i maveregionen, og mange patienter føler sig unormalt trætte, eventuelt med lav blodprocent på grund af blødning fra kræftknuden. Smerter er et hyppigt symptom, der ofte kræver smertestillende medicin.

Forekomst
I 2019 blev der i Danmark registreret 1.167 nye tilfælde af patienter med kræft i spiserør, mavesæk eller mavemund ifølge Dansk EsophagoGastrisk Cancer Gruppe (DEGC)

database [1]. Af disse var der 626 tilfælde af adenokarcinom i mavemunden, 221 tilfælde af adenokarcinom i mavesækken og 320 tilfælde af planocellulær spiserørskræft. Behandlingen med nivolumab vil være relevant for de patienter med planocellulær spiserørskræft, der er kandidater til 2. linjebehandling (se afsnit 3.3).

3.2 Nivolumab

Nivolumab, som markedsføres under handelsnavnet Opdivo®, er et monoklonalt antistof, som bindes til PD-1-receptorerne og derigennem øger immunsystemets antineoplastiske respons. Nivolumab tilhører den nye behandlingsmodalitet inden for immunterapi, som også kaldes "check-point inhibition". Baggrunden for denne behandlingstype er, at tumorceller gennem binding af overfladeproteinet PD-L1 til en receptor på immunforsvarets celler, kaldet *Programmed Cell Death Protein 1 (PD-1),* kan nedregulere/hæmme immunforsvarets angreb [2]. Specifikke antistoffer, som blokerer PD-1 eller PD-L1, kan derfor reaktivere immunforsvarets cytotoksiske T-cellers mulighed for at angribe tumorceller. Udtryk af PD-L1 kan vurderes ved immunhistokemisk undersøgelse på histologisk materiale, hvor det opgøres, hvor mange celler i tumor der udtrykker PD-L1 i forhold til det samlede antal tumorceller. Hvis udtrykket vurderes på tumorceller, kaldes undersøgelsen Tumor Proportion Score (TPS). Hvis udtrykket vurderes på både tumorceller og associerede immunceller, kaldes undersøgelsen Combined Positive Score (CPS).

Nivolumab har indikation til en række forskellige kræftformer, hvoraf nogle har været vurderet af Medicinrådet (angivet i kursiv):

- Inoperabel eller metastatisk melanom som monoterapi eller i kombination med ipilimumab.
- Efter komplet resektion af melanom med lymfeknudeinvolvering eller metastase(r) som monoterapi (adjuverende behandling). *Anbefalet af Medicinrådet til patienter med komplet reseceret modermærkekræft stadium III og IV*.
- Lokalt fremskreden eller metastatisk planocellulært ikke-småcellet lungecancer efter tidligere kemoterapi.
- Fremskredent renalcellekarcinom (nyrekræft) som 1. linjebehandling i kombination med ipilimumab eller som monoterapi efter tidligere kemoterapi. *Anbefalet af Medicinrådet i kombination med ipilimumab til patienter med lokalavanceret inoperabel eller metastaserende nyrekræft (mRCC) i intermediær eller dårlig prognosegruppe, der ikke tidligere har modtaget behandling.*
- Recidiverende eller refraktært klassisk Hodgkins lymfom efter autolog stamcelletransplantation og behandling med brentuximab vedotin.
- Recidiverende eller metastatisk planocellulær hoved-hals-cancer under eller efter platinbaseret kemoterapi.
- Lokalt fremskredent inoperabelt eller metastatisk urothelkarcinom (kræft i blære og urinveje) efter tidligere platinbaseret kemoterapi. *Anbefalet af Medicinrådet til patienter i performancestatus 0-1 med sygdomsprogression efter platinbaseret kemoterapi.*

Den aktuelle indikationsudvidelse gælder planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi. Nivolumab administreres intravenøst (i.v.) og doseres med 240 mg hver 2. uge. Behandlingen fortsættes indtil sygdomsprogression eller uacceptable bivirkninger.

Nivolumab har ikke status af *orphan drug* til behandling af planocellulært karcinom i spiserøret og har ikke været igennem *accelerated assessment* i EMA i forbindelse med denne indikation.

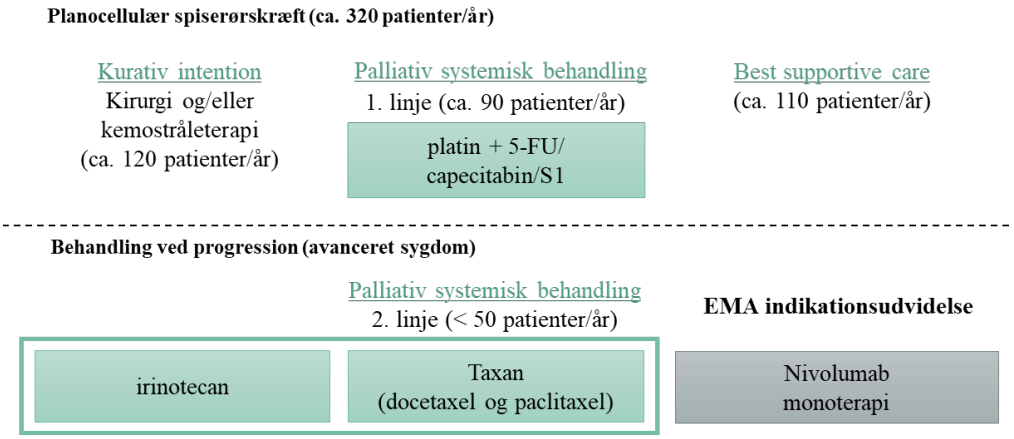
Check-point inhibitorer
Behandling med check-point inhibitorer er undersøgt i flere studier til patienter med planocellulær spiserørskræft. I et fase II enkeltarm-studie med pembrolizumab i 3. eller senere linje viste subgruppeanalyser lovende responsrater hos patienter med planocellulært karcinom og hos patienter med PD-L1-positive tumorer [3]. I et fase III-studie blev 628 patienter randomiseret til pembrolizumab eller standard kemoterapi (taxan eller irinotecan) i 2. linje [4]. Den største effekt sås i gruppen af patienter med planocellulært karcinom og CPS > 10, svarende til højt PD-L1-udtryk. Her blev overlevelsen forlænget fra 6,7 til 10,3 måneder (HR 0,64 [95 % CI 0,46; 0,90]) samt i gruppen af asiatiske patienter uanset PD-L1-udtryk (HR 0,66 [95 % CI 0,50; 0,87]) [4]. Tilsvarende viser de foreløbige data fra et randomiseret fase III-studie i 1. linje til patienter med spiserørskræft især overlevelsesgevinst i gruppen af patienter med planocellulært karcinom og et højt PD-L1-udtryk (HR 0,57 [95 % CI 0,43; 0,75] samt i en asiatisk subpopulation (HR 0,64 [95 % CI 0,51; 0,81]) [5].

Pembrolizumab er godkendt af FDA til behandling af planocellulært karcinom i spiserøret. I forbindelse med den europæiske ansøgning noterede EMA, at effekten ikke var dokumenteret i de præspecificerede grupper. I en ikke-præspecificeret subgruppe (PDL-1 > 10 og ESCC) var der en overlevelsesgevinst, men denne var drevet af en asiatisk subpopulation. Herefter trak firmaet (Merck) ansøgningen tilbage [6].

3.3 Nuværende behandling

De kliniske retningslinjer er beskrevet af Danske Multidisciplinære Cancer Grupper (DMCG) [1]. Behandlingsmulighederne er i al væsentlighed de samme for planocellulært karcinom og adenokarcinom. Datagrundlaget for behandling af planocellulær spiserørskræft er dog sparsomt, og retningslinjerne baserer sig overvejende på undersøgelser af patienter med adenokarcinom i mavesæk og mavemund [1].

Patienter, der diagnosticeres med kræft i spiserøret, vil – afhængigt af udbredelsen af sygdommen – kunne behandles med enten kurativ intention ved kirurgi og/eller kemostråleterapi eller palliativ kemoterapi, eventuelt palliativ stråleterapi, se figur 1. Patienter, der ikke er kandidater til disse behandlinger på grund af dårlig almentilstand, modtager symptomlindrende behandling (best supportive care).



Figur 1. Oversigt over behandling for patienter med spiserørskræft

Af de årligt 320 nydiagnosticerede tilfælde af planocellulær kræft i spiserøret anslår fagudvalget, at ca. 120 blev behandlet med kurativ intention. Heraf fik ca. 40 patienter foretaget kurativt kirurgisk indgreb, og ca. 80 patienter modtog behandling med kurativt intenderet kemoradioterapi. Ca. 110 patienter havde for dårlig almen tilstand til at være kandidater til kemoterapi og fik derfor *best supportive care*.

Samlet anslår fagudvalget derfor, at der årligt er ca. 90 patienter med planocellulær spiserørskræft, der påbegynder palliativ systemisk 1. linjebehandling, og færre end 50 patienter årligt, der påbegynder palliativ systemisk 2. linjebehandling og dermed vil være kandidater til nivolumab.

1. linjebehandling

Der er sparsom evidens for effekten af palliativ systemisk behandling til planocellulær spiserørskræft [7]. Europæiske guidelines [8] foreslår derfor, at *best supportive care* eller kemoterapi som monoterapi bør overvejes som 1. linje palliativ systemisk behandling. Der er dog generel konsensus om, at palliativ kemoterapi til tidligere ubehandlede patienter eller patienter med recidiverende uhelbredelig kræft i spiserøret består af en kombination af et platinholdigt kemoterapeutikum (cis-, oxali- eller carboplatin) og en antimetabolit (5-Fluoropyrimidin (5-FU), capecitabin eller S1), eventuelt med tillæg af taxan.

Ved avanceret kræft i mavesækken, som i nogen grad har samme prognose som spiserørskræft, er kemoterapi forbundet med en median overlevelsesgevinst på 7 måneder (fra 4 til ca. 11 måneder) sammenlignet med *best supportive care* [9]. Det er vist, at kombinationsbehandling er mere effektiv end enkeltstofbehandling [9]. Andelen af patienter, der overlever 1 år efter start på 1. linjebehandling er i Danmark 34 % [1]. Efter 1. linjebehandling er behandlingsmulighederne begrænsede. Uden behandling er den forventede progressionsfri overlevelse (PFS) mindre end 2 måneder og overlevelse (OS) 2-4 måneder [10–13].

2. linjebehandling

Indikationen, der ligger til grund for denne vurdering, er patienter, som tidligere har modtaget kemoterapi og er kandidater til 2. linje systemisk behandling af spiserørskræft.

Som 2. linjebehandling anbefaler både europæiske (ESMO [6]) og amerikanske (NCCN [7]) guidelines et taxan eller irinotecan ved progression under eller efter 1. linjebehandling med platinholdigt kemoterapeutikum og antimetabolit.

I Danmark følges disse anbefalinger med brugen af de to taxaner, paclitaxel og docetaxel, samt irinotecan. Disse lægemidler er ikke godkendt til behandling af kræft i spiserøret i 2. linje (off label-anvendelse). Dog er docetaxel godkendt i 1. linje til adenokarcinom i mavesæk/mavemund i kombination med platin/5-FU. Desuden har alle tre lægemidler den tidligere anvendte danske indikation "visse maligne lidelser" og har været anvendt i Danmark i en årrække.

Brugen af lægemidlerne understøttes af studier, som viser effekt i 2. linje for patienter med adenokarcinom i mavesæk eller mavemund. Tabel 1 viser en oversigt over resultater på OS og PFS i kliniske studier for de forskellige 2. linjebehandlinger til patienter med adenokarcinom i spiserør, mavemund og mavesæk. Ved behandling med et taxan er den mediane OS 5-6 måneder – i nyere, randomiserede studier dog 7-8 måneder [14–16]. Ved behandling med irinotecan er den mediane OS 4-6,5 måneder og median PFS 2,5 måneder. Etårsoverlevelsen efter start på 2. linjebehandling er i randomiserede studier mellem 20-30 % [10–16]. Af ovenstående årsager er 2. linje kemoterapi standard til patienter i god almen tilstand og normalt eller let nedsat funktionsniveau [10,12,13,16,17].

Paclitaxel, docetaxel og irinotecan anses som ligeværdige behandlinger til 2. linjebehandling af kræft i spiserøret. Da der er betydelig toksicitet ved behandling med irinotecan, opstartes behandling hermed ofte i en lavere dosis (80 % af anbefalet dosis), som øges, hvis patienten har et acceptabelt niveau af bivirkninger ved kontrol efter 1. cyklus af behandlingen. De typiske akutte bivirkninger til kemoterapi er træthed, der påvirker patienternes funktionsniveau. Kemoterapi medfører ofte kvalme, opkastninger, nedsat appetit, mundhulegener, mavesmerter eller diarré, hvilket yderligere øger risikoen for vægttab, som er et kardinalsymptom hos denne patientgruppe. Påvirkning af knoglemarven kan give nedsat immunforsvar, blodmangel og risiko for blødninger. Af mere kronisk karakter kan være risikoen for påvirkning af hørelse, nedsat nyrefunktion, nervebetændelse samt påvirkning af hjerte- og lungefunktion.

Tabel 1. PFS og OS ved 2. linjebehandling hos patienter med adenokarcinom i mavesæk eller mavemund

	Best supportive care [10–13]	Thuss-Patience 2011 [12]	Kang 2012 [13]		Ford 2014 [10]	Wilke 2014 [14]	Thuss-Patience 2017 [15]	Shitara 2018 [16]
		Irinotecan	Irinotecan	Taxan	Taxan	Taxan	Taxan	Taxan
Antal patienter		21	133		84	335	117	296
Median PFS, måneder	1-2	2,5				2,9	2,9	4,1
Median OS, måneder	2-4	4,0	6,5	5,2	5,2	7,4	8,6	8,3
OS-rate	23-32 %* v. 6 mdr. 12 % v. 12 mdr.	-	-	-	39 % v. 6 mdr.	30 % v. 12 mdr.	-	27 % v. 12 mdr.

*OS-raterne ved 6 måneder er kun rapporteret i to af studierne: Ford 2014 [10] og Fuchs 2013 [11]. Ford 2014 er et relativt lille studie med højere andel af patienter med kræft i spiserør/mavemund (84 patienter sv.t. 54 %) end i Fuchs 2013 (238 patienter sv.t. 25 %). Der er generelt bedre prognose ved kræft i mavesækken sammenlignet med kræft i spiserør/mavemund, hvilket forklarer forskellen i overlevelsesraten ved 6 måneder (henholdsvis 23 % og 32 %), da studierne omhandler forskellige populationer.

4. Metode

Medicinrådets protokol for vurdering af nivolumab til planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

Hvilken værdi har nivolumab sammenlignet med paclitaxel, docetaxel eller irinotecan for patienter med planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi?

5.1.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøgningen er baseret på det kliniske studie (ATTRACTION-3), der er angivet i protokollen. Studiekarakteristika er angivet i tabel 2. Fagudvalget bemærker, at dosis af paclitaxel er højere end i dansk praksis, hvor der gives 80 mg/m^2 på dag 1, 8 og 15 hver 4. uge.

Tabel 2. Oversigt over studiekarakteristika

Publikationer	Klinisk forsøg	NCT-nummer	Population	Behandlingsarme
Kato 2019. The Lancet Oncology 20(11): 1506-1517 [18] Chin 2021. Abstract; ASCO 2021 [19]	ATTRACTION-3: fase III-randomiseret, internationalt, multicenter, open label-studie	NCT02569242	Inoperabel, avanceret eller tilbagevendende spiserørskræft efter tidligere behandling med palliativ kemoterapi (platin + 5-FU/capecitabin/ S1), uanset PD-L1-udtryk	Nivolumab 240 mg i.v. hver 2. uge Kemoterapi (lægens valg): paclitaxel 100 mg/m^2 i.v. hver uge i 6 uger + 1 uges pause; *eller* docetaxel 75 mg/m^2 i.v. hver 3. uge

ATTRACTION-3 rekrutterede patienter fra 90 hospitaler og kræftcentre i Danmark, Tyskland, Italien, Japan, Sydkorea, Taiwan, Storbritannien og USA. Patienterne havde ECOG performance status 0 eller 1, var refraktære eller intolerante for tidligere behandling med palliativ kemoterapi (platin + 5-FU/capecitabin/S1) og havde en forventet levetid på mindst tre måneder. Baselinekarakteristika for patienterne ses i tabel 3.

Tabel 3. Baselinekarakteristika [18,19]

	Nivolumab N=210a	Kemoterapi N=209b
Alder, median (range) < 65, n (%) ≥ 65, n (%)	64 (57 - 69) 112 (53) 98 (47)	67 (57 – 72) 85 (41) 124 (59)
Køn, mænd, n (%)	179 (85)	185 (89)
ECOG PS, n (%)		
0	101 (48)	107 (51)
1	109 (52)	102 (49)
Race, n (%)		
Asiatisk	201 (96)	200 (96)
Kaukasisk	9 (4)	9 (4)
Tilbagevendende sygdom, n (%)		
Nej	107 (51)	120 (57)
Ja	103 (49)	89 (43)
Sygdomsstadie (TNM classification), n (%)		
II-III	8 (7)	13 (11)
IV	94 (88)	100 (83)

	Nivolumab N=210a	Kemoterapi N=209b
Ukendt	5 (5)	7 (6)
Tidligere behandlinger, n (%)		
Kirurgi	111 (53)	94 (45)
Radioterapi	153 (73)	142 (68)
Systemisk anticancer-terapi	210 (100)	209 (100)
Rygehistorik, n (%)		
Aldrig	30 (14)	32 (15)
Tidligere	159 (76)	147 (70)
Nuværende	21 (10)	30 (14)
Antal organer med metastaser, n (%)		
≤ 1	89 (42)	91 (44)
≥ 2	121 (58)	118 (56)
Lokalisation af metastaser, n (%)		
Lymfeknude	159 (76)	163 (78)
Lever	57 (27)	54 (26)
Lunge	98 (47)	92 (44)
Knogle	23 (11)	25 (12)
PD-L1-udtryk, n (%)		
< 1 %	109 (52)	107 (51)
≥ 1 %	101 (48)	102 (49)
< 5 %	136 (65)	137 (66)
≥ 5 %	74 (35)	72 (34)
< 10 %	146 (70)	152 (73)
≥ 10 %	64 (30)	57 (27)

ECOG: Eastern Cooperative Oncology Group. TNM: Tumour, node and metastases.
a: Intention-to-treat population. b: Docetaxel (n = 65) and paclitaxel (n = 144).

Baselinekarakteristika var ikke væsentligt forskellige mellem grupperne. Størstedelen (96 %) af patienterne var asiater. Knap halvdelen af alle patienterne havde tumorer med PD-L1-udtryk ≥ 1 %. PD-L1-udtryk blev målt på mindst 100 tumorceller.

Fagudvalget bemærker, at patientpopulationen adskiller sig væsentligt fra den danske patientpopulation, idet der næsten kun indgår asiatiske patienter i studiet. Effekten hos ikke-asiater er ikke tilstrækkeligt dokumenteret, og derfor er der usikkerhed om overførbarheden af resultaterne fra ATTRACTION-3 til danske patienter.

I EMAs EPAR beskrives denne problemstilling, og det fremgår, at der er argumenter både for og imod, at resultaterne kan overføres. EMA konkluderer, at ikke-asiatiske patienter også vil have gavn af nivolumab, men at effektstørrelsen ikke er fastslået.

Fagudvalget fremhæver et studie, hvor effekten af pembrolizumab til spiserørskræft undersøges (KEYNOTE-181). I dette studie var der en større andel af ikke-asiater, men ellers var populationen sammenlignelig med ATTRACTION-3. Studiet viser, at anti-PD-1-behandling er mere effektiv ved asiatiske patienter sammenlignet med ikke-asiater. Derfor har fagudvalget forbehold for at overføre effekten til en dansk patientpopulation.

I afsnit 6, *Andre overvejelser*, gennemgås ansøgers svar på fagudvalgets spørgsmål vedrørende overførbarhed.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Analyserne i ansøgningen er baseret på data fra alle 419 randomiserede patienter (210 i nivolumab-armen og 209 i kemoterapi-armen) i ATTRACTION-3-studiet. Det primære effektmål var samlet overlevelse (OS). Øvrige relevante effektmål, som blev rapporteret i studiet, var PFS (sekundært effektmål), helbredsrelateret livskvalitet (præspecificeret eksplorativt effektmål) og bivirkninger.

Overlevelse
For effektmålet *Samlet overlevelse* har ansøger indsendt data i overensstemmelse med protokollen. Ansøger bemærker, at overlevelseskurven følger et mønster, som også tidligere er observeret ved nivolumab og andre immunterapier til solide tumorer. Her ser effekten ud til at være bedre i kontrolgruppen i starten, men kurverne krydser ved fem måneder og forbliver adskilt herefter, hvilket indikerer en bedre effekt af nivolumab.

At kurverne krydser indikerer, at antagelsen om proportional hazard ikke er opfyldt, hvilket også er indikeret ved en test for dette. Derfor er effektforskellen også målt i en post-hoc-analyse, hvor halen af kurven er vægtet højere end starten, men med hovedvægt på det midterste segment. Post-hoc-analysen bekræfter en statistisk forskel mellem nivolumab og kemoterapi. Resultaterne for sammenligningen er dog usikre, idet antagelserne om proportional hazards ikke er opfyldt.

Fagudvalget vurderer, at data for overlevelse kan anvendes i vurderingen, dog med forbehold for den nævnte usikkerhed. Usikkerheden overføres også til den interaktionsanalyse, som ansøger har foretaget for at identificere, hvilke patienter der har størst effekt af behandlingen.

Bivirkninger
Sikkerhed blev evalueret blandt alle patienter, som modtog mindst en behandlingsdosis (209 i nivolumab-armen og 208 i kemoterapi-armen). Der blev registreret tilfælde af uønskede hændelser op til 28 dage fra sidste dosis samt alvorlige uønskede hændelser gennem behandlingsperioden og 100 dage efter ophør af behandling. Sikkerhedsdata blev registreret ifølge CTCAE, version 4.0.

For effektmålet *Andel af patienter, der oplever grad 3-5-bivirkninger* har ansøger indsendt data for andelen, der oplever grad 3-4-bivirkninger (treatment related adverse events). Fagudvalget vurderer, at disse data kan anvendes i vurderingen.

Livskvalitet
Effektmålet *Livskvalitet* er ikke opgjort ved EORTC-QOL-C30 og EORTC-QOL-OES18 som anført i protokollen. Ansøger har i stedet indsendt data for livskvalitet opgjort ved EuroQoL five-dimension three-level questionnaire (EQ-5D-3L) utility index (UI) og visuel analog skala (VAS). Ansøger har indsendt data for den gennemsnitlige ændring fra baseline i henholdsvis nivolumab-armen og kemoterapi-armen, baseret på målinger af livskvalitet hver 6. uge fra uge 6 til 42. Andelen af udfyldte livskvalitetsspørgeskemaer

var faldende over tid, fra 96 % og 97 % i uge 6 til 16 % og 6 % i uge 42, i henholdsvis nivolumab- og kemoterapigruppen.

EQ-5D-3L UI omfatter fem domæner: mobilitet, personlig pleje, almindelige aktiviteter, smerte/ubehag og angst/depression. Der er for hvert domæne tre svarmuligheder: Ingen problemer, nogle/moderate problemer og ekstreme problemer (kan ikke udføre). Baseret på patientens svar kan index-scoren udregnes på en skala fra 0 til 1, hvor 0 er død (negative værdier indikerer et helbredsstadie værre end død), og 1 er perfekt helbred. Ansøger har angivet den mindste klinisk relevante forskel til 0,08 [20].

EQ-5D-3L VAS måler personens selvvurderede helbredstilstand på en skala fra 0 til 100, hvor 0 er værst tænkelige helbredstilstand, og 100 er bedst tænkelige helbredstilstand. Ansøger har angivet den mindste klinisk relevante forskel til 7 [20].

Fagudvalget vurderer, at de indsendte data for livskvalitet kan anvendes. Dog er estimaterne baseret på få patienter og er derfor usikre. Derfor vil effektmålet livskvalitet ikke vægte højt i den samlede vurdering.

Progressionsfri overlevelse
For effektmålet *Progressionsfri overlevelse* har ansøger indsendt data i overensstemmelse med protokollen. Overlevelseskurverne for PFS krydser, hvilket indikerer, at antagelsen om proportional hazard ikke er opfyldt. Da dette også er indikeret ved en test, vurderes det, at antagelserne om proportional hazards ikke er opfyldt. Resultaterne er dermed usikre.

Fagudvalget vurderer, at data for PFS kan anvendes i vurderingen, dog med forbehold for den nævnte usikkerhed.

5.1.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 1. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 2).

Evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen. Årsagen til den lave vurdering af evidensens kvalitet er dels, at der kun findes et studie, dels at populationen i dette studie næsten udelukkende er af asiatisk herkomst. Da der er usikkerhed om overførbarheden af resultaterne fra studiet til en dansk population, vurderes evidensens kvalitet samlet set at være meget lav.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 4. Resultater for klinisk spørgsmål 1, baseret på resultater fra ATTRACTION-3 [18] **(nivolumab sammenlignet med docetaxel eller paclitaxel), samt EMAs EPAR for nivolumab** [21]

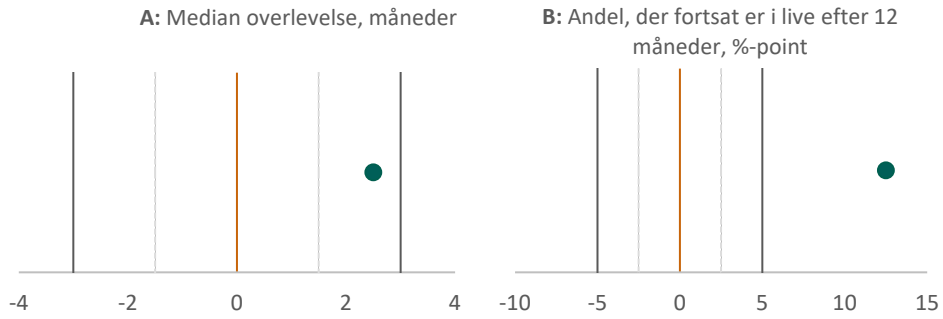
Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel [95 % CI]	Foreløbig værdi	Forskel [95 % CI]	Foreløbig værdi	
Samlet overlevelse (overall survival, OS)	Median overlevelse (3 mdr.)	Kritisk	2,5 måneder	Kan ikke kategoriseres	HR 0,77 [0,62 - 0,96]	Merværdi af ukendt størrelse	Merværdi af ukendt størrelse
	Andel, der fortsat er i live efter 12 måneder (5 %-point)		12,5 %-point*	Kan ikke kategoriseres			
Bivirkninger	Andel, der oplever grad 3-4 bivirkninger (10 %-point)	Kritisk	-44,8 %-point [-49,6; -38,3]	Merværdi af ukendt størrelse	RR 0,29 [0,21 - 0,39]	Stor merværdi	Stor merværdi
	Kvalitativ gennemgang af bivirkninger		Se tekst nedenfor				
Livskvalitet	EQ-5D-3L UI (0,08)	Vigtig	0,076 [0,011; 0,142]	Ingen dokumenteret merværdi			Ingen dokumenteret merværdi
	EQ-5D-3L VAS (7 point)		6,9 [3; 10,9]	Ingen dokumenteret merværdi			
Progressionsfri overlevelse (PFS)	Median PFS (3 mdr.)	Vigtig	-1,7 måneder*	Kan ikke kategoriseres	HR 1,08 [0,87 - 1,34]	Kan ikke kategoriseres	Ingen dokumenteret merværdi
	Andel, der fortsat er i PFS efter 12 måneder (5 %-point)		4,7 %-point*	Kan ikke kategoriseres			
Konklusion							
Samlet kategori for lægemidlets værdi	Merværdi af ukendt størrelse						
Kvalitet af den samlede evidens	Meget lav						

MKRF = Mindste klinisk relevante forskel. CI = Konfidensinterval, HR = Hazard Ratio, RR = Relativ risiko,
grå celle: kan ikke beregnes.
*Resultat beregnet ud fra data angivet i EMAs EPAR.

Samlet overlevelse
Som beskrevet i protokollen er effektmålet samlet overlevelse kritisk for vurderingen af lægemidlets værdi for patienterne, fordi spiserørskræft er en livstruende sygdom, og forbedret overlevelse med mindst mulig toksicitet er det primære behandlingsmål.

Overlevelse er opgjort som median overlevelse i antal måneder og som en overlevelsesrate efter 12 måneder.

I interventionsarmen var den mediane overlevelse 10,9 måneder [9,2; 13,3]. I komparatorarmen var den mediane overlevelse 8,4 måneder [7,2; 9,9]. Andelen af patienter i live efter 12 måneder var 46,9 % [39,9; 53,5] ved behandling med nivolumab. I komparatorarmen var andelen i live efter 12 måneder 34,4 % [27,8; 40,9].



Figur 2. Punktestimater for den absolutte forskel for A) median overlevelse, og B) andel, der fortsat er i live efter 12 måneder. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Punktestimatet for den absolutte effektforskel på 2,5 måneder i median overlevelse afspejler ikke en klinisk relevant effektforskel (figur 2A). Punktestimatet for den absolutte effektforskel på 12,5 %-point for overlevelsesraterne ved 12 måneder afspejler derimod en klinisk relevant effektforskel (figur 2B). Der er ikke beregnet konfidensintervaller for forskelle i median overlevelse og overlevelsesrater, da metoden for dette ikke er veldefineret. Effektforskellen mellem nivolumab og komparator kan derfor ikke kategoriseres i henhold til Medicinrådets metoder.

Baseret på den relative effektforskel på HR 0,77 (0,62; 0,96), som fremgår af tabel 4, har nivolumab foreløbigt en merværdi af ukendt størrelse vedr. samlet overlevelse. Der er dog tale om to forskellige kurveforløb, hvor antagelsen om proportionelle hazards ikke er opfyldt, hvilket betyder, at der er usikkerhed om estimatet.

Fagudvalget vurderer, at nivolumab aggregeret har en merværdi af ukendt størrelse vedr. *samlet overlevelse*. Fagudvalget lægger vægt på, at såvel de absolutte som den relative effektforskel peger på en bedre effekt af nivolumab sammenlignet med kemoterapi. Kurveforløbene og den mediane overlevelse indikerer, at effekten af nivolumab først sætter ind efter ca. fire måneder, hvilket forklarer den forholdsvis lille forskel på medianerne. Men den klinisk relevante forskel på overlevelsesraterne efter 12 måneder viser, at nivolumab giver en bedre overlevelse. Effektstørrelsen er dog usikker,

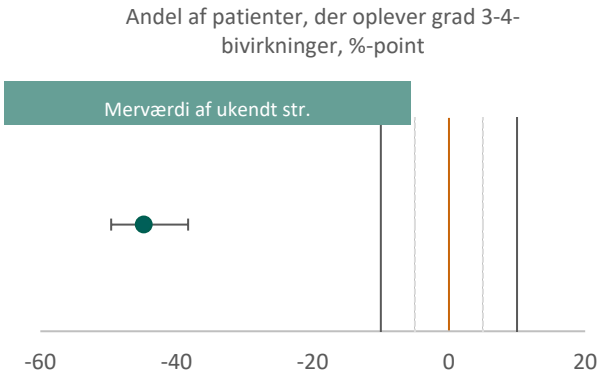
også på grund af tvivl om overførbarheden af resultaterne fra den asiatiske studiepopulation til den danske patientpopulation.

Bivirkninger

Andelen, der oplever grad 3-4-bivirkninger

Som beskrevet i protokollen er effektmålet bivirkninger kritisk for vurderingen af lægemidlets værdi for patienterne, fordi bivirkningerne ved behandling af spiserørskræft i 2. linje kan være meget alvorlige og i nogle tilfælde kan medføre døden. Behandlingen er ikke kurativ, og det er derfor afgørende for valg af behandling, at patienterne ikke er påvirket af bivirkninger i deres resterende levetid. Den mindste klinisk relevante forskel er 10 %-point.

Bivirkninger er opgjort som andelen af patienter, der oplever grad 3-4-bivirkninger. I interventionsarmen oplevede 18,2 % (38/209) en grad 3-4-bivirkning. I komparatorarmen oplevede 63,0 % (131/208) en grad 3-4-bivirkning.



Figur 3. Punktestimat for den absolutte forskel for andel, der oplever grad 3-4-bivirkninger. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Punktestimat og konfidensinterval for den absolutte effektforskel på -44,8 [-49,6; -38,3] %-point afspejler en klinisk relevant effektforskel (se figur 3). Baseret på denne forskel har nivolumab en merværdi af ukendt størrelse sammenlignet med komparator.

Baseret på den relative effektforskel på RR 0,29 [0,21; 0,39], som fremgår af tabel 4, har nivolumab foreløbigt en stor merværdi vedr. *andelen af patienter, der oplever grad 3-4-bivirkninger*.

Gennemgang af bivirkninger

Ansøger bemærker, at kun i forvejen kendte bivirkninger til nivolumab blev rapporteret i ATTRACTION-3. Dermed blev ingen nye bivirkninger opdaget. Nivolumab og kemoterapi har forskellige bivirkningsprofiler. Nivolumab er primært karakteriseret ved immunrelateret toksicitet, mens taxan-baseret kemoterapi er karakteriseret ved hæmatologiske bivirkninger, neurotoksicitet og hårtab. Hyppigheden af uønskede hændelser (uanset grad), alvorlige uønskede hændelser (uanset grad) og

behandlingsrelaterede uønskede hændelser er lavere ved nivolumab sammenlignet med kemoterapi som vist i tabel 5.

Tabel 5. Oversigt over behandlingsrelaterede uønskede hændelser (uanset grad) [21]

Hændelser, n (%)	Nivolumab, n = 209	Kemoterapi, n = 208
Alle hændelser	137 (65,6)	198 (95,2)
Alvorlige hændelser (alle grader)	33 (15,8)	47 (22,6)
Hændelser, som fører til dosisforsinkelse	(16,3)*	104 (50)
Hændelser, som fører til dosisreduktion	-[a]	75 (36,1)
Hændelser, som fører til ophør i studiet	18 (8,6)	19 (9,1)
Hændelser, som fører til død[b]	2 (1)	3 (1,4)

[a] Dosisreduktion var ikke tilladt i nivolumab-gruppen. [b] To dødsfald i nivolumab-gruppen skyldtes interstitiel lungesygdom og lungebetændelse; de tre dødsfald i kemoterapigruppen skyldtes lungeinfektion, rygmarvsinfektion og interstitiel lungesygdom. Nogle patienter havde uønskede hændelser lavere end grad 5, som slutteligt ledte til dødsfald. *Antal ikke angivet.

I ATTRACTION-3 blev hændelser med potentiel immunologisk ætiologi (immun-medierede hændelser) registreret ved NCI CTCAE (version 4.0) under behandling og op til 28 dage efter sidste dosis eller til start af efterfølgende behandling. Immunmedierede hændelser (f.eks. endokrine lidelser, diarré/tyktarmsbetændelse, leverbetændelse, lungebetændelse, nyrebetændelse og udslæt) er observeret i andre nivolumab-studier og kan tilskrives virkningsmekanismen ved nivolumab. Der var flere af disse hændelser i nivolumab-gruppen sammenlignet med kemoterapigruppen, men størstedelen var grad 1-2. Grad 3-4 forekom hos færre end 2 % af patienterne.

De behandlingsrelaterede uønskede hændelser, som forekom hyppigere i nivolumab-gruppen sammenlignet med kemoterapigruppen (forskel på mindst 5 %-point) var lavt stofskifte (8,1 % vs. 0,5 %).

De behandlingsrelaterede uønskede hændelser, som forekom hyppigere i kemoterapigruppen sammenlignet med nivolumab-gruppen (forskel på mindst 5 %-point) var hårtab (1,4 % vs. 47,1 %), fald i neutrofile granulocytter (1,4 % vs. 36,5 %), fald i hvide blodlegemer (1 % vs. 34,6 %), perifer sensorisk neuropati (0,5 % vs. 22,6 %), blodmangel (2,4 % vs. 23,6 %), lav appetit (7,7 % vs. 26,9 %), neutropeni (0,5 % vs. 19,2 %), utilpashed (4,3 % vs. 21,6 %), svimmelhed (1,9 % vs. 16,3 %), udmattende træthed (7,2 % vs. 20,7 %), febril neutropeni (0 % vs. 10,6 %), perifer neuropati (0 % vs. 10,6 %), mundbetændelse (2,4 % vs. 12 %), ledsmerter (1,4 % vs. 10,1 %), leukopeni (0 % vs. 8,2 %), muskelsmerter (1,4 % vs. 8,7 %), fald i lymfocytter (1,9 % vs. 8,7 %), opkast (0,5 % vs. 6,7 %), forstoppelse (1,9 % vs. 7,7 %) og smagsforstyrrelse (1,4 % vs. 6,7 %) [21].

Ansøger bemærker, at immunterapi efterhånden er velkendt i onkologisk behandling i Danmark, og at antallet af patienter, som oplever immunrelaterede uønskede hændelser, dermed også er øget. Derfor er der opbygget en standardiseret håndtering af

disse hændelser, og de fleste bliver opdaget hurtigt og kan håndteres ved behandling eller dosisjustering. Nogle af de mindre hyppige hændelser kræver involvering af specialister, hvorfor der på de større onkologiske afdelinger er etableret samarbejde med de relevante øvrige afdelinger.

Fagudvalget bemærker, at bivirkningsprofilerne svarer til deres kliniske erfaring med lægemidlerne. Bivirkningerne ved kemoterapi er velkendte. Nogle af dem, f.eks. febril neutropeni, er indlæggelseskrævende. Men på grund af erfaringerne med behandlingerne, er det i langt de fleste tilfælde muligt at forebygge og mindske de alvorlige gener, som bivirkningerne kan medføre for patienten. Fagudvalget er enigt med ansøger i, at der også er standardiseret håndtering af bivirkningerne ved immunterapi.

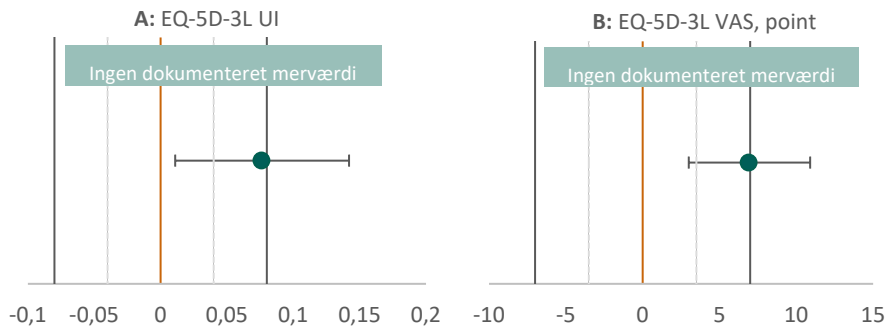
Fagudvalget vurderer, at nivolumab aggregeret har en stor merværdi vedr. *bivirkninger*, fordi der overordnet forekommer langt færre bivirkninger ved nivolumab end ved kemoterapi, og fordi bivirkningerne ved nivolumab har mindre betydning for patienterne og for fortsættelse af behandlingen. Fagudvalget bemærker, at dosis for paclitaxel var større end i dansk klinisk praksis, hvilket kan have øget bivirkningsfrekvensen og dermed potentielt overvurdere effektforskellen i forhold til nivolumab. Forskellen er imidlertid så stor, at uoverensstemmelsen i dosis vurderes ikke at have nogen betydning for konklusionen.

Fagudvalget vurderer, at resultaterne for bivirkninger kan overføres til en dansk patientpopulation, da der ikke er grund til at antage forskelle i bivirkninger sammenlignet med en asiatisk population.

Livskvalitet

Som beskrevet i protokollen er effektmålet *Livskvalitet* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi påvirkning af livskvaliteten som følge af behandling og grundsygdom betyder meget for den enkelte patient. Den potentielle negative effekt på livskvaliteten vil ofte være afgørende for valg af behandling, særligt i en population med kort restlevetid. Det er vanskeligt at måle effekten på livskvalitet af en behandling i 2. linje, idet behandlingen forventes at medføre betydelige bivirkninger og desuden gives til progression. Dermed er patientens livskvalitet sandsynligvis påvirket af enten bivirkninger eller af sygdomsprogression, uanset hvilket tidspunkt det opgøres på. Livskvalitet er således i denne sammenhæng et mål for bivirkningsbyrden under behandlingen.

Livskvalitet er opgjort ved EQ-5D-3L UI og VAS. Ansøger har ikke rapporteret niveauerne for henholdsvis interventionsarmen og komparatorarmen.



Figur 4. Punktestimater og 95 % konfidensinterval for de absolutte forskelle for A) EQ-5D-3L UI, og B) EQ-5D-3L VAS. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Punktestimatet for den absolutte effektforskel på 0,076 målt ved EQ-5D-3L UI afspejler ikke en klinisk relevant effektforskel (figur 4A). Punktestimatet for den absolutte effektforskel på 6,9 point for EQ-5D-3L VAS afspejler ikke en klinisk relevant effektforskel (figur 4B). For begge effektmål ligger den nedre grænse af konfidensintervallet tættere på 0 (ingen forskel) end på en klinisk relevant forskel. Derfor har nivolumab foreløbigt ingen dokumenteret merværdi vedr. livskvalitet.

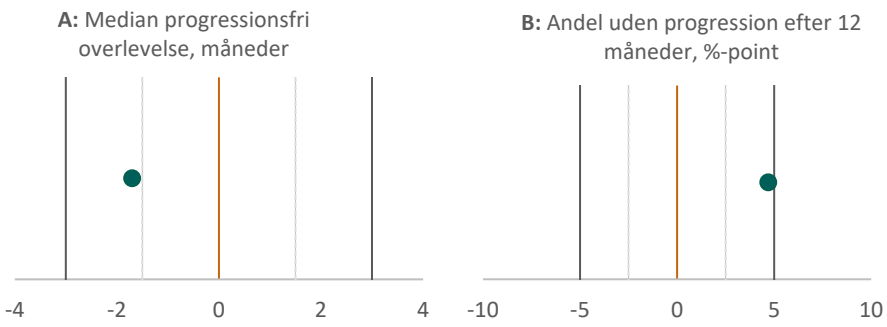
Fagudvalget vurderer, at nivolumab aggregeret har ingen dokumenteret merværdi vedr. *livskvalitet*. Forskellen er dog statistisk signifikant og tæt på klinisk relevant. Det er plausibelt, at patienterne oplever en bedre livskvalitet, når man tager den store forskel i bivirkningsprofilen i betragtning. Dog er der usikkerhed om effektmålet, og det er baseret på en lille andel af patienterne. Derfor kan data ikke dokumentere, at der er en merværdi af nivolumab sammenlignet med kemoterapi.

Progressionsfri overlevelse

Som beskrevet i protokollen er effektmålet progressionsfri overlevelse vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi tiden uden sygdomsprogression typisk er præget af stabilitet eller bedring i symptomerne, herunder færre smerter og gener samt bedre spisefunktion, hvilket har stor indflydelse på patientens dagligdag og livskvalitet.

Progressionsfri overlevelse er opgjort som median progressionsfri overlevelse i antal måneder og som andelen uden progression efter 12 måneder.

I interventionsarmen var den mediane progressionsfri overlevelse 1,68 måneder [1,51; 2,73]. I komparatorarmen var den mediane progressionsfri overlevelse 3,35 måneder [2,99; 4,21]. Andelen af patienter uden progression efter 12 måneder var 11,9 % [7,8; 16,8] ved behandling med nivolumab. I komparatorarmen var andelen uden progression efter 12 måneder 7,2 % [3,8; 12,0].



Figur 5. Punktestimater for den absolutte forskel for A) median PFS, og B) andel uden progression efter 12 måneder. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Punktestimatet for den absolutte effektforskel på -1,7 måneder i median progressionsfri overlevelse afspejler ikke en klinisk relevant effektforskel (figur 5A). Det viser, at den mediane progressionsfri overlevelse numerisk er bedre i komparatorarmen. Punktestimatet for den absolutte effektforskel på 4,7 %-point for progressionsfri overlevelsesrater ved 12 måneder afspejler ikke en klinisk relevant effektforskel (figur 5B). Beregning af konfidensintervaller for forskelle i median progressionsfri overlevelse og progressionsfri overlevelsesrater er ikke veldefinerede, og effektforskellen mellem nivolumab og komparator kan derfor ikke kategoriseres i henhold til Medicinrådets metoder.

Baseret på den relative effektforskel på HR 1,08 (0,87; 1,34), som fremgår af Tabel 3, kan værdien af nivolumab foreløbigt ikke kategoriseres for effektmålet progressionsfri overlevelse. Grunden til, at den foreløbige kategori for den relative effektforskel ikke kan kategoriseres, er det brede konfidensinterval, som indeholder både positive og negative værdier. Punktestimatet for HR antyder, at der ikke er forskel mellem interventions- og komparatorarmen i studiet. Forløbet af kurverne for de to behandlingsarme er forskellige, hvilket betyder, at antagelsen om proportionelle hazards ikke er opfyldt. Dermed bør den relative forskel beregnet ved HR ikke tillægges stor betydning, da denne er meget usikker.

Fagudvalget vurderer, at nivolumab aggregeret har ingen dokumenteret merværdi vedr. *progressionsfri overlevelse*. Selvom effektforskellene ikke kan kategoriseres efter Medicinrådets metoder, indikerer estimaterne, at der ikke er nogen forskel på PFS. Der er en lavere median PFS i nivolumab-gruppen, dog er forskellen ikke klinisk relevant. Omvendt er der flere i PFS efter 12 måneder med nivolumab, men igen er forskellen ikke klinisk relevant. Disse resultater afspejler kurvens forløb, som indikerer, at effekten af nivolumab sætter ind senere end kemoterapi.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at nivolumab til patienter med planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi giver en merværdi af ukendt størrelse sammenlignet med kemoterapi (paclitaxel eller docetaxel).

I den samlede kliniske vurdering af lægemidlet vægter fagudvalget værdien af effektmålet overlevelse højt og finder, at EMAs bemærkning om, at effektstørrelsen ikke er fastslået i ikke-asiatisk population, understøtter, at den samlede vurdering bliver merværdi af ukendt størrelse.

Fagudvalget lægger vægt på, at resultaterne viser en bedre overlevelse og væsentligt færre bivirkninger med nivolumab. Især den klinisk relevante forskel på overlevelsesraterne efter 12 måneder bemærkes. Desuden er livskvaliteten mindst lige så god og formentlig bedre sammenlignet med kemoterapi. Data viser ikke, at der er forskel på progressionsfri overlevelse. Resultaterne i sig selv viser, at nivolumab er en væsentlig bedre behandling end kemoterapi. Idet fagudvalget tager forbehold for usikkerheden vedrørende overførbarheden fra den asiatiske studiepopulation, er den samlede merværdi af ukendt størrelse.

Fagudvalget bemærker, at data indikerer, at kun en del af populationen vil have bedre effekt af nivolumab. Dette understreges af data fra ATTRACTION-studiet, som ikke er medtaget i vurderingen. Her er rapporteret, at væsentligt flere patienter i nivolumab-gruppen oplever progression sammenlignet med kontrolgruppen (55 % vs. 32 %). Tilsvarende er der væsentligt færre i nivolumab-gruppen, der oplever stabil sygdom sammenlignet med kontrolgruppen (18 % vs. 41 %). Den positive effekt af nivolumab hos en lille gruppe af patienterne ledsages således af manglende effekt hos en væsentlig del af patienterne. Beklageligvis er der ikke påvist parametre ved subgruppe- og interaktionsanalyser, herunder tumors PDL-1-ekspression, der kan selektere patienterne til behandling.

6. Andre overvejelser

6.1 PD-L1-ekspression

Jf. protokollen blev ansøger bedt om data for, hvorvidt behandlingseffekten af nivolumab er afhængig af tumors ekspression af PD-L1 vurderet ved immunhistokemisk undersøgelse, herunder hvorvidt PD-L1-status kan relateres til de valgte effektmål. Fagudvalget ønsker i den forbindelse oplyst, hvilket setup der er anvendt for at teste ekspression af PD-L1, herunder platform, antistof (clon) og scoringsprincipper.

Svar fra ansøger

Patienter blev inkluderet i ATTRACTION-3 uanset PD-L1-udtryk. Der var signifikant effekt på overlevelse og færre bivirkninger med nivolumab sammenlignet med kemoterapi. Der var ikke signifikant forskel mellem overlevelseseffekten på tværs af PD-L1-niveauer. Den

mediane overlevelse var 10,9 måneder for både PD-L1 < 1 % og ≥ 1 %. Det understøttes af en interaktionstest, som ikke finder, at OS er afhængig af PD-L1-niveau. Der er således ikke datagrundlag for at selektere patienter til behandling med nivolumab på baggrund af PD-L1-udtryk.

Fagudvalget er enigt i ansøgers betragtninger.

6.2 Overførbarhed af data til dansk population

Jf. protokollen blev ansøger bedt om at redegøre for, om resultater baseret på den overvejende asiatiske studiepopulation i ATTRACTION-3 er overførbare til den danske patientpopulation, herunder om der er forskel på effektstørrelsen mellem etniske grupper.

Svar fra ansøger

Ansøger argumenter for, at resultaterne fra ATTRACTION-3 er overførbare til den danske patientpopulation. Ansøger fremfører EMAs konklusion om, at resultaterne er overførbare, men at størrelsesordenen ikke er fastslået.

Yderligere bemærker ansøger, at farmakokinetiske analyser på tværs af forskellige tumortyper viser, at nivolumab-eksponering og -clearance er ens i forskellige etniske grupper, herunder asiatiske og ikke-asiatiske patienter med spiserørskræft.

Ansøger beskriver blandt andet følgende data for at belyse betydningen af herkomst på overlevelse hos patienter med spiserørskræft:

- Et registerstudie (Zhang et al.) viste, at patienter med spiserørskræft fra henholdsvis østlige og vestlige lande adskiller sig; der var signifikant flere kvinder i den kaukasiske gruppe, og diagnosen blev stillet tidligere (alder og sygdomsstadie) i den kinesiske gruppe. Effekten på overlevelse adskilte sig ikke mellem grupperne, dog var der signifikant forskel i subgruppen af mænd.
- Et andet registerstudie (Lin et al.) viste, at for patienter med spiserørskræft, bosiddende i USA, var kinesisk herkomst uafhængigt associeret med en bedre overlevelse sammenlignet med kaukasere.
- KEYNOTE-181 er et randomiseret, ublindet fase III-studie, hvor effekten af pembrolizumab blev sammenlignet med docetaxel, paclitaxel eller irinotecan til patienter med avanceret/metastatisk spiserørskræft (planocellulær og adenokarcinom samt kræft i mavemund, Siewert type 1). I KEYNOTE var 42 % ikke-asiater. Subgruppeanalyser viste, at anti-PD-L1-behandling er mere effektivt til asiatiske patienter med planocellulær spiserørskræft end til ikke-asiater. Ansøger mener dog ikke, at KEYNOTE-181 bør sammenlignes med ATTRACTION-3 på grund af forskelle i studiedesign, populationer, lægemidler, dosering og administration (Kojima 2020).
- Data fra et igangværende randomiseret dobbeltblindet, placebokontrolleret studie (CA209-566, som undersøger nivolumab til 2. linjebehandling af spiserørskræft og kræft i mavemund (NCT02743494), blev præsenteret på

ESMO 2020 (Kelly 2020). De foreløbige data viser samme 'disease-free survival', uanset herkomst, i en population med 85 % ikke-asiater.

Ansøger fremhæver, at selvom data fra ATTRACTION-3 næsten udelukkende er baseret på asiatiske patienter, er bivirkningsprofilen ved nivolumab sammenlignelig med, hvad der er observeret i populationer med andre sygdomme, bestående af både asiatiske og ikke-asiatiske patienter.

6.3 Dosering

Jf. protokollen blev ansøger bedt om at fremsende eventuelle data, som kan understøtte brugen af fast vs. vægtjusteret dosis (kan der som alternativ til 240 mg nivolumab hver 2. uge anvendes 480 mg hver 4. uge eller en vægtbaseret dosis (f.eks. 3 mg/kg hver 2. uge eller 6 mg/kg hver 4. uge)). Ansøger blev ligeledes bedt om at beskrive, om der er forskel på at give fast eller vægtjusteret dosis for effektmålene og i givet fald hvorfor.

Svar fra ansøger

Ansøger anfører, baseret på data fra nivolumab-studier, at der ikke er forskel i effekt eller bivirkninger for fast dosis sammenlignet med vægtjusteret dosis.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning fra Medicinrådet på området.

8. Referencer

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kræft i mavesæk og mavemund

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Lene Bæksgaard Jensen *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Mette Karen Nytoft Yilmaz *Overlæge*	Region Nordjylland
Marianne Nordsmark *Overlæge*	Region Midtjylland
Helle Anita Jensen *Overlæge*	Region Syddanmark
Kenneth Hofland *Overlæge*	Region Sjælland
Jon Kroll Bjerregaard *Overlæge*	Region Hovedstaden
Natalia Marta Luczak *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Zandra Nymand Ennis *Afdelingslæge*	Dansk Selskab for Klinisk Farmakologi
Mikkel Eld *Overlæge*	Dansk Patologiselskab
En patient/patientrepræsentant	Danske Patienter
Kan ikke udpege	Dansk Esophagus-, Gastroesophageal overgangscancer og Ventrikel-cancergruppe

Medicinrådets sekretariat

Medicinrådet

Dampfærgevej 27-29, 3.th.

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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	26. maj 2021	Godkendt af Medicinrådet.

11. Bilag

Bilag 1: Cochrane – risiko for bias

Tabel 6. Vurdering af risiko for bias ved Cochrane risk of bias tool 2.0. Kato 2019: ATTRACTION-3 NCT02569242

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	Lav	Randomisation was done using an interactive web response system. Investigators registered patients at each site via the web registration system. An authorised vendor used their original internal system to generate the sequentially numbered containers to ensure random allocation, and to assign patients to study treatments. The web registration system ensured that the container sequence was concealed until the treatment allocation was completed.
Effekt af tildeling til intervention	Forbehold	Patients and investigators were not masked to treatment allocation. Intention-to-treat analysis. Der synes ikke at være forskel på grupperne ud over interventionerne.
Manglende data for effektmål	Forbehold	Der er en høj andel af behandlingsophør, men dette gælder i både nivolumab- og kemoterapigruppen (hhv. 193/209 og 205/208). Det har betydning for effektmålet livskvalitet, hvor ændring fra baseline er baseret på en lille andel af populationen.
Risiko for bias ved indsamlingen af data	Forbehold	Den manglende blinding kan have betydning for effektmålet livskvalitet, hvor patienterne kan overestimere effekten på grund af forventninger om en bedre behandling. Potentielt kan bivirkninger underrapporteres ved en ny behandling med forventet færre bivirkninger. Men det er anført, at: *An independent data monitoring committee monitored safety data.* Under antagelse om, at datakomiteen er blindet, vurderes risikoen for dette ikke at være af betydning.
Risiko for bias ved udvælgelse af resultater, der rapporteres	Lav	Ikke noget der tyder på selektionsbias ved tjek af clinicaltrials.gov.
Overordnet risiko for bias	Forbehold	Den manglende blinding giver anledning til forbehold for, at der kan være risiko for bias. Det formodes dog kun at have betydning for effektmålet livskvalitet, som kan være påvirket af den forventede effekt.

Bilag 2: GRADE

Tabel 7. GRADE evidensprofil for klinisk spørgsmål 1 – nivolumab sammenlignet med kemoterapi til behandling af spiserørskræft (direkte sammenligning fra ATTRACTION-3)

Sikkerhedsvurdering							Antal patienter		Effekt		Sikkerhed	Vigtighed
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Nivolumab	Kemoterapi	Relativ [95 % CI]	Absolut [95 % CI]		
Samlet overlevelse (overall survival, OS): Median overlevelse												
1	RCT	Ikke alvorlig	Alvorlig[a]	Meget alvorlig[b]	Alvorlig[c]	Ingen	210	209	HR 0,77 [0,62 - 0,96]	2,5 måneder	⨁◯◯◯ MEGET LAV	KRITISK
Samlet overlevelse (overall survival, OS): Andel, der fortsat er i live efter 12 måneder												
1	RCT	Ikke alvorlig	Alvorlig[a]	Meget alvorlig[b]	Alvorlig[c]	Ingen	210	209	HR 0,77 [0,62 - 0,96]	12,5 %-point	⨁◯◯◯ MEGET LAV	KRITISK
Bivirkninger: Andel, der oplever grad 3-4-bivirkninger												
1	RCT	Ikke alvorlig	Alvorlig[a]	Meget alvorlig[b]	Ikke alvorlig	Ingen	209	208	RR 0,29 [0,21 - 0,39]	-44,8 %-point [-49,6; -38,3]	⨁◯◯◯ MEGET LAV	KRITISK
Livskvalitet: EQ-5D-3L UI												
1	RCT	Alvorlig[d]	Alvorlig[a]	Meget alvorlig[b]	Ikke alvorlig	Ingen	34	13	-	0,076 [0,011; 0,142]	⨁◯◯◯ MEGET LAV	VIGTIG
Livskvalitet: EQ-5D-3L VAS												
1	RCT	Alvorlig[d]	Alvorlig[a]	Meget alvorlig[b]	Ikke alvorlig	Ingen	34	13	-	6,9 [3; 10,9]	⨁◯◯◯ MEGET LAV	VIGTIG
Progressionsfri overlevelse (PFS): Median PFS												
1	RCT	Ikke alvorlig	Alvorlig[a]	Meget alvorlig[b]	Alvorlig[c]	Ingen	210	209	HR 1,08 [0,87 - 1,34]	-1,7 måneder	⨁◯◯◯ MEGET LAV	VIGTIG
Progressionsfri overlevelse (PFS): Andel, der fortsat er i PFS efter 12 måneder												
1	RCT	Ikke alvorlig	Alvorlig[a]	Meget alvorlig[b]	Alvorlig[c]	Ingen	210	209	HR 1,08 [0,87 - 1,34]	4,7 %-point	⨁◯◯◯ MEGET LAV	VIGTIG
Kvalitet af den samlede evidens			MEGET LAV[e]									

[a] Der er nedgraderet ét niveau, da evidensgrundlaget kun består af ét studie. [b] Der er nedgraderet to niveauer, da studiepopulationen adskiller sig fra den danske patientpopulation, hvilket betyder at der er væsentlig usikkerhed forbundet med at overføre resultaterne. [c] Der er nedgraderet ét niveau, da konfidensintervallet indeholder en beslutningsgrænse, hvilket betyder at værdien kan tilhøre forskellige kategorier jf. Medicinrådets metoder. [d] Der er nedgraderet ét niveau, da der var nogle forbehold i vurderingen af risiko for bias for effektmålet livskvalitet. [e] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Medicinrådet

Application for the assessment of nivolumab for the treatment of esophageal squamous cell carcinoma with advanced disease following prior chemotherapy

Medicinrådet

Contents

1 Basic information

Table 1 Contact information

Name	Lars Oddershede, Ph.d.
Title	Market Access Manager
Area of responsibility	Primary contact
Phone	+45 42 56 60 30
E-mail	Lars.oddershede@bms.com

Table 2 Overview of the pharmaceutical

Proprietary name	Opdivo®
Generic name	Nivolumab
Marketing authorization holder in Denmark	Bristol-Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 Dublin 15, D15 T867 Irland
ATC code	L01XC17
Pharmacotherapeutic group	Human immunoglobulin G4 monoclonal antibody (HuMAb), which binds to the programmed death-1 receptor and blocks its interaction with PD-L1 and PD-L2
Active substance(s)	Nivolumab
Pharmaceutical form(s)	IV
Mechanism of action	Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumors or other cells in the tumor microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumor responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumor growth (Nivolumab Summary of Product Characteristics)
Dosage regimen	The recommended dosing schedule is 240 mg nivolumab every 2 weeks. Nivolumab is for intravenous use only. It is to be administered as an intravenous infusion over a period of 30 minutes. The infusion must be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm. Nivolumab must not be administered as an intravenous push or bolus injection. The total dose of nivolumab required can be infused directly as a 10 mg/mL solution or can be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection.

	Treatment with nivolumab should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	OPDIVO® (nivolumab) as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy
Other approved therapeutic indications	**Melanoma** OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. **Adjuvant treatment of melanoma** OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection **Non-Small Cell Lung Cancer (NSCLC)** OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults. OPDIVO in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumors have no sensitising EGFR mutation or ALK translocation. **Renal Cell Carcinoma (RCC)** OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults. OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma **Classical Hodgkin Lymphoma (cHL)** OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin. **Squamous Cell Cancer of the Head and Neck (SCCHN)** OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy **Urothelial Carcinoma** OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Nivolumab (10.0 mg/mL) single-use vials: 40 mg/4 mL 240 mg/24 mL 100 mg/10 mL
Orphan drug designation	No

Abbreviations: cHL, classical Hodgkin lymphoma; HuMAb, Human immunoglobulin monoclonal antibody; IgG4, human immunoglobulin G4; NSCLC, non-small cell lung cancer; PDL1, Programmed death-ligand; RCC, renal cell carcinoma; SCCHN, squamous Cell Cancer of the Head and Neck

2 Abbreviations

Table 3: Table of abbreviations

Abbreviation	Description of abbreviation
1L	**First-line**
2L	**Second-line**
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ASCT	Autologous stem cell transplant
ATC	Anatomical therapeutic chemical
BOR	Best overall response
BSA	Body surface area
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRT	Chemo-radiation therapy
CT	Computed tomography
CTC	Common terminology criteria
DCR	Disease control rate
DoR	Duration of Response
DECG	Dansk EsophagoGastrisk Cancer group
DFS	Disease-free survival
EAC	Oesophageal adenocarcinoma
EC	Oesophageal cancer
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	Epidermal growth factor receptor
EMA	European Medical Association
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European public assessment report
EQ-5D-3L	EuroQoL five-dimension three-level questionnaire
ESCC	Esophageal squamous cell carcinoma
GEJ	Gastroesophageal junction
GEJC	Gastroesophageal junction Cancer
HRQoL	Health-related quality of life
IFN$^{\gamma}$	Interferon-gamma
IQR	Interquartile range
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive Web Response Systems
KM	Kaplan Meier
LS	Least squares
LSMD	Least squares mean difference
MAH	Medical authorization holder
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
NBHW	The Swedish National Board of Health and Welfare

NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PF	Progression-free
PFS	Progression-free survival
PK	Pharmacokinetics
PPK	Population pharmacokinetics
QoL	Quality of life
QW	Once a week
RCC	Renal cell carcinoma
RECIST	Response evaluation criteria in solid tumors
RES	Response evaluable set
RP2D	Recommended phase 2 dose
RR	Relative risk
SCCHN	Squamous Cell Cancer of the Head and Neck
SE	Standard error
SEER	Surveillance, Epidemiology, and End Results
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TTR	Time to response
UI	Utility index
VAS	Visual analogue scale

3 Summary

This application concerns the reimbursement of nivolumab (Opdivo) in adults with unresectable advanced or recurrent **esophageal squamous cell carcinoma** (ESCC) after prior fluoropyrimidine- and platinum-based combination therapy.

Esophageal cancer (EC) is a disease in which malignant (cancer) cells form in the tissues of the esophagus, the muscular tube that moves food and liquids from the throat to the stomach (NCI 2018). There are two major histological types of EC—esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC)—which differ greatly in terms of physiology, epidemiology, and risk factors (Arnold 2015). ESCC most commonly forms in the middle third of the esophagus, whereas EAC usually forms in the lower third of the esophagus (Kleinberg 2014). ESCC accounts for approximately 87% of ECs worldwide and is the dominant histology in Asian and many European countries (Arnold 2015). Major risk factors for ESCC include smoking and alcohol consumption (Kleinberg 2014).

About 1150 new cases of gastroesophageal junction (GEJ), gastric and esophageal cancer were registered in Denmark from Jan – Dec 2018 (Dansk DECV Cancer Gruppe Årsrapport 2018). **Anually, around 300 patients are diagnosed with esophageal cancer, most cases being ESCC.** In Denmark, the multidisciplinary cancer group DECG (*Dansk EsophagoGastrisk Cancer group*) is continuously developing and coordinating the Danish national treatment guidelines for GEJ, gastric and esophageal cancer across stage and disease location. Patients will be referred to one of four Center of Excellences *i.e.* the university hospitals in Aalborg, Aarhus, Odense, and Rigshospitalet for treatment.

Prognosis of esophageal cancer is strongly correlated to stage of disease, co-morbidities, and performance status. Stage I-III accounts for 45% and > 40% of patients are stage IV at time of diagnosis (Dansk DECV Cancer Gruppe Årsrapport 2018). The majority of diagnosed patients receives palliative therapy (Dansk DECV Cancer Gruppe Årsrapport 2018). The five year OS rate for esophageal cancer patients treated with curative intended resection is 45% (95% CI: 39-51] (Dansk DECV Cancer Gruppe Årsrapport 2018). In contrast, around 31% of patients treated with palliative systemic care are alive at 1 year follow-up (Dansk DECV Cancer Gruppe Årsrapport 2018).

In Europe, advanced/metastatic EACs are mostly managed according to the recommendations for gastric cancer. Generally, fluoropyrimidine/platinum combinations are recommended; taxanes are recommended in 1L-combinations and taxane monotherapy is recommended for 2L therapy. In advanced/metastatic ESCC, the value of palliative chemotherapy is less proven and fewer treatment options exist for ESCC compared with EAC.

Nivolumab is a new treatment modality for adults with ESCC refractory to or intolerant of 1L therapies. Nivolumab is a fully human, IgG_4 PD-1 receptor-blocking monoclonal antibody that prevents inactivation or reactivates the ability of T cells to attack the tumor (Brahmer 2010, Menzies 2013). Nivolumab binds to PD-1 receptors on T cells with high affinity (Brahmer 2010) and selectively disrupts inhibitory signalling triggered by PD-L1 and PD L2, thereby restoring normal T-cell antitumor function.

The pivotal phase 3 study, ATTRACTION-3 (NCT02569242), is randomised, international, multicenter, open-label study evaluating the efficacy and safety of nivolumab in adults with unresectable advanced or recurrent ESCC after prior fluoropyrimidine- and platinum-based combination therapy (Kato 2019). The study was conducted at 90 hospitals and cancer centers in Denmark, Germany, Italy, Japan, South Korea, Taiwan, the UK, and the USA.

At a minimum follow-up time (i.e., time from random assignment of the last patient to data cutoff) of **17.6 months**, nivolumab demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS) versus taxane monotherapy (mOS 10.9 m (95% CI, 9.2–13.3) vs 8.4 m (95% CI, 7.2–9.9). **Risk of death was reduced by 23%** (HR, 0.77; 95% CI, 0.62–0.96; P=0.019). At 12 and 18 months, 47% and 31% of patients treated with nivolumab were still alive, compared with 34% and 21% of patients treated with taxane monotherapy, suggesting nivolumab provides a durable OS benefit. The objective response rate (ORR) was 19% (95% CI, 14–26) in patients treated with nivolumab and 22% (95% CI, 15–29) in patients treated with taxane monotherapy. The median duration of response (DoR) was 6.9 months in patients with nivolumab and 3.9 in patients treated with taxane monotherapy. There was no significant difference in progression free survival (PFS) between the treatment arms (hazard ratio for progression or death, 1.08; 95% CI, 0.87–1.34) (Kato 2019).

Patients treated with nivolumab had a lower incidence of grade 3 or 4 treatment-related adverse events (TRAEs) (18%) compared with patients treated with taxane monotherapy (63%) (Kato 2019).

4 Literature search

The clinical question posed by the Medicines Council is the following: *What is the value of nivolumab compared to paclitaxel, docetaxel or irinotecan in patients with advanced esophageal squamous cell carcinoma after previous chemotherapy treatment?*

The Medicines Council has not requested a literature search as the study ATTRACTION-3 (NCT02569242) has been identified to compare nivolumab directly to the requested chemotherapy comparators—paclitaxel or docetaxel—which allows for enough data for a comparative analysis, requiring no indirect treatment comparision.

As the clinical trial ATTRACTION-3 data does not include irinotecane and a direct treatment comparision to nivolumab is not available, irinotecane will not be included as a comparator in this application document.

4.1 Main characteristics of included studies

4.1.1 ATTRACTION-3

ATTRACTION-3 (NCT02569242) is a phase 3 randomied, international, multicenter, open-label study to evaluate the efficacy and safety of nivolumab in adults with unresectable advanced or recurrent ESCC after prior fluoropyrimidine- and platinum-based combination therapy (Kato 2019). Please see the Appendix Table 14 for additional study details.

The study was conducted at **90 hospitals and cancer centres in Denmark, Germany, Italy, Japan, South Korea, Taiwan, the UK, and the US**. Key inclusion criteria were unresectable advanced or recurrent ESCC, regardless of programmed death-ligand 1 (PD-L1) expression, at least one measurable or non-measurable lesion according to RECIST version 1.1, baseline Eastern Co-operative Oncology Group (ECOG) performance status (PS) of 0 or 1, refractory disease or intolerance to one previous fluoropyrimidine-based and platinum-based chemotherapy, and a life expectancy of at least three months (Kato 2019).

Between January 2016 and May 2017, **419 patients** were randomised (1:1) to either nivolumab (240 mg) administered IV over 30 minutes every 2 weeks or investigator's choice of chemotherapy (paclitaxel 100 mg/m2 administered IV over at least 60 minutes every week for 6 weeks then 1 week off; docetaxel 75 mg/m2 administered IV over at least 60 minutes every 3 weeks). Randomisation was conducted using an interactive web response system with a block size of four and stratified according to geographical region (Japan versus rest of world), number of organs with metastases (≤1 versus ≥2), and tumor PD-L1 expression on at least 100 viable tumor (≥1% versus <1%); patients and investigators were not masked to treatment allocation. Treatment continued until evidence of disease progression (as assessed by the investigator per RECIST version 1.1) or unacceptable toxicity. Dose reductions were allowed for paclitaxel and docetaxel for toxicities prespecified in the protocol. Dose reductions were not permitted in the nivolumab group (Kato 2019). Table 4 below includes the baseline caracteristics of the study.

Table 4: Demographics and baseline characteristics of the intented-to treat population

Characteristic	**Nivolumab** N=210[a]	**Chemotherapy** N=209[b]
Median age (range), years	64 (57 -- 69)	67 (57 – 72)
<65	112 (53%)	85 (41%)
≥65	98 (47%)	124 (59%)
Male, n (%)	179 (85)	185 (89)
ECOG PS, n (%)		
0	101 (48)	107 (51)
1	109 (52)	102 (49)
Race, n (%)		
Asian	201 (96)	200 (96)
Caucasion	9 (4)	9 (4)
Recurrent disease, n (%)		
No	107 (51)	120 (57)
Yes	103 (49)	89 (43)
Disease stage (TNM classification), n (%)		
II-III	8 (7)	13 (11)

Characteristic	Nivolumab N=210[a]	Chemotherapy N=209[b]
IV	94 (88)	100 (83)
Unknown	5 (5)	7 (6)
Prior therapies, n (%)		
Surgery	111 (53)	94 (45)
Radiotherapy	153 (73)	142 (68)
Systemic anticancer therapy	210 (100)	209 (100)
History of smoking, n (%)		
Never	30 (14)	32 (15)
Former	159 (76)	147 (70)
Current	21 (10)	30 (14)
Number of organs with metastases§, n (%)		
≤1	89 (42)	91 (44)
≥2	121 (58)	118 (56)
Site of metastases, n (%)		
Lymph node	159 (76)	163 (78)
Liver	57 (27)	54 (26)
Lung	98 (47)	92 (44)
Bone	23 (11)	25 (12)
PD-L1 expression¶, n (%)		
<1%	109 (52)	107 (51)
≥1%	101 (48)	102 (49)
<5%	136 (65)	137 (66)
≥5%	74 (35)	72 (34)
<10%	146 (70)	152 (73)
≥10%	64 (30)	57 (27)
History of smoking		
Never	30 (14)	32 (15)
Former	159 (76)	147 (70)
Current	21 (10)	30 (14)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. TNM=tumour, node, and metastases.*Included 65 patients treated with docetaxel and 144 patients treated with paclitaxel. †Summarised at randomisation for patients with non-recurrent oesophageal cancer (nivolumab [n=107] and chemotherapy [n=120]). ‡Union for International Cancer Control TNM Classification of Malignant Tumours, 7th edn. Wiley-Blackwell; 2011. §Per interactive web response system. ¶Per test results. a Intent-to-treat population; bDocetaxel (n = 65) and paclitaxel (n = 144); cSummarized at randomization for patients with non-recurrent ESCC (nivolumab, n = 107 and chemotherapy, n = 120). Disease stage could not be classified for five patients in the nivolumab arm and seven patients in the chemotherapy arm.
Source: (Kato 2019, Chin 2021)

The analyses presented here describes data from all 419 randomised patients: the nivolumab group included 210 patients and the taxane monotherapy group comprised 209 patients. Baseline characteristics were similar across the treatment groups (Kato 2019).

The majority (96%) of patients were Asian. All patients had received prior systemic anticancer therapy and 49% and 70% of patients had previous surgery and radiotherapy, respectively. Nearly half of all patients had tumor PD-L1 expression ≥1% (Table 14) (Kato 2019). Tumor cell **PD-L1 expression was assessed on at least 100 viable tumor cells** by a central laboratory using immunohistochemistry (PD-L1 IHC 28-8 pharmDx assay; Dako, an Agilent Technologies company, Santa Clara, CA, USA)

The **primary endpoint was OS.** Pre-specified exploratory analyses to assess the association between OS and stratification factors or patient baseline characteristics were also conducted. Secondary endpoints included ORR (proportion of patients with a complete or partial response, as assessed by investigator), best overall response, PFS, disease control rate, maximum percent change from baseline in the sum of the diameters of target lesions, time to response, and duration of response. HRQoL, assessed by EQ-5D-3L and comprising the visual analue scale (VAS) and descriptive system, was a pre-specified exploratory endpoint in the study. Safety was assessed in all patients who received at least one dose of the assigned treatment; safety endpoints included the incidence of adverse events in all treated patients up to 28 days from the last dose. Serious adverse events were assessed throughout the treatment period and for 100 days after treatment discontinuation per CTCAE version 4.0 (Kato 2019).

5 Clinical questions

5.1 Clinical question: What is the value of nivolumab compared to paclitaxel, docetaxel or irinotecan in patients with advanced esophageal squamous cell carcinoma after previous chemotherapy treatment?

5.1.1 Presentation of relevant studies

The following studies are used in the assessment of clinical question:

- ATTRACTION-3 (NCT02569242)

5.1.2 Results per study

Overall survival

Median survival

Nivolumab demonstrated a statistically significant and clinically meaningful improvement in OS versus taxane mono-therapy. Median OS was 10.9 months (95% CI, 9.2–13.3) with nivolumab and 8.4 months (95% CI, 7.2–9.9) with taxane monotherapy, resulting in a 2.5 month increase in survival with nivolumab treatment, and the risk of death was reduced by 23% (HR: 0.77; 95% CI, 0.62–0.96; *P*=0.019) (Kato 2019) (Table 5).

Table 5: Median overall survivial, ITT population

	ATTRACTION-3	
	Nivolumab N= 210	Taxane monotherapy N= 209
Median overall survival, months (95% CI)	10.9 (9.2–13.3)	8.4 (7.2–9.9)
Estimated relative difference in effect, hazard ratio (95% CI, p-value)	0.77 (0.62–0.96; 0.019)	

Abbreviations: CI, confidence interval.
Source: (Kato 2019)

Proportion of patients alive after 12 months

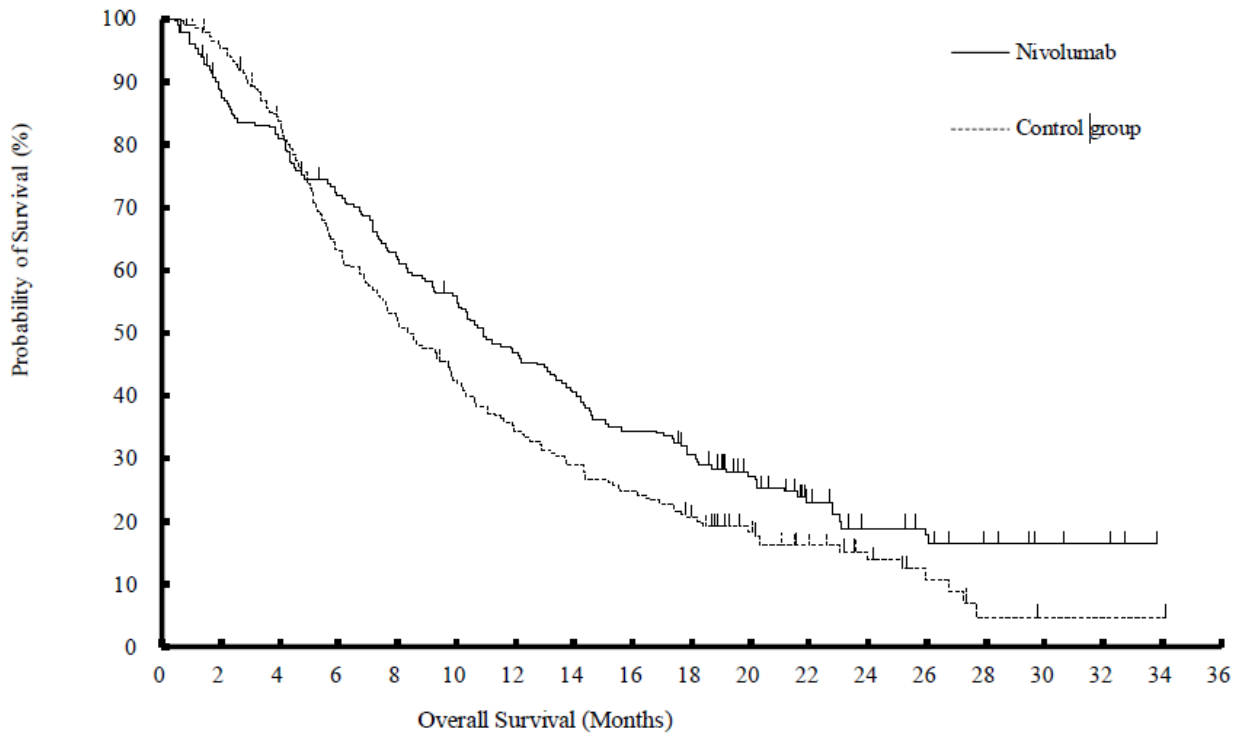
At 12 months, a substantial higher number of nivolumab-treated patients were still alive **47% compared with 34**% of patients treated with taxane monotherapy. The OS curves followed a pattern observed with nivolumab and other im-munotherapies in some solid tumors, with crossing of curves and sustained separation favouring nivolumab beyond five months; post hoc analysis corroborated the OS benefit with nivolumab versus taxane mono-therapy (Kato 2019) (Table 6 and Figure 1).

Table 6: Proportion of patients alive after 12 months, ITT population

	ATTRACTION-3	
	Nivolumab N= 210	Taxane monotherapy N= 209
Percentage still alive after 12 months, % (95% CI)	46.9 (39.9–53.5)	34.4 (27.8–40.9)
Estimated relative difference in effect, hazard ratio (95% CI, p-value)	0.77 (0.62–0.96; 0.019)	

Abbreviations: CI, confidence interval.
Source: (EMA 2020)

Figure 1: Kaplan-Meier plot of overall survival - ITT patient population



Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Nivolumab	210	182	167	147	126	111	95	82	70	60	43	25	17	13	7	4	3	0	0
Control group	209	196	169	126	105	84	68	57	49	40	27	17	12	6	2	1	1	1	0

Abbreviations: ITT, intent to treat.
Source: (EMA 2020)

Treatment related adverse events

Proportion of patients experiencing grade 3-4 treatment related adverse events

Nivolumab was associated with a more than threefold lower incidence of grade 3 or 4 TRAEs vs. taxane monotherapy: 18% of patients treated with nivolumab experienced a grade 3 or 4 TRAEs compared with 63% of patients treated with taxane monotherapy. The relative risk (RR) of experiencing a grade 3-4 TRAE with nivolumab treatment versus taxane monotherapy was 0.29 (95% CI: 0.21 – 0.39). The absolute risk difference associated with nivolumab treatment was -44.8% (95% CI: -49.6% – 38.3%) is clinically meaningful (Kato 2019) (**Error! Reference source not found.**Table 7).

Table 7: Proportion of patients experiencing grade 3-4 treatment-related adverse events, ITT population

	ATTRACTION-3	
	Nivolumab N= 209	Taxane monotherapy N= 208
Grade 3-4 treatment-related adverse events, n (%)	38 (18.2%)	131 (63.0%)
Estimated relative difference in effect, relative risk (95% CI)	0.29 (0.21–0.39)	
Estimated absolute difference in effect, %-point (95% CI)	-44.8% (-49.6% to -38.3%)	

Abbreviations: CI, confidence interval.
Source: (Kato 2019)

The safety profile of nivolumab observed in the ATTRACTION-3 study was **consistent with the already known safety** information (Nivolumab Summary of Product Caracteristics). The most common TRAEs were rash, diarrhoea and decreased appetite in the nivolumab group; and alopecia, decreased neutrophil count and decreased white blood cell count in the chemotherapy group. The most common treatment related grade 3 or 4 AE with nivolumab was anaemia (2%) and with taxane monotherapy was decreased neutrophil count (28%). Nivolumab was associated with an almost twofold reduction in the incidence of grade 3 or 4 serious TRAEs compared to taxane monotherapy (10% versus 19%) (Kato 2019).

Qualitative review of treatment related adverse events

Regarding safety, the AEs that were commonly reported in ATTRACTION-3, were those that can be expected when being treated with nivolumab**.** No new safety signals were reported. **Nivolumab and chemotherapy have a distinct safety profile; nivolumab is mostly characterised by immune-related toxicity, while for instance haematological toxicity, neurotoxicity and alopecia are more characteristic of taxane-based chemotherapy**. Considering the frequency of AEs (any grade, grade 3-4) and SAEs (any grade, grade 3-4), nivolumab compares favourably to chemotherapy (EMA 2020). In further detail, patients treated with nivolumab had a numerically lower incidence of any-grade TRAE than patients treated with taxane monotherapy (66% versus 95%, respectively) (EMA 2020). The incidence of serious events was also lower in patients treated with nivolumab than with taxane monotherapy, as was the number of events leading to dose delay (Table 8) (Kato 2019, EMA 2020).

Table 8: Any-grade treatment-related adverse events

Event, n (%)	Nivolumab group, N=209	Chemotherapy group, N=208
All events	137 (65.6)	198 (95.2)
Serious events (alle grades)	33 (15.8)	47 (22.6)
Events leading to dose delay	(16.3)	104 (50.0)
Events leading to dose reduction[a]	-[a]	75 (36.1)
Events leading to discontinuation	18 (8.6)	19 (9.1)
Events leading to death[b]	2 (1)	3 (1.4)

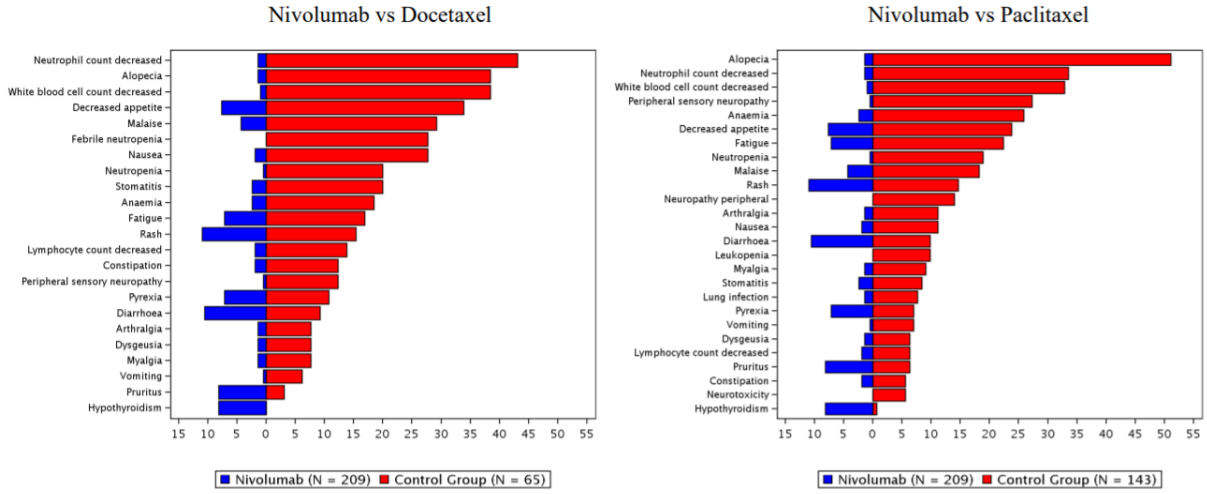
Source: (EMA 2020)
Notes: [a]Dose reductions were not permitted in the nivolumab group. [b] Two deaths in the nivolumab group were due to interstitial lung disease and pneumonitis; the three deaths in the chemotherapy group were due to pneumonia, spinal cord abscess, and interstitial lung disease. Some patients had adverse events lower than grade 5 that subsequently led to death.

During the ATTRACTION-3 study "Select TRAEs" (events with potential immunologic etiology, also referred to as immune-mediated AEs) were assessed during treatment and for up to 28 days after the last dose of study treatment or start of subsequent cancer therapy per NCI CTCAE (version 4.0). These types of potential immune-mediated AEs are already observed across studies of nivolumab monotherapy and can be related to the mode of action of nivolumab, i.e. endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, nephritis and rash. There were numerically more "Select TRAES" in the nivolumab treated group compared to the chemotherapy group, but the majority was low grade (1-2). Grade 3-4 occurred in ≤ 2% of patients.

The drug-related AE with a higher incidence in the nivolumab group than in the chemotherapy group (difference ≥5%) was hypothyroidism (8.1% [nivolumab] vs 0.5% [chemotherapy]). TRAEs with a lower incidence in the nivolumab group than in the chemotherapy group (difference ≥5%) were alopecia (1.4% vs. 47.1%), neutrophil count decreased (1.4% vs. 36.5%), white blood cell count decreased (1.0% vs. 34.6%), peripheral sensory neuropathy (0.5% vs. 22.6%), anaemia (2.4% vs. 23.6%), decreased appetite (7.7% vs. 26.9%), neutropenia (0.5% vs. 19.2%), malaise (4.3% vs. 21.6%), nausea (1.9% vs. 16.3%), fatigue (7.2% vs. 20.7%), febrile neutropenia (0% vs. 10.6%), neuropathy peripheral (0% vs. 10.6%), stomatitis (2.4% vs. 12.0%), arthralgia (1.4% vs. 10.1%), leukopenia (0% vs. 8.2%), myalgia (1.4% vs. 8.7%), lymphocyte count decreased (1.9% vs. 8.7%), vomiting (0.5% vs. 6.7%), constipation (1.9% vs. 7.7%), and dysgeusia (1.4% vs. 6.7%) (EMA 2020).

Plots showing the comparison of TRAEs (≥5% of any grade) between the nivolumab group and total chemotherapy group, and nivolumab vs. either the docetaxel or paclitaxel group are provided in Figure 2 (EMA 2020).

Figure 2: Treatment-related adverse events in ≥5% all treated with nivolumab or chemotherapy patients



Note: MedDRA Version: 21.1, CTC Version 4.0 Includes events reported between the start date of the first administration of the product and 28 days after the last dose or the start date of subsequence anti-cancer therapy after the last dose whichever comes first were tabulated. Drug-related AEs were defined as any AEs with causal relationship with the product is =Related or missing.
Source: Figure 5.3.1 (nivolumab vs docetaxel) and Figure 5.4.1 (nivolumab vs paclitaxel) in Appendix 2
Source: (EMA 2020)

No new safety signals were identified for nivolumab in this patient population and the nivolumab safety profile is consistent with that observed in other trials in ESCC and other solid tumors (Kato 2019).

As immune checkpoint inhibitors have settled in the oncology arena in Denmark and are prescribed in a wide variety of cancers, the number of patients experiencing immune related AEs have also increased. A standardized collaboration between patient, nurse and treating physician have ensured fast, proactive detection and proper management of most types of side effects well known from checkpoint inhibition therapy. The diversity of less frequent side effects have required the availability of a network of organ specialists. These structures have already been well established at the main oncology centers today.

Quality of life

The ATTRACTION-3 trial collected patient reported outcomes, where health-related quality of life (HRQoL) was assessed using the three level EQ-5D (EQ-5D-3L) utility index (UI) score and the EQ 100- point visual analog scale (EQ-VAS) tool. The trial did not collect data for EORTC-QOL-C30 or EORTC-QOL-OES18.

The EQ-5D-3L questionnaire was used to assess the overall state of health among participants of the ATTRACTION-3 trial, by asking them to rate their current health state. This was measured using the EQ-5D-3L and the EQ-VAS. The EQ-5D-3L system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems and extreme problems. A unique health state is defined by combining one level from each of the five dimensions. For the EQ-5D VAS, participants were asked to rate their current health giving a maximum score of 100 points for best imaginable health state. A score difference of 0.08 for the EQ-5D-3L utility score and of 7 for the EQ-5D VAS was used as minimally important difference estimates for the EQ-5D-3L (Pickard 2007).

Changes from baseline and differences between treatment groups in HRQoL were assessed post hoc using a longitudinal mixed model repeated measures (MMRM) approach. For time-to-event analyses, a stratified Cox regression model was used to estimate hazard ratios, and an un-stratified Kaplan-Meier method was used to estimate median times to event and the proportion of patients who were event-free. Significance testing was two-sided at the 0.05 level, with no adjustment for multiplicity. Comparisons between treatment groups were made at all on-treatment time points (through week 42) where there were at least 10 patients in each treatment group with a valid EQ-5D-3L assessment. Compliance rates were high, with >85% of expected assessments completed through week 42. The absolute number of completed EQ-5D-3L questionnaires in the chemotherapy group, however, decreased to 20 (10%) and 13 (6%) at week 36 and week 42, respectively. For EQ-5D-3L UI, the difference between treatment groups numerically favoured nivolumab at all time

points and for the overall time-averaged mean estimate (least squares means difference [LSMD]) in both EQ-5D-3L VAS of 6.9 (95% CI 3.0–10.9; p=0·00069) and EQ-5D-UI 0.076, (95% CI: 0.011–0·142; p=0·02). The estimated difference between treatment groups exceeded the threshold for meaningful change in EQ-5D-UI (≥0.08 points) (Pickard 2007) at week 24, 30, 36, and 42 (Kato 2019).

Patients treated with nivolumab had a decreased risk of deterioration in quality of life compared with patients treated with chemotherapy for the VAS (HR 0.65, 95% CI 0.49 – 0.86, p=0.0030; median time to deterioration 4.3 months, 95% CI 2.8 – 8.2 vs 2.7 months, 1.7 – 2.9) and the utility index (HR 0.73, 95% CI 0.55 – 0.97, p=0.032; median time to deterioration 4.2 months, 95% CI 2.8 – 7.0 vs 2.9 months, 1.8 – 3.1) (Kato 2019).

Progression free survival

Median progression free survival

Median progression free survival (PFS) was 1.68 months in the nivolumab group and 3.35 months in the chemotherapy group, with an HR of 1.08 (95% CI, 0.87 – 1.34) (Table 9) (EMA 2020)

Table 9: Progression free survival results from all randomised patients

	Nivolumab (N = 210)	**Taxane-based chemotherapy (N = 209)**
Median PFS, months (95% CI)[a]	1.68 (1.51, 2.73)	3.35 (2.99, 4.21)
Estimated relative difference in effect, hazard ratio (95% CI)[b]	1.08 (0.87–1.34)	

Abbreviation: CI, confidence interval; PFS, progression free survival.
Note: aThis estimation was conducted by using the KM method. b HR and the corresponding two-sided 95% CI for the nivolumab group relative to the each column group was calculated using the stratified Cox proportional-hazards model adjusted by the 3 stratification factors as mentioned in footnote 'c'. Nivolumab group and total of control group were used for the calculation of p-value. The calculation of p-value was conducted by using the two-sided stratified log-rank test adjusted by the following 3 factors (IWRS source): 1) location (Japan vs Rest of World) 2) the number of organs with metastases (≤ 1 vs ≥ 2) 3) PD-L1 expression (≥ 1% vs < 1% or indeterminate) *: p=0.05
Source: (EMA 2020)

Proportion of patients remaining progression free after 12 months

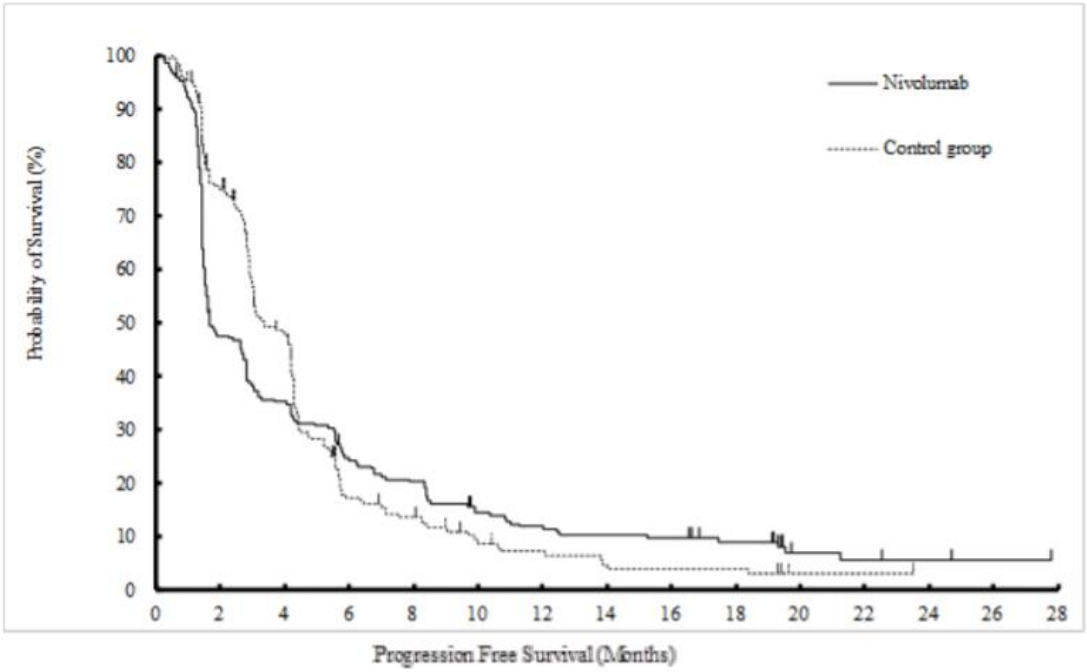
At 12 months, 12% of patients treated with nivolumab had not experienced disease progression, compared with 7% of patients treated with taxane monotherapy. There was no significant difference in PFS between the treatment arms (HR for progression or death, 1.08; 95% CI, 0.87–1.34) (Table 10 and Figure 3) (Kato 2019).

Table 10: Proportion of patients remaining progression free after 12 months

	Nivolumab (N = 210)	**Taxane-based chemotherapy (N = 209)**
Proportion of patients remaining progression free after 12 months, % (95% CI)[a]	12% (8–17)	7% (4–12)
Estimated relative difference in effect, hazard ratio (95% CI)[b]	1.08 (0.87–1.34)	

Abbreviation: CI, confidence interval.
Source: (Kato 2019)

Figure 3: Kaplan-Mayer plot of progression-free survival in ITT patient population



Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Nivolumab	210	96	71	48	40	27	22	19	18	13	5	4	3	1	0
Control group	209	147	89	29	22	12	9	5	5	5	1	1	0	0	0

Abbreviations: ITT, intent to treat.
Source: (EMA 2020)

5.1.2.1 3-year data from the ATTRACTION-3 trial

Overall, the updated OS results are consistent with those previously reported at the primary analysis and further elucidate the long-term benefit of nivolumab vs chemotherapy in patients with advanced ESCC. Nivolumab continued to show increased survival benefit over chemotherapy in patients with advanced ESCC. The **durable clinical response**, which has also been confirmed in other solids tumors treated with nivolumab, is demonstrated by >15% survival rate of nivolumab-treated patients after 3 years in contrast to just 8.7% being alive in the chemotherapy arm.

The upper boundary of the updated OS hazard ratio is still below 1. Updated OS for nivolumab versus chemotherapy was HR 0.79 (95% CI: 0.64, 0.97); descriptive p-value = 0.0264, which is similar to the OS HR previously reported at the primary analysis (HR = 0.77 [95% CI: 0.62, 0.96]; p = 0.0189).

Updated mOS was 10.9 months (95% CI: 9.2, 13.3) in the nivolumab group and 8.5 months (95% CI: 7.3, 9.9) in the chemotherapy group. Median OS in the chemotherapy group was numerically increased when compared with the mOS reported at the primary analysis: 8.38 months (95% CI: 7.29, 9.86) (Table 11).

Also, the updated PFS results are consistent with those previously reported at the primary analysis. Updated median PFS was 1.68 months (95% CI: 1.51, 2.73) in the nivolumab group and 3.4 months (95% CI: 3.0, 4.2) in the chemotherapy group, with the HR of 1.07 (95% CI: 0.87, 1.33) (Table 11).

The updated ORR for the response evaluable set (RES) remain unchanged from what was previously reported at the primary analysis: 19.3% [redacted] in the nivolumab group vs 21.5% [redacted] in the chemotherapy group (Chin 2021).

Table 11: Key Efficacy Results of ATTRACTION-3 based on the 25 May-2020 DBL

Efficacy Parameter, ITT Population	**Nivolumab** N=210	**Chemotherapy** N=209
Overall survival		
Median, months (95% CI)	10.9 (9.2, 13.3)	8.5 (7.3, 9.9)
HR (95% CI)[b]	0.79 (0.64, 0.97)	
p-value	p = 0.0264*	
Overall survival rate at 36-month (95% CI)	15.3 (10.7, 20.6)	8.7 (5.3, 13.2)
Progression free survival		
Median, months (95% CI)	1.7 (1.5, 2.7)	3.4 (3.0, 4.2)
HR (95% CI)	1.07 (0.87,1.33)	

Abbreviations: HR, hazard ratio; CI, confidence interval
Source. (Chin 2021)

Most patients experienced the first "Select TRAE" within three months of starting nivolumab. Incidence rates of the first select TRAEs were comparable between 6 – 9 months and 1 – 3 years. No new safety concerns were reported during the three-years of follow-up (Chin 2021) (Figure 4).

5.1.3 Comparative analyses of nivolumab and paclitaxel, docetaxel, or irinotecan

As the ATTRACTION-3 study presented the direct comparision of nivolumab with requested chemotherapy comparators—paclitaxel or docetaxel—no additional comparative analysis was required.

6 Other considerations

The Danish Medicines Council has requested data within three areas, *i:* Clinical benefit of nivolumab and PD-L1 expression and test method used for PD-L1 protein, *ii:* Clinical benefit across different patient populations (Asian and Caucasian); *iii:* data on alternative dosing regimens for nivolumab.

6.1 Effect of PD-L1 expression

6.1.1 Clinical data on ITT and on PD-L1 positive and lower expression levels in ATTRACTION-3

ATTRACTION-3 was designed to directly compare nivolumab versus chemotherapy in patients with unresectable advanced or recurrent ESCC, refractory or intolerant to one prior fluoropyrimidine/platinum-based chemotherapy. In a previous trial, ATTRACTION-1, clinical benefit (ORR measured per RECIST and disease control) occurred regardless of tumor PD-L1 expression in patients with unresectable advanced or recurrent ESCC. Therefore, there was no rationale to exclude patients with lower PD-L1 expression in ATTRACTION-3 and the study was conducted in an all-comers population. However, the numerically greater clinical benefit in terms of ORR in patients with tumor **PD-L1 expression** of ≥1% versus those with < 1% in ATTRACTION-1 (ORR, 23.8% vs 12.5%, respectively)(Hara 2016) led to tumor PD-L1 expression being selected as a relevant biomarker and **stratification factor** for the ATTRACTION-3 study.

In ATTRACTION-3, treatment with nivolumab was associated with significant improvement in OS and a favourable safety profile versus chemotherapy, in previously treated advanced ESCC patients. The HR for the risk of death favoured nivolumab over chemotherapy across tumor PD-L1 expression levels, at different cutoffs (1%, 5%, and 10%), meaning the survival benefit with nivolumab occurred regardless of patients' level of tumor PD-L1 expression (Kato 2019).

Mature OS data showed a statistically significant benefit for nivolumab over chemotherapy (HR, 0.77; p=0.0189; median OS 10.91 vs. 8.38 months). In a preplanned subgroup analysis, the HR for risk of death in ATTRACTION-3 for patients with tumor PD-L1 expression <1% was 0.84 (95% CI, 0.62-1.14) compared with 0.69 (95% CI, 0.51-0.94) for patients with tumor PD-L1 expression ≥1%.

Important to note, there is no statistically significant difference in the HRs for patients with PD-L1 expression ≥1% compared to <1%. This can be seen from the fact that the median value for HR for PD-L1 <1% (0.84) is covered by the 95% CI for PD-L1 ≥ 1% (0.51-0.94) and vice versa. This is also demonstrated by a statistical interaction test that finds no evidence of interaction between OS and PD-L1 expression (with a 1% cut-off), as shown by the p-value of 0.3763 (which is substantial higher than the predefined significance level for the interaction test p<0.15 or 15%).

6.1.2 Similar median OS regardless of PD-L1 expression in the nivolumab treated patients

In ATTRACTION-3, the median OS among patients in the nivolumab-arm with tumor PD-L1 ≥1% and <1% was 10.9 months vs. 10.9 months, respectively. Thus, it appears that the clinical benefit in terms of mOS is similar, regardless of PD-L1 expression level on tumor cells, while the chemotherapy arm was numerically different, i.e., median OS was 9.3 months (<1%) vs 8.1 (≥1%) months, respectively (Kato 2019) (see Table 12). This could be driven by the chemotherapy group curves with poorer outcome in patients with ≥1% PD-L1 expression. Overall PD-L1 seems to be a marker for response to chemotherapy but not an obvious selection marker for the clinical benefit for nivolumab.

The OS results of the subgroup analysis by PD-L1 expression is adequately included in section 5.1 of the Summary of Product caracteristics (EMA 2020).

Table 12: Overall survival in ATTRACTION-3, PD-L1 status

		Tumor PD-L1 < 1%	**Tumor PD-L1 ≥ 1%**
Median OS, month (95% CI)	Nivolumab	10.9 (8.4-13.9)	10.9 (8.0-14.2)
	Chemotherapy	9.3 (7.2-12.0)	8.1 (6.0-9.9)
HR for death (95% CI)		0.84 (0.62-1.14)	0.69 (0.51-0.94)

Abbreviations: HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1
Sources: (Kato 2019)

6.1.3 Method used to measure PD-L1 in ATTRACTION-3

As pre-specified in the ATTRACTION-3 protocol, tumor cell PD-L1 expression (≥1% versus <1%) at baseline was used as a stratification factor in this study. Thus, all randomised patients had a tumor sample at baseline tested for PD-L1 expression. Tumor cell PD-L1 expression was assessed on at least 100 viable tumor cells by a central laboratory using immunohistochemistry (PD-L1 IHC 28-8 pharmDx assay), using the platform DAKO Autostainer Link-48 system. Patients

tested positive for PD-L1, when tumor cells with stained cell membranes accounted for ≥1% of at least 100 viable tumor cells, and patients tested negative for PD-L1 when such cells accounted for <1%.

6.1.4 Generalisability of effects across Asian and Western populations.

The EMA has reviewed the totality of the data provided to support the results of the ATTRACTION-3 study and the clinical benefit in ESCC patients. EMA considered data generalisable and therefore it is expected that ESCC Western patients will also benefit from receiving nivolumab in the intended line of treatment albeit the magnitude of benefit in that particular group of patients has not been fully established. The majority of the ITT patient population in ATTRACTION-3 was Asian/from Asia and only a small minority (18/419 = 4.3%) was white/from non-Asian countries. The following section discusses the generalisability of clinical efficacy across Asian and Western populations in futher detail.

The implementation of early screening programs for gastric cancer in Japan and Korea may explain the larger proportion of patients diagnosed with early-stage disease in Asia compared to Western countries. However, at the initiation of 1L therapy for ESCC, no differences were observed in patients by tumor stage across regions (Asian vs Western countries: Stage III/IV - 88.5% vs 90.1%; Stage IV - 67.7% vs 71.2%) and at the initiation of 2L therapy, no statistically significant differences in ECOG PS were observed between Asian and Western patients (Shin 2018, EMA 2020).

Nivolumab exposure and clearance is similar across different ethnical origins of patients (as supported by pharmacokinetic analysis across various tumor types) (EMA 2020). Compared to small molecules there are fewer conventional concerns for ethnic differences in pharmacokinetic (PK) of monoclonal antibodies between different races. Based on the data provided it was agreed that PK is sufficiently comparable between Asian and non-Asian ESCC patients and thatnivolumab exposure following IV administration are similar in Asian and non-Asian, suggesting that no dose adjustment is needed based on race. (EMA 2020). Current evidence indicates that ESCC is molecularly distinct from EAC. Although the disease and molecular biology of ESCC is not yet fully understood, the similarities in various molecular aspects of ESCC between Asian and Caucasian patients suggest that they have similar underlying disease biology (EMA 2020).

Risk factors for ESCC are primarily tobacco smoking (including swallowed toxins from cigarette smoke) and alcohol overconsumption (Lagergren et al. 2017). Some risk factors such as betel quid chewing or consuming hot beverages appear to be region specific and differences in exposure to risk factors and/or different levels of exposure to risk factors may contribute to the observed regional differences in ESCC incidence (EMA 2020).

Regarding a possible effect of region on overall survival in ESCC patients, there is some data in scientific literature (EMA 2020).

- Zhang et al performed an observational comparison of clinicopathologic features and survival between Eastern and Western population with ESCC, i.e. between the (Chinese) Shanghai Cancer Registries (n = 1 718) and the US SEER database (n = 1,624). They concluded that ESCC from Eastern and Western countries might have some different features (Zhang 2015). They found that the Caucasian group had a significantly higher proportion of female patients than the Chinese group (38.24% vs. 18.68%; p <0.01). ESCC was diagnosed in Chinese patients at an earlier age and stage than in Caucasians. The Chinese patients had similar overall survival rate with Caucasian by both univariate and multivariate analysis. Median OS was 15.3 months for Chinese patients vs. 14.2 months in Caucasians (p=0.13). The difference in median OS was statistically significant for male patients (median OS 14.5 vs. 12.8 months; p <0.01), but not in female patients (median OS 18.5 vs. 16.9 months; p=0.14).
- Lin et al. used the Surveillance, Epidemiology, and End Results (SEER) database to compare the clinicopathologic characteristics and survival of 479 Chinese and 35 748 Caucasian patients with ESCC (both) residing in the US (Lin 2016). They found that, for patients with ESCC residing in the US, Chinese race was independently associated with a better OS compared to Caucasians (hazard ratio 1.330; 95% CI: 1.159, 1.527; p <0.001).
- KEYNOTE-181 is a phase 3 randomised open-label study evaluating pembrolizumab vs single agent of docetaxel, paclitaxel or irinotecan in patients with advanced/metastatic EAC, ESCC and Siewart type 1 adenocarcinoma of the esophagogastric junction. The three primary endpoints for this study were OS in ESCC, OS in PD-L1 CPS≥10 and OS in all patients. The KEYNOTE-181 included a larger percentage of non-Asian patients with ESCC compared to ATTRACTION-3, i.e. 170/401 = 42.4% vs. 18/419 = 4.3%. At final analysis, mOS was prolonged with pembrolizumab versus chemotherapy for patients with PD-L1 CPS ≥ 10 (9.3 v 6.7 months; [HR], 0.69 [95% CI, 0.52 to 0.93]; P 5 .0074). Subgroup analysis of KEYNOTE-181 trial suggests anti-PD-1 therapy is more effective in Asian patients with oesophageal squamous cell carcinoma than in non-Asian patients (comment to the published article for ATTRACTION-3 by Smyth (2019)).

Although the subgroup with 2L ESCC patients in the KEYNOTE-181 trial seems similar to the patient population included in ATTRACTION-3, inter-trial comparisons should not be made due to differences in study design (Kojima 2020). ATTRACTION-3 and KEYNOTE-181 are different trials using different designs, patient populations, drugs, dosing and schedules, and one cannot make direct comparisons or draw conclusions from one trial to another.

- Additional data with nivolumab in the EC patient segment have recently been presented during virtual ESMO 2020 (Kelly 2020). Nivolumab is being investigated in an ongoing, global phase 3, randomised, double blinded, placebo-controlled study (**CA209-577 (NCT02743494**)) evaluating adjuvant nivolumab in stage II/III EC and GEJC patients that have completed neoadjuvant chemotherapy and radiotherapy, followed by complete surgical resection (R0) and have residual pathologic disease. Preliminary data demonstrated a similar disease-free survival (DFS) benefit regardless of race (EMA 2020). The study included a larger percentage of non-Asian patients compared to ATTRACTION-3 (648/117 = 85%) and indicate proof of concept for efficacy of nivolumab in Western patients with ESCC (EMA 2020).

In ATTRACTION-3, demographics, and baseline characteristics of the 18 patients of western origin were comparable to those in the ITT population with respect to Key Baseline Factors (i.e. ECOG PS, prior and subsequent of therapies). An exploratory analysis also indicated a hazard ratio (HR) of 0.53 (95% CI: 0.17, 1.65) and mOS of 6.21 months (95% CI: 1.41, 20.14) in the nivolumab group compared to 6.11 months (95% CI: 2.60, 13.24) in the chemotherapy group. (EMA 2020)

[redacted]

It has been noted by EMA that even if there is somewhat limited information on intrinsic and extrinsic factors, the available data do not indicate that there are important differences between regions (Asian vs Western) that would hamper generalisation. Overall it has been the conclusion by EMA, based on the totality of data, it is expected that Western patients with ESCC will also benefit from 2L nivolumab, albeit the magnitude of benefit in Western patients has not been fully established. EMA has therefore approved nivolumab across races for 2L ESCC (EMA 2020).

Regarding safety, the AEs that were commonly reported in ATTRACTION-3 were those that can be expected when-treating with nivolumab and no new safety signals were reported. The safety profile in white/non-Asian patients with ESCC is limited by the small sample size in the ATTRACTION-3 study and the safety profile is predominantly based on a selected population of Asian patients. However, the safety profile of nivolumab has been well characterized in white patients/non-Asian based on previous experience, and it is not expected that safety in white patients with ESCC will be considerably different (EMA 2020, EMA 2020).

6.2 Effect based on weight-based dosing vs flat dosing

6.2.1 Data on weight-based dosing of nivolumab

A **weight-based dosing** regimen of nivolumab has been tested in a smaller but similar patient population in **ATTRACTION-1**; a phase 2, open-label, multicentre, uncontrolled study conducted in Japanese patients with esophageal cancer. Patients included were refractory or intolerant to fluoropyrimidine-, platinum-based, and taxane-based chemotherapy. In total 65 patients were treated with nivolumab 3 mg/kg Q2W (Kudo 2017).

The primary endpoint, ORR, was 17% (11 out of 64) in evaluable patients (centrally assessed). Furthermore, the median overall survival with nivolumab was 10.8 months (95% CI 7.4–13.39) and is comparable to the mOS for nivolumab-treated patients in the ATTRACTION-3 study (median OS 10.91). The 5-year follow-up data from the ATTRACTION-1 study were recently presented during virtual ASCO-GI-2021, with a mOS 10.8 months, a 1 year landmark OS of 45.3%; and 36 months OS rate of 10.9% (Kato 2021) (see Figure 5).

6.2.2 Safety ATTRACTION-1 and ATTRACTION-3

The number of adverse events in the ATTRACTION-1 study group treated with 3 mg/kg nivolumab Q2W (n=65) was in range with ATTRACTION-3. There were 55% grade 1-2, 14% grade 3, and 3% grade 4 TRAEs in ATTRACTION-1(Kudo 2017) (n=65), which is similar to the number of TRAEs in ATTRACTION-3; grade 1-2: 47%, grade 3: 16% and grade 4: 2%.

6.3 Effect based on dosing Q2W vs Q4W

6.3.1 Data on alternative dosing regimens in upper gastrointestinal cancers

Nivolumab is also being investigated in an ongoing phase 3 study (Checkmate 577, NCT02743494), evaluating patients (n=793) with either adenocarcinoma or squamous carcinoma, stage II/III EC and GEJC and that have completed preoperative chemo-radiotherapy (CRT) followed by complete surgical resection and have residual pathologic disease (CA209-577/ NCT02743494). The primary endpoint is Disease Free Survival (DFS) and secondary endpoint OS, and OS rate year 1, 2, 3. The Checkmate 577 study was presented at ESMO 2020 (Kelly 2020). In the Checkmate 577 study, nivolumab is dosed as monotherapy 240mg or placebo Q2W for 16 weeks, followed by nivolumab 480 mg Q4W or placebo for a total treatment duration of up to 12 months.

Nivolumab 240mg Q2W was chosen based on available PK, safety, and efficacy data. Population pharmacokinetics (PPK) analyses have shown that the simulated average serum concentration at steady state following administration of nivolumab 240mg Q2W is similar to those following nivolumab 3 mg/kg Q2W across tumor types. Based on flat exposure-response relationships across indications, the benefit-risk profile of nivolumab 240 mg Q2W is likely to be similar to 3 mg/kg Q2W (Zhao 2016, Zhao 2017).

In the CheckMate 577 study after 16 weeks of nivolumab 240mg Q2W, patients were switched to nivolumab 480mg Q4W with the intention to provide a more flexible dosing regimen for patients. PPK analyses have shown that the simulated average serum concentration at steady state following administration of nivolumab 480mg Q4W is predicted to be similar to those following nivolumab 240mg Q2W and nivolumab 3 mg/kg Q2W across tumor types. Exposure-response analyses have indicated that the efficacy of flat dose 480mg regimen is similar to that of the flat-dose 240mg Q2W regimen. Exposure response safety analyses demonstrated that the exposure margins for safety were maintained (Long 2018, Zhao 2020).

Table 13 below gives an overview, for purely descriptive purposes, of the safety profile of nivolumab in metastatic and adjuvant settings. Please note the safety profile across the adjuvant and metastatic clinical trials cannot be compared

due to the differences in disease stage, patient populations, dosing regimens, and drug exposure, e.g., patients in the metastatic esophageal setting have a more advanced disease and greater degree of comorbidities.

Table 13: Safety profile of nivolumab in metastatic and adjuvant disease

	CheckMate 577				**ATTRACTION-3**					
Phase	3				3					
Patient population	Stage II/II Esophageal/Gastroesophageal Junction Cancer				2L ESCC					
Median follow-up	24.4 months (range, 6.2–44.9)				Nivolumab: 10.5 months (IQR, 4.5–19.0) Chemotherapy: 8.0 months (IQR, 4.6–15.2)					
Treatment flow	CRT + surgery, then nivolumab		CRT + surgery, then placebo		Nivolumab			Chemotherapy		
%	Any grade	Grade 3–4	Any grade	Grade 3–4	Grade 1—2	Grade 3	Grade 4	Grade 1—2	Grade 3	Grade 4
Any TRAEs	71	13	46	6	47	16	2	31	41	22
Serious TRAE	8	5	3	1	6	8	2	3	15	4
TRAE leading to discontinuation	9	5	3	3	5	4	0	3	4	1

Abbreviations: CRT, chemo radiotherapy; TRAE, treatment-related adverse events.
Source: (Kato 2019, Kelly 2020)

Please note the use of nivolumab as adjuvant therapy for the treatment of EC/GEJC is considered investigational and BMS cannot recommend the use outside approved EMA label.

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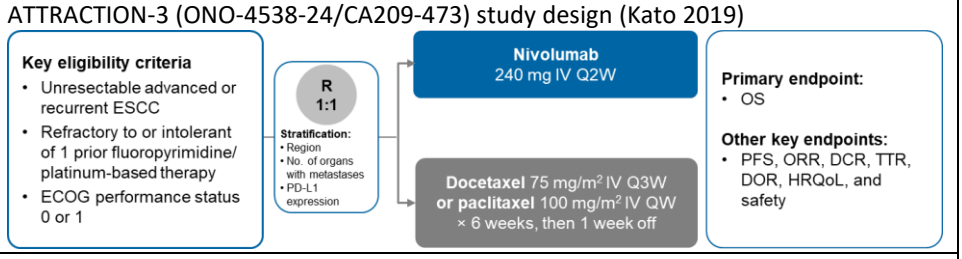
8 Appendices

8.1 Main characteristics of included studies

Table 14: ATTRACTION-3 study - Main study characteristics

Trial name	ATTRACTION-3, ONO-4538-24/CA209-473
NCT number	NCT02569242
Objective	To compare overall survival between the nivolumab group and control group (docetaxel or paclitaxel) in patients with esophageal cancer refractory or intolerant to combination therapy with fluoropyrimidine and platinum-based drugs
Publications – title, author, journal, year	Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial (Kato 2019)
Study type and design	Multicenter, randomised, open label, phase III trial. Patients were randomly assigned, in a 1:1 ratio to either nivolumab or investigator's choice of chemotherapy (paclitaxel or docetaxel). Randomisation was done using an interactive web response system with a block size of four and stratified according to geographical region (Japan vs the rest of the world), number of organs with metastases (≤1 vs ≥2), and expression of PD-L1 (<1% vs ≥1%). Investigators registered patients at each site via the web registration system. An authorized vendor used their original internal system to generate the sequentially numbered containers to ensure random allocation, and to assign patients to study treatments. The web registration system ensured that the container sequence was concealed until the treatment allocation was completed. Patients and investigators were not masked to treatment allocation ATTRACTION-3 (ONO-4538-24/CA209-473) study design (Kato 2019) 
Follow-up time	Minimum follow-up (*i.e,* time from random assignment of the last patient to data cutoff) was 17.6 at database cut-off Nov 12, 2018 (Kato 2019)
Population (inclusion and exclusion criteria)	Below are listed the main inclusion and exclusions criteria of the ATTRACTION-3 study. The full list of the study criteria isavailable in the ATTRACTION-3 study protocol in section 7 of the supplement (provided with the preliminary application and available here on the Lancet Oncol website). **Inclusion Criteria:** • Men & women ≥20 years of age

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Histologically confirmed unresectable advanced or recurrent esophageal cancer
Refractory to or intolerant of 1 prior fluoropyrimidine/ platinum-based therapy ECOG Performance Status score 0 or 1
A life expectancy of at least 3 months

Exclusion Criteria:

Patients with apparent tumor invasion on organs located adjacent to the esophageal disease (e.g, the aorta or respiratory tract)
Current or past history of severe hypersensitivity to any other antibody products
Patients with multiple primary cancers
Patients with any metastasis in the brain or meninx that is symptomatic or requires treatment
Patients with active, known or suspected autoimmune disease

</td></tr>
<tr><td>Intervention</td><td>Nivolumab 240 mg IV Q2W with treatment until documented disease progression, discontinuation due to toxicity, withdrawal of consent, or study end.
Patients were permitted to continue treatment beyond initial disease progression based on the investigators' judgement.

Comparator
Investigator's choice of chemotherapy (Docetaxel 75 mg/m^2 IV Q3W or paclitaxel 100 mg/m^2 IV QW × 6 weeks, then 1 week off) with treatment until documented disease progression, discontinuation due to toxicity, withdrawal of consent, or study end. Patients were permitted to continue treatment beyond initial disease progression based on the investigators' judgement.</td></tr>
<tr><td>Baseline characteristics</td><td>Baseline characteristics of the intent-to-treat population
<table>
<tr><th>Characteristic</th><th>Nivolumab, N=210</th><th>Taxane monotherapy, N=209[a]</th></tr>
<tr><td>Median age, years</td><td>64</td><td>67</td></tr>
<tr><td>Male, %</td><td>85</td><td>89</td></tr>
<tr><td>Race, %</td><td></td><td></td></tr>
<tr><td>Asian</td><td>96</td><td>96</td></tr>
<tr><td>White</td><td>4</td><td>4</td></tr>
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<tr><td>1</td><td>52</td><td>49</td></tr>
<tr><td>Recurrent disease, %</td><td></td><td></td></tr>
<tr><td>No</td><td>51</td><td>57</td></tr>
<tr><td>Yes</td><td>49</td><td>43</td></tr>
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<tr><td>Radiotherapy</td><td>73</td><td>68</td></tr>
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<tr><td>Number of organs with metastases, %</td><td></td><td></td></tr>
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	≤1	42	44
	≥2	58	56
	Site of metastases, %		
	Lymph node	76	78
	Liver	27	26
	Lung	47	44
	Bone	11	12
	PD-L1 expression, %		
	<1%	52	51
	≥1%	48	49
	History of smoking, %		
	Never	14	15
	Former	76	70
	Current	10	14

aIncluded 65 patients treated with docetaxel and 144 patients treated with paclitaxel. bSummarized at randomization for patients with non-recurrent esophageal cancer (nivolumab [n=107] and chemotherapy [n=120]). cPer interactive web response system.
ECOG, Eastern Cooperative Oncology Group; TNM, tumor, node, and metastases; PD-L1, programmed death ligand 1.
Source: (Kato 2019)

Primary and secondary end-points

Primary endpoint

- Overall survival

The analysis was based on the intention-to-treat population (ITT).

Secondary endpoints

- Investigator-assessed objective response rate (ORR)
- Best overall response (BOR)
- Progression-free survival (PFS)
- Proportion of patients with disease control, defined as the percentage of patients whose BOR was assessed as a complete response, partial response, or stable disease
- Maximum percentage change from baseline in the sum of the diameters of target lesions
- Time to response, defined as the time from randomization to the first confirmed complete or partial response.
- Duration of response (DoR), defined as the time from the first response date to the date of the first documented tumor progression or death.

Tumors were assessed using CT or MRI per RECIST version 1.1 at baseline, every 6 weeks from the start of cycle 1 for 1 year, and every 12 weeks thereafter, until either initiation of post-study treatment or progression or recurrence during follow-up. Complete and partial responses were confirmed by two or more successive scans within a minimum of 4 weeks

Exploratory endpoints

- Health-related quality of life (HRQoL).
  Assessed based on the three-level version of the EuroQol 5D questionnaire (EQ-5D), comprising the visual analogue scale (VAS) and 3 Level descriptive system, which is used to generate the utility index. Assessments were done every 6 weeks from the start of cycle 1 until the end of the treatment phase and every 12 weeks during the follow-up phase.

Method of analysis	The stratified Cox proportional hazards regression model with randomisation factors as stratification factors and treatment group as single covariate was used to assess differences between treatment groups in OS and PFS; a 5% significance level was used to determine superiority of nivolumab over chemotherapy. When superiority in OS was determined, a hierarchical hypothesis testing approach for the key secondary endpoints was used to preserve a study-wise type I error rate at 5%. The key secondary endpoints were tested in the following hierarchical order: ORR, PFS (Kato 2019).
Subgroup analyses	**Prespecified, exploratory subgroup analyses** The following were conducted to assess the association between overall survival and stratification factors or baseline variables: • PD-L1 expression (<1%, ≥1%, <5%, ≥5%, <10%, and ≥10%) • Age (<65 years vs ≥65 years) • Gender (male vs female) • Race (Asian vs white) • ECOG performance status (0 vs 1) • Previous surgery (no vs yes) • Previous radiotherapy (no vs yes) • History of smoking (never, former, or current)

Abbreviations: BOR, best overall response; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EQ-5D, EuroQol 5D questionnaire; ESCC, oesophageal squamous cell cancer; HRQoL, health-related quality of life; ORR, overall response rate; ITT, intent to treat; OS, overall survival; PD-L, Programmed death-ligand; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; Q#W, every # weeks; TNM, tumor, node, and metastases; TTR, time to response; VAS, visual analogue scale

Source: (Kato 2019) and clinicaltrails.org

8.2 Results per study

Table 15: The study – Results

Trial name:	ATTRACTION-3									
NCT number:	NCT02569242									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95%CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Overall Survival (medium)	Nivolumab	210	10.9 months (9.2–13.3)	2.5 months			HR: 0.77	0.62–0.96	0.019	Kaplan-Meier methods, and the corresponding two-sided 95% CIs were calculated using the Brookmeyer and Crowley method based on a log-log transformation. The stratified Cox proportional hazards regression modelwith the randomisation factors as the stratification factors and treatment group as a single covariate was used to assess differences between treatment groups.	(Kato 2019)
	chemotherapy	209	8.4 months (7.2–9.9)								
Overall survival (Proportion alive after 12 months)	Nivolumab	210	47% (40 – 54)	13%			HR: 0.77	0.62–0.96	0.019	Kaplan-Meier method with corresponding two-sided 95% CIs calculated based on the Greenwood formula for variance derivation based on log-log transformation. Used a two-sided stratified log-rank test using randomisation stratification factors with a 5% significance level.	(Kato 2019)
	chemotherapy	209	34% (28 – 41)								
Treatment related adverse events (Grade 3 or 4)	Nivolumab	209	38 (18.2%)	-44.8%	-49.6% - -38.3%		RR: 0.29	0.21 – 0.39		Population: Patients who received at least one dose of the assigned treatment	
	chemotherapy	208	131 (63%)								

EQ-5D-3L UI LS mean	Nivolumab chemotherapy			0.076	0.11 – 0.142	0.023		Measured outcomes were mean change from baseline using both descriptive analyses and a mixed model for repeated measures (MMRM) to compare between-treatment differences in least square mean changes from baseline. Changes from baseline of seven points and 0.08 points for the VAS and utility index, respectively, were considered clinically meaningful, and were used as the threshold for determining deterioration	(Kato 2019)
EQ-5D-3L VAS (LS mean)	Nivolumab chemotherapy			6.9	3.0 – 10.9	0.00069			(Kato 2019)
PFS (median)	Nivolumab chemotherapy	210 209	1.68 months (1.51, 2.73) 3.35 months (2.99, 4.21)	-1.67 months			HR: 1.08	0.87–1.34	Kaplan-Meier methods, and the corresponding two-sided 95% CIs were calculated using the Brookmeyer and Crowley method based on a log-log transformation. The stratified Cox proportional hazards regression model with the randomisation factors as the stratification factors and treatment group as a single covariate was used to assess differences between treatment groups.	(EMA 2020)
PFS (Proportion remaining progression free after 12 months)	Nivolumab chemotherapy	210 209	12% (8–17) 7% (4–12)	5%			HR: 1.08	0.87–1.34	Kaplan-Meier method with corresponding two-sided 95% CIs calculated based on the Greenwood formula for variance derivation based on log-log transformation. Used a two-sided stratified	(Kato 2019)

			log-rank test using randomisation stratification factors with a 5% significance level.	

Abbreviations: EQ-5D, EuroQol 5D questionnaire; PFS, progression-free survival; VAS, visual analogue scale

Cost analysis and budget impact analysis of nivolumab (Opdivo®) for the 2L treatment of adults with esophageal squamous cell carcinoma refractory to or intolerant to first-line chemotherapies

Questions around this document may be posed to:

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Table of contents

1. Executive summary

Nivolumab is a new 2L treatment alternative for adults with esophageal squamous cell carcinoma (ESCC) refractory to or intolerant of first-line chemotherapies.

To evaluate the cost of introducing nivolumab in Denmark for the treatment patients with unresectable advanced, recurrent or metastatic ESCC a joint cost-effectiveness and budget impact model has been developed. The main comparator in the model is physician's choice of taxane-based chemotherapy, as was the case in the ATTRACTION-3 trial where Danish patients participated. The model assumptions and input has been validated by a Danish clinical expert.

The results of the cost analysis show an increase of 254 026 DKK per patient over a 10-year time horizon (and an incremental cost-effectiveness ratio of 950 442 DKK per QALY gained).

If nivolumab is introduced 66.6% of these patients are assumed to be treated with nivolumab. If nivolumab is not introduced all patients are assumed to be treated with taxane-based chemotherapy.

The total annual budget impact of the drug costs related to nivolumab is about 5 037 578 DKK in year 5.

2. Background

Esophageal cancer is a malignant disease that originates from the tissues of the esophagus. It is the sixth leading cause of cancer death in the world (Adenis 2019), and a complex disease which differ by histological type and the population it is found in (Adenis 2019). There are two major histological types of esophageal cancer, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), which differ greatly in terms of physiology, epidemiology, and risk factors (Adenis 2019).

Prognosis of esophageal cancer is strongly correlated to stage of disease, co-morbidities and performance status. More than 40% of patients are stage IV at time of diagnosis (Kato 2019). The majority receives palliative therapy (Brahmer 2010). Around 31% of patients treated with palliative systemic care are alive at 1-year follow-up (Menzies 2013).

In advanced/metastatic ESCC, the value of palliative chemotherapy is less proven and fewer treatment options exist for ESCC compared with EAC. A large percentage of patients with ESCC (>40%) remain untreated in the second line setting and among the proportion of patients eligible for treatment, nearly half (45%) receive taxanes (Jaffe 2019).

Survival outcomes are poor with a median OS of around six months in the real-world setting (Shirakawa 2014, BMS DOF 2019, Danese 2019). Patients treated in the second line setting either progress quickly or discontinue treatment due to adverse events (Kato 2011, Shirakawa 2014).

Nivolumab as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based combination chemotherapy (BMS Data on File 2020b).

The safety and efficacy of nivolumab 240 mg monotherapy for the treatment of unresectable advanced, recurrent or metastatic ESCC, regardless of tumor PD-L1 expression level, was evaluated in the phase 3 randomized active-controlled, open-label study ATTRACTION-3 (also referred to as ONO-4538-24/CA209473). The study included 419 adult patients that were refractory or intolerant to at least one fluoropyrimidine- and platinum-based combination regimen (Kato 2019, EPAR 2020).

Nivolumab demonstrated a statistically significant improvement in overall survival (OS) compared with investigator's choice of taxane chemotherapy (docetaxel or paclitaxel) at a minimum follow-up of 17.6 months. The median OS for patients treated with nivolumab was 10.9 months (95% CI, 9.2–13.3) compared with 8.4 months for patients treated with taxanes (95% CI, 7.2–9.9) corresponding to a hazard ratio (HR) of 0.77 (95% CI, 0.62–0.96; P=0.019) (EPAR 2020).

Based on figures from the DECV (Dansk DECV Cancer Gruppe) there were about 1150 new cases of gastroesophageal junction (GEJ), gastric and esophageal cancer registered in Denmark from Jan-Dec 2018 and around 300 of those were ESCC (Dansk DECV Cancer Gruppe Årsrapport 2018) .

Based on clinical expert advice (Holtved 2020) It is estimated that on a yearly basis 130 esophageal cancer patients will be referred to systemic palliative therapy in Denmark, but only 60% corresponding to ~80 pts will receive first-line systemic therapy. About 25-50% of 1L treated patients will be eligible for second-line systemic chemotherapy, corresponding to 20-40 patients.

2.1 Modelling approach

To evaluate the cost of introducing nivolumab in Denmark for the treatment of patients with unresectable advanced, recurrent or metastatic ESCC a joint cost-effectiveness and budget impact model has been

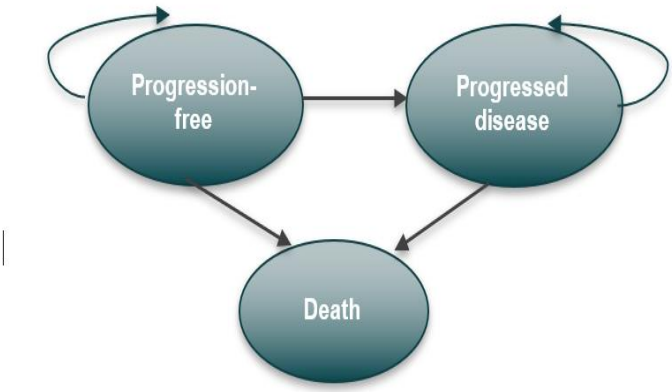
developed. The main comparator in the model is physician's choice of taxane-based chemotherapy, as was the case in the ATTRACTION-3 trial where Danish patients participated.

Figure 1 provides an overview of the model structure, a three-health state cohort-based partitioned survival model (PSM). This structure is consistent with approaches adopted in previous published economic evaluations and technology appraisals.

The health state occupancy in the health states, progression-free (PF), progressed disease (PD) and death, are determined by the primary and secondary endpoints of the ATTRACTION-3 trial, i.e., overall survival (OS) and progression-free survival (PFS), respectively. The cycle length is 1 week.

The model was developed in Microsoft Excel® and programmed using standard Excel functions wherever possible. Visual basic programming was mainly limited to the running of Monte-Carlo simulations in the probabilistic sensitivity analysis (PSA) and for generating survival estimates.

*Figure 1: Health state structure for the economic model**



*Health state transitions are not explicitly modelled in the partitioned survival analysis; the direction of transition in the model is provided as an illustration

The cost analysis is based on the structure above and estimates the total cost per patient based on the time spent in the PF and PD states, and costs assigned to those states where resource usage related to patient management has been estimated by a Danish clinical expert (Holtved 2020).

The analyses have been carried out using a restricted societal perspective as suggested in the DMC guidelines (Medicinrådet 2020c). The following cost-items are included:

- Drug acquisition costs
- Drug administration costs
- Patient costs
- Monitoring costs
- Disease management costs
- Subsequent treatment costs
- Adverse event costs
- One-off terminal care costs

The cost of treatment acquisition is based on observed duration of therapy (DoT) in the ATTRACTION-3 trial. The data regarding DoT is not available in the public domain, and therefore, more details on the extrapolation of DoT can be found in the model sheets "DoT" and "survival results", and not in the report.

The cost analysis results (section 3) are presented for a ten-year time horizon, with 3.5% yearly discounting of costs. The budget impact results (also section 3) are presented over a five-year time horizon without any discounting.

The budget impact analysis assumes that the costs incurred by the patients are carried over to later years. In consequence the costs that occur after the year when the patient initiated the treatment are accounted for in the following year.

A technical description of the cost analysis is presented in Table 1 below.

Table 1: Technical description of the cost analysis

Aspect	Details
Analytical method	Cohort-based partitioned survival model
Software used	Microsoft Excel 2010 (with limited visual basic for application)
Time horizon	10 years
Cycle length	1 week
Discounting options	Costs and health outcomes
Treatments	Nivolumab: 3 mg/kg, administered as an IV infusion Q2W until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression Taxane-based chemotherapy arm:
Population	ITT
Half-cycle correction	Yes
Clinical efficacy and safety	ATTRACTION-3 trial
Costs	Unit costs related to each healthcare resources are sourced from Sundhedsdatastyrelsen (2020). Resource consumption is estimated by Danish physician (physician interview Dec 4, 2020).
Utilities	Calculated from the EQ-5D data collected in ATTRACTION-3 trial

Abbreviations: DRG: Diagnosis-related group; ITT: Intention-to-treat; PD: Progressed disease; PD-L1: Programmed cell death ligand 1; PF: Progression-free; PSM: Partitioned survival model

2.2 Patient population

The patient population in this analysis is based on the intention to treat (ITT) population in the ATTRACTION-3 clinical trial, i.e. patients with advanced, unresectable or recurrent ESCC who are refractory or intolerant to combination therapy with fluoropyrimidine and platinum-based drugs.

In the ATTRACTION-3 trial most of the patients were of Asian origin. After consultation with Danish clinical expert , the mean age was kept as it was considered close to what could be expected in clinical practice, the proportion of female patients was adjusted to 40%, and the mean body weight was increased to 60.2kg, assuming the average weight would be higher than in the trial but lower than for the general population. The average body surface area 1.71 m^2 was calculated using the DuBois method. Table 2 outlines the baseline characteristics of the trial and the base case settings in the model.

Table 2: Patient population in the ATTRACTION-3 clinical trial versus the model

Patient population	ATTRACTION-3	Used in model
Mean age	63.9 years	63.9 years
Mean body surface area	1.60 m2	1.71 m^2
Mean weight	55.2 kg	60.2 kg
Proportion of females	13.2%	40%

Abbreviations: kg: kilogram

2.3 Market shares

In the scenario where nivolumab is not reimbursed, it is assumed that all eligible patients, 30 patients, will receive taxanes (Holtved 2020).

In the scenario where nivolumab is reimbursed, 66.6 % of the patients, 20 patients, are assumed to receive nivolumab and the remaining 33.4 %, 10 patients, taxanes (Holtved 2020).

Assuming a gradual uptake in the first calendar year (corresponding to a Q2 recommendation) only 12 patients (40 %) are assumed to be treated with nivolumab the first calendar year. The patient number estimates are shown on the 'Settings' sheet of the Excel model and in Table 3 below.

Table 3: Estimated market shares and patients depending on whether nivolumab is reimbursed or not

	If nivolumab is reimbursed		If nivolumab is not reimbursed	
	nivolumab	taxanes	nivolumab	taxanes
Year 1	40 %, 12 patients	60 %, 18 patients	0 %, 0 patients	100 %, 30 patients
Year 2	66.7 %, 20 patients	33.3 %, 10 patients	0 %, 0 patients	100 %, 30 patients
Year 3	66.7 %, 20 patients	33.3 %, 10 patients	0 %, 0 patients	100 %, 30 patients
Year 4	66.7%, 20 patients	33.3 %, 10 patients	0 %, 0 patients	100 %, 30 patients
Year 5	66.7 %, 20 patients	33.3%, 10 patients	0 %, 0 patients	100 %, 30 patients

Source: BMS Data on file

2.4 Efficacy inputs

As mentioned previously, PFS and OS outcomes from the ATTRACTION-3 trial are used to estimate time spent in the PF and PD states of the model.

This patient population has a poor prognosis which is also reflected in the ATTRACTION-3 trial. Most patients had already died at the minimum follow-up of 17.6 months (see page 72 in the EPAR).

The survival (OS and PFS) of the proportion of patients that were still event-free at the end of the trial was extrapolated over the model 10-year time horizon. The process for fitting parametric survival curves to patient-level data from ATTRACTION-3 was based on methods guidance from the Danish Medicines Council and the Decision Support Unit (DSU) at the National Institute for Health and Care Excellence (NICE) (Latimer 2011, Medicinrådet 2020c). Due to the poor prognosis of patients, and consequently the maturity of the trial data, the different parametric curves explored yielded very similar landmark OS estimates at 10 years. More details on the extrapolation of PFS, OS, and duration of therapy can be found in Appendix I.

Health-related quality of life (HRQoL) data collected in the ATTRACTION-3 trial (EQ-5D-3L) was used to inform the utility values for the PF and PD states. The UK value set was applied to the EQ-5D-3L responses as this is a submission belonging to the methods applicable before 01 January 2021. More details can be found in Appendix II.

A summary of the 36-month data cut, published at ASCO is available in Appendix III.

2.5 Resource use and costs

Drug costs are based on the pharmacy purchase prices (PPP), i.e., excluding value added taxes, derived from Lægemiddelstyrelsen's online price lists (Medicinpriser.dk 2021). The costs do not include any negotiated discounts.

2.5.1 Drug acquisition costs

Patients in the nivolumab arm of ATTRACTION-3 received 240 mg nivolumab every 2 weeks. In the taxane control arm 31% of the patients received docetaxel and 69% paclitaxel. [redacted]

The details on the extrapolation of DoT can be found in Appendix I.

In the base case, the ATTRACTION-3 mean dose intensity was adopted for the nivolumab and taxane-based chemotherapy arms and it was assumed that vial sharing occurred. Vial combinations with the minimum total cost per dose for docetaxel and paclitaxel were used in the base case.

Table 4 lists treatment dosing and acquisition costs for nivolumab and comparators in the base case of the model based on the ATTRACTION-3 trial.

In a scenario analysis weight based dosing for nivolumab, off-label dosing of 3 mg/kg every 2 weeks, was also explored at the same time assuming vial sharing (see section 3.1).

Table 4: Drug acquisition costs used in the base case model (vial sharing)

Treatment	Dose	Target dose	Frequency	Strength per vial	Size per pack	Unit cost per pack (DKK)	Dose intensity	Cost per dose (DKK)†	Cost per week (DKK)†
Nivolumab	240 mg	240 mg	Every 2 weeks	10 mg/ml	10 ml	9 403.31	95%	21 534.33	10 767.17
					4 ml	3 785.32	95%		
Docetaxel	75 mg/m^2	120.2 mg	Every 3 weeks	20 mg/ml	4 ml	150.00	85%	203.56	67.85
					1 ml	71.00	85%		
Paclitaxel	100 mg/m^2	160.3 mg	Weekly*	6 mg/ml	50 ml	201.50	78%	146.88	146.88
					17 ml	110.50	78%		

Abbreviations: DKK, Danish kroner
*Paclitaxel was assumed to be given every week for 6 weeks, and then 1-week holiday, as per ATTRACTION-3
† Weighted by dose intensity, and assuming vial sharing using the package with lowest cost per mg
Source: (Medicinpriser.dk 2021)

2.5.2 Administration costs

The same administration cost, 5 297 DKK per infusion event, is assumed for both intravenous infusion treatments, nivolumab and taxane-based chemotherapy, see Table 5, below. The cost has been sourced from Sundhedsdatastyrelsen (DRG code 06MA11 (BWAA60), 2021). Please note that in the model the patient costs associated with receiving treatment (see section 2.5.7 on patient costs below)

have been added directly to the unit cost for drug administration (model sheet "Tx_related costs" cells G65 and H65).

Table 5: Administration cost per included treatment

Resource	Unit cost (DKK)	Reference for cost
Infusion	5 297 DKK	Sundhedsdatastyrelsen (2021). Interactive DRG: 06MA11 (BWAA60) Medicingivning ved intravenøs injektion, (DK229) Sygdom i øsofagus UNS. Available at: http://interaktivdrg.sundhedsdata.dk/

Abbreviations: HCPCS: Healthcare Common Procedure Coding System; DKK: Danish kroner

2.5.3 Monitoring costs

The unit costs and estimated resource use frequencies associated with monitoring for nivolumab and taxanes are summarized in Table 6.

The monitoring frequencies for nivolumab, docetaxel and paclitaxel have been estimated by a Danish physician and the estimates for the combined taxane-based chemotherapy arm has been calculated based on proportion of patients on each taxane in the comparator arm in the ATTRACTION-3 trial.

Table 6: Monitoring costs associated with nivolumab, taxane-based chemotherapy, docetaxel and paclitaxel

Resource item	Nivolumab (per week)	Taxane-based chemotherapy (per week)	Unit cost (DKK)	Reference for costs
Outpatient visit	0.25	0.33	1 462	Kommunernes og Regionernes Løndatakontor 2021, Specialeansvarlige overlæger (Overlæger, lægelige chefer m.v.). bruttolön NOV 2020 (103696DKK). available from: https://krl.dk/#/sirka Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.
CT scan	0.125	0.125	2 032.00	Sundhedsdatastyrelsen (2021). Interactive DRG: 30PR06 (UXCB00) CT-skanning af hals (DK229) Sygdom i øsofagus UNS. Available at: http://interaktivdrg.sundhedsdata.dk/
Hepatic function test	0.25	0.33	213	Rigshospitalets Labportal (2021). Test code for hepatic tests included (codes): NPU19651, NPU19654, NPU27783, NPU19673, NPU01370, NPU03278. https://labportal.rh.dk/Labportal.asp
Renal function test	0.25	0.33	261	Rigshospitalets Labportal (2021). Test code for renal tests included (codes): NPU01459, NPU01472, NPU03429, NPU03230, NPU01536, NPU23745, NPU02192, NPU04998, NPU19673 https://labportal.rh.dk/Labportal.asp
Complete blood count	0.25	0.33	460	Rigshospitalets Labportal (2021). Test code for CBC tests included (codes): NPU02902 (cost for test assumed as proxy for codes: NPU01960, NPU01961, NPU02593), NPU01473 (cost for test assumed as proxy for codes: B-Hb (Hemoglobin), Erc(B)-MCV, Erc(B)-MCH, Erc(B)-MCHC), and RGH00982. https://labportal.rh.dk/Labportal.asp

Abbreviations: CT: Computerized tomography; DKK: Danish kroner

2.5.4 Disease management costs

Resource use estimates for disease management were based on input from a Danish clinical expert (Holtved 2020). This expert specified disease management costs associated with patients in the PF and PD health states as described in Table 7.

Table 7: Disease management costs in the progression-free and progressed disease health states

Resource name	Weekly resource use PF	Weekly resource use PD	Unit cost (DKK)	Reference for costs
Outpatient visit	0.125	0.125	1 4621 437.00	Kommunernes og Regionernes Løndatakontor 2021, Specialeansvarlige overlæger (Overlæger, lægelige chefer m.v.). bruttolön NOV 2020 (103696 DKK). available from: https://krl.dk/#/sirka Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.
CT scan	0.125	0.125	2 032.00	Sundhedsdatastyrelsen (2021). Interactive DRG: 30PR06 (UXCB00) CT-skanning af hals (DK229) Sygdom i øsofagus UNS. Available at: http://interaktivdrg.sundhedsdata.dk/
Complete blood count	0.125	0.125	460	Rigshospitalets Labportal (2021). Test code for CBC tests included (codes): NPU02902 (cost for test assumed as proxy for codes: NPU01960, NPU01961, NPU02593), NPU01473 (cost for test assumed as proxy for codes: B-Hb (Hemoglobin), Erc(B)-MCV, Erc(B)-MCH, Erc(B)-MCHC), and RGH00982. https://labportal.rh.dk/Labportal.asp

Abbreviations: CT: Computed tomography; DRG: Diagnosis-related group; HCPCS: Healthcare Common Procedure Coding System; MRI: Magnetic resonance imaging; DKK: Danish Kroner; PD: Progressive disease; PF: Progression-free

2.5.5 Adverse events and adverse-event costs

The model accounts for costs due to management of all treatment-related Grade 3+ AEs registered in the ATTRACTION-3 trial, which have ≥ 5% frequency in either treatment arm. It was assumed that the costs due to AE-related mortality were already captured by the terminal care costs in the model, since all mortality events are reflected in the OS curve. The costs of these AEs and respective codes are provided in Table 8.

Table 8: Grade 3-4 adverse events for each comparator included in the model, and related costs

AEs	Nivolumab	Taxane-based arm	Costs (DKK)	Reference for costs
Anaemia	1.9%	9.1%	4 732	Physician estimate, blood transfusion outpatientSundhedsdatastyrelsen (2021). Interactive DRG: 16PR02 (BOQA0) Blodtransfusion (DK229) Sygdom i øsofagus UNS. Available at: http://interaktivdrg.sundhedsdata.dk/
Decreased appetite	1.0%	4.8%	0	No resource needed
Febrile neutropenia	0.0%	10.6%	1 462	Kommunernes og Regionernes Løndatakontor 2021, Specialeansvarlige overlæger (Overlæger, lægelige chefer m.v.). bruttolön NOV 2020 (103696DKK). available from: https://krl.dk/#/sirka Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.
Leukopenia	0.0%	6.7%	0	No resource needed
Lymphocyte count decreased	1.0%	5.8%	1 922	KOL states patient visit and CBC. Kommunernes og Regionernes Løndatakontor 2021, Specialeansvarlige overlæger (Overlæger, lægelige chefer m.v.). bruttolön NOV 2020 (103696DKK). available from: https://krl.dk/#/sirka Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Rigshospitalets Labportal (2021). Test code for CBC tests included (codes): NPU02902 (cost for test assumed as proxy for codes: NPU01960, NPU01961, NPU02593), NPU01473 (cost for test assumed as proxy for codes: B-Hb (Hemoglobin), Erc(B)-MCV, Erc(B)-MCH, Erc(B)-MCHC), and RGH00982. https://labportal.rh.dk/Labportal.asp
Neutropenia/Neutrophil count decreased	0.5%	42.3%	1 922	KOL states patient visit and CBC. Kommunernes og Regionernes Løndatakontor 2021, Specialeansvarlige overlæger (Overlæger, lægelige chefer m.v.). bruttolön NOV 2020 (103696DKK). available from: https://krl.dk/#/sirka Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.
White blood cell count decreased	0.5%	22.1%	1 462	Kommunernes og Regionernes Løndatakontor 2021, Specialeansvarlige overlæger (Overlæger, lægelige chefer m.v.). bruttolön NOV 2020 (103696DKK). available from: https://krl.dk/#/sirka Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.

Abbreviations: AE: Adverse event; DKK: Danish kroner

2.5.6 Subsequent treatment

In ATTRACTION-3, a proportion of patients receiving second-line nivolumab or taxane-based chemotherapy went on to receive subsequent therapy. Since taxanes (docetaxel and paclitaxel) were the most commonly used subsequent treatments identified during the trial, these were included in the model. In the model, the percentage of patients receiving subsequent therapy was kept at the overall level as observed in the trial, i.e. 53.3% for nivolumab and 47.4% for the chemotherapy arm (Kato 2019). To determine the proportion receiving each treatment, a weighted average was calculated considering the number of subjects that received docetaxel or paclitaxel as subsequent therapies within the taxane category and the total number of subjects that received subsequent pharmacotherapy (Table 9 and Table 10, below). All patients who receive docetaxel or paclitaxel as subsequent treatment does so as third line treatment, i.e. immediately following the nivolumab or taxane-based chemotherapy received in second line.

Table 9: Summary of subsequent anti-cancer therapies in the ATTRACTION-3 study

	Nivolumab (N = 210)	Taxane-based chemotherapy (N = 209)
Subjects who received any subsequent pharmacotherapy (%)†	112 (53.3)	99 (47.4)
Docetaxel (%) Paclitaxel (%)	44 (21.0) 75 (35.7)	15 (7.2) 29 (13.9)

† In the trial, it was possible for patients to receive more than one subsequent treatment; hence the sum of patients receiving docetaxel and patients receiving paclitaxel is higher than the number of patients receiving any subsequent pharmacotherapy.

Table 10: Subsequent treatments in the base case model

Subsequent treatments	Nivolumab	Taxane based chemotherapy
Docetaxel	19.7%	16.2%
Paclitaxel	33.6%	31.2%

Costs incurred for subsequent treatments consist of acquisition, administration, monitoring and adverse events costs and are equivalent to those presented for second line treatment. The cost of subsequent treatment is applied to all patients who leave the PF health state, which may be considered conservative since some patients die from the PF health state without progressing.

2.5.7 Patient costs

As per the guidelines, patient costs associated with receiving treatment should be included in the analysis. These include costs of lost leisure time (currently valued to 179 DKK per hour) and transportation costs (100 DKK) (Medicinrådet 2020). According to the SmPC, nivolumab takes 30 minutes to administer and it is assumed that each visit including the travel to and from the hospital would take 2 hours. This means that the total patient cost per visit is 458 DKK.

The assumption was made that costs for patients' time and transportation would apply every time the drug is administered. Drug administration is required every 14 days for nivolumab, every 21 days for docetaxel and every 7 days for paclitaxel (see Table 4, above). The frequency of visits for taxane-based chemotherapy was calculated as a weighted average of the weekly frequencies, assuming that 31% of patients receive docetaxel and 69%

receive paclitaxel. The resulting frequency and unit costs for patient visits is shown below in Table 11.Table 11: Patient time and transportation costs (weekly)

Resource name	Weekly patient time (hours) †	Unit cost patient time (DKK per hour)	Weekly patient transports	Unit cost patient transport (DKK)
Nivolumab	1.00	179	0.50	100
Taxane-based	1.59	179	0.79	100

† Every administration is assumed to require 2 hours of the patient s time.
Abbreviations: DKK: Danish Kroner
Source: (Medicinrådet 2020)

Considering both the severity of the health state and that patients are approaching the end of working life, the average age of the population is 63.9 years, the productivity loss is expected to be low. Other indirect costs have therefore not been included in this analysis.

Patient costs are not included in the budget impact analysis.

2.5.8 End of life costs

The model includes specific end-of-life costs. These enter into the analysis as a one-time cost when a patient dies, to capture the average costs associated with terminal care in Denmark. A one-time cost of 59 556 DKK was used, sourced from Sundhedsdatastyrelsen (2021) [DRG code 06MA11: (BXBA) Specialiseret palliativ indsats in (DK229) Sygdom i øsofagus UNS, for 30 days] (Table 12)(Sundhedsdatastyrelsen 2021).

Table 12: Cost for terminal care

Resource	Frequency	Cost (DKK)	Reference
Terminal Care	For 30 days	59 556	Sundhedsdatastyrelsen (2021). Interactive DRG: 06MA11 (BXBA) Specialiseret palliativ indsats (DK229) Sygdom i øsofagus UNS; Kontaktdage: 30. Takst 5,297 DKK Available at: http://interaktivdrg.sundhedsdata.dk/

2.6 Base settings and scenario analysis

Table 13 provides a summary of the base case analysis setting of the model.

Table 13: Base case assumptions

Input	Value
Health economic model	Partitioned survival model
Time horizon	10 years
Perspective	Restricted societal perspective
Efficacy data source	ATTRACTION-3
Comparators	Physician's choice of taxane-based chemotherapy
Model cycle length	One week
Population	ITT
Starting age of cohort	63.9 years
Weight	60.2 kg
Body surface area	1.71 m2
Proportion female	40%
Treatment costs	Pharmacy purchase price (PPP), dose regimen as in the ATTRACTION-3 trial and no wastage
Wastage	Vial-sharing is assumed based on Danish physician interview
Health state utilities	From ATTRACTION-3
Extrapolation of PFS	2 spline hazard for the nivolumab arm and loglogistic for the taxane arm
Extrapolation of OS	1 spline normal for the nivolumab arm and lognormal for the taxane arm
Extrapolation of DoT	1 spline normal for both treatment arms
Resource usage	Estimated in Danish physician interview
Discounting	3.5% for costs and effectiveness in the cost and cost-effectiveness comparison (section 3.1). 0% in the budget impact analysis (section 3.2).
Patient costs	Included

Abbreviations: DoT, duration of therapy; OS, overall survival; PFS, progression-free survival

3. Results

3.1 Cost (and cost-effectiveness) analysis

3.1.1 Cost analysis

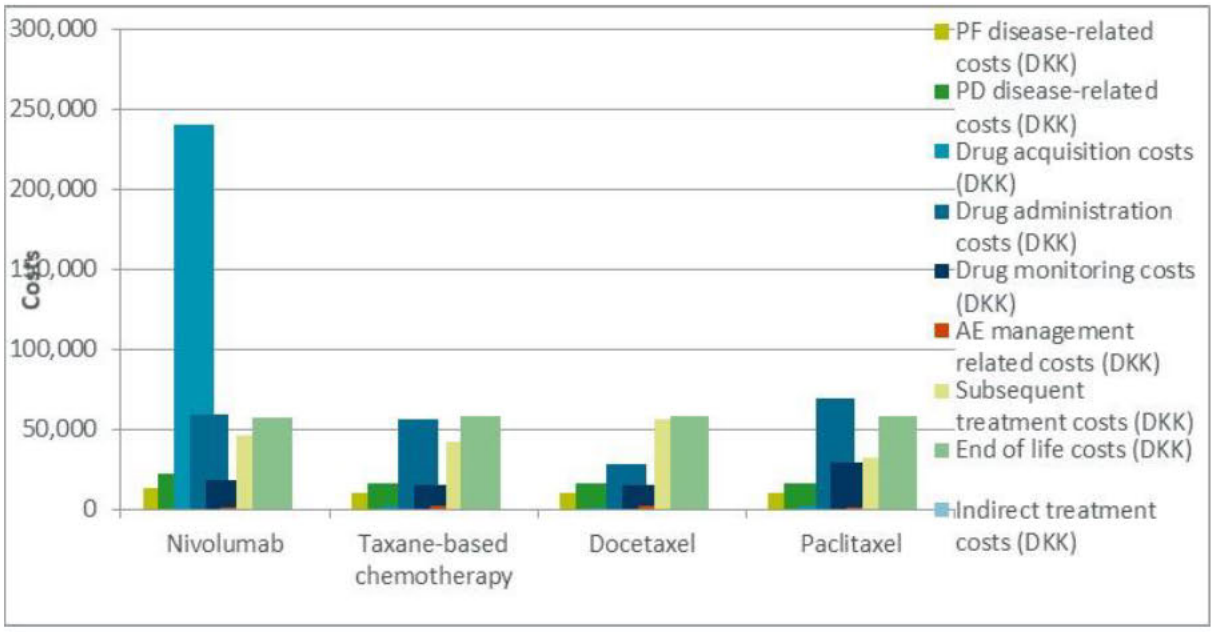
Table 14 and Figure 2 shows the cost per patient for nivolumab and taxane-based chemotherapy, including a breakdown of costs.

Table 14: Comparison of costs, including breakdown of costs, per patient treated with nivolumab or taxane, over a 10-year time horizon (with a 3.5% yearly discount)

Per patient	Nivolumab (DKK)	Taxanes (DKK)	Difference (DKK)
Total costs	**461 483**	**207 457**	**254 026**
Drug acquisition costs	240 434	1 664	238 769
Drug administration costs	59 142	56 652	2 489
Drug monitoring costs	18 178	14 972	3 206
AE management related costs	125	1 834	-1 709
PF disease management costs	13 515	10 298	3 217
PD management costs	22 082	16 286	5 797
Subsequent treatment costs	45 938	42 222	3 716
End-of life costs	57 190	58 326	-1 136
Patient costs	4 880	5 203	-323

Abbreviations: PD, progressive disease; PF, progression-free; DKK, Danish krona

Figure 2: Illustration of costs, including breakdown of costs, per patient treated with nivolumab, taxane, docetaxel or paclitaxel, over a 10-year time horizon (with a 3.5% yearly discount)



Abbreviations: DKK, Danish krona

3.1.2 Cost-effectiveness analysis

Compared with patients in the taxane-based chemotherapy arm patients in the nivolumab treatment arm gain 0.267 QALYs over the 10-year time horizon at a cost difference of 254 026 DKK. The incremental cost per QALY (ICER) of nivolumab versus taxane-based chemotherapy is estimated to 950 442 DKK (as outlined in Table 15).

Table 15: Base case result, nivolumab versus taxane-based chemotherapy

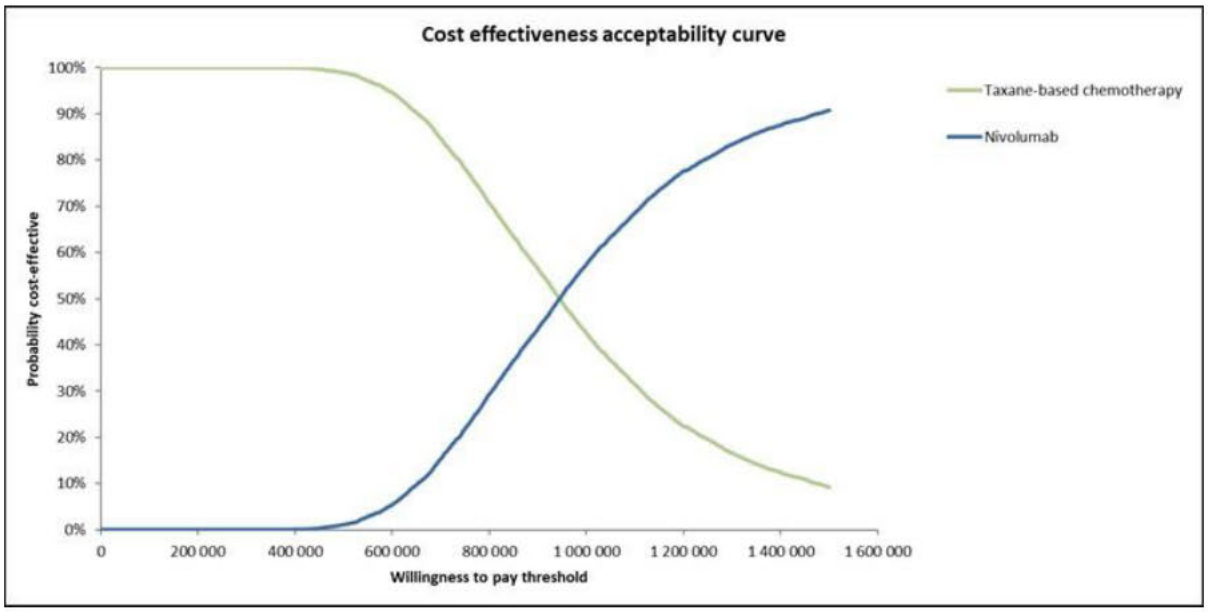
Per patient	Nivolumab	Taxane-based chemotherapy	Difference
Total costs (DKK)	461 483	207 457	254 026
Total QALYs	0.804	0.537	0.267
ICER (cost per QALY)	950 442 DKK		

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; DKK, Danish krona

3.1.2.1 Probabilistic sensitivity analysis

Figure 3 presents the results of the probabilistic sensitivity analysis in the format of a cost-effectiveness acceptability curve. Please note that nivolumab currently has a discounted price (also see next section).

Figure 3: Cost-effectiveness acceptability curve



3.1.3 Incremental costs ratio as a function of discount levels

In Denmark nivolumab has a discounted price. The cost difference and the incremental cost related to discount levels are outlined in Table 16, below.

Table 16: Incremental cost per QALY as a function of discount levels

Discount level (%)	Incremental cost per QALY (DKK per QALY)
0	950 442
10	860 484
20	770 525
30	680 567
40	590 608
50	500 650
60	410 691
70	320 733
80	230 774
90	140 816

Abbreviations: DKK, Danish kroner; QALY, Quality adjusted life-year

3.1.4 Scenario analyses

Scenario analyses were also carried out. Table 17 presents the results of these analyses. Reducing the time-horizon down to five years had a minor effect on the overall results, as can be expected given the poor prognosis of the patient population. Also, the result is not affected to a large extent by discounting, as illustrated in a scenario where no discount is applied to either costs or health outcomes. This is also in line with what can be expected based on the prognosis of these patients and the maturity of the clinical data used in the health economic analysis.

The influence of off-label weight-based dosing of nivolumab, 3 mg/kg every 2 weeks (including the assumption of vial sharing), instead of a flat dose of 240 mg every 2 weeks, was also explored in a scenario analysis.

Table 17: Scenario analyses for the comparison of nivolumab versus taxane-based chemotherapy

Base-case setting	Scenario	Incremental cost (DKK)	Incremental QALY	ICER (DKK)
Base case	Base case	254 026	0.267	950 442
10 years	5 years	249 533	0.232	1 075 260
3.5 % discount	0% discount	258 535	0.287	900 345
Flat dose, vial sharing	Weight based dose, vial sharing	194 519	0.267	727 795
Flat dose, vial sharing	Flat dose, no vial sharing	265 043	0.267	991 659
DoT, extrapolated	DoT, Kaplan-Meier data only	307 277	0.267	1 149 679
Disease management costs included	Disease management costs excluded	245 012	0.267	916 716
Patient costs included	Patient costs excluded	254 349	0.267	951 650

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; DKK, Danish kroner; QALY, quality-adjusted life year

3.2 Budget impact on the drug budget of the national insurance scheme

3.2.1 Expenditure per patient

The drug costs per patient is calculated from the pharmacy purchase price with no discounts applied. Breakdowns of the expenditure per patient per year for nivolumab and taxane-based chemotherapy respectively are found in Table 18 below.

Table 18: Drug expenditure per patient and year for a patient starting treatment in year 1 (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Nivolumab	358 553	62 184	20 997	9 347	4 872
Taxane based chemotherapy	168 986	23 074	6 772	2 674	1 240

Abbreviations: DKK, Danish kroner

3.2.2 Budget impact

As described in section 2.3, in Denmark 30 new patients with advanced ESCC are estimated to be eligible for treatment with either nivolumab or taxane-based chemotherapy each year.

If nivolumab is introduced, 66.6% of these patients are assumed to be treated with nivolumab. If nivolumab is not introduced all patients are assumed to be treated with taxane-based chemotherapy.

The total annual budget impact of the drug costs related to nivolumab is about 5 037 578 DKK in year 5. The total annual drug costs are presented in Table 21.

Table 19: Budget impact if nivolumab is accepted as standard treatment (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Nivolumab					
Number of patients	12	20	20	20	20
Cost of new patients	4 302 632	7 174 640	7 174 640	7 174 640	7 174 640
Cost of patients from previous years		746 206	1 496 267	1 776 621	1 909 955
Cost summary	4 302 632	7 920 846	8 670 907	8 951 261	9 084 595
Taxane-based chemotherapy					
Number of patients	18	10	10	10	10
Cost of new patients	3 041 745	1 688 168	1 688 168	1 688 168	1 688 168
Cost of patients from previous years		415 326	352 406	346 300	347 195
Cost summary	3 041 745	2 103 494	2 040 574	2 034 468	2 035 363
Total cost	7 344 377	10 024 340	10 711 481	10 985 729	11 119 958

Abbreviations: DKK, Danish kroner

Table 20: Budget impact if nivolumab is not accepted as standard treatment (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Nivolumab					
Number of patients	0	0	0	0	0
Cost of new patients	0	0	0	0	0
Cost of patients from previous years		0	0	0	0
Cost summary	0	0	0	0	0
Taxane-based chemotherapy					
Number of patients	30	30	30	30	30
Cost of new patients	5 069 575	5 069 575	5 069 575	5 069 575	5 069 575
Cost of patients from previous years		692 209	895 376	975 609	1 012 805
Cost summary	5 069 575	5 761 784	5 964 951	6 045 184	6 082 380
Total cost	5 069 575	5 761 784	5 964 951	6 045 184	6 082 380

Abbreviations: DKK, Danish kroner

Table 21: Expected annual budget impact for nivolumab (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
nivolumab treatment granted pre-approved reimbursement	7 344 377	10 024 340	10 711 481	10 985 729	11 119 958
nivolumab not granted pre-approved reimbursement	5 069 575	5 761 784	5 964 951	6 045 184	6 082 380
Budget impact of the decision	2 274 802	4 262 556	4 746 530	4 940 545	5 037 578

Abbreviations: DKK, Danish kroner

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Appendix I Extrapolation

In the three-state PSM, the proportion of patients in prespecified PF, PD, and death states beyond the trial follow-up are estimated by fitting parametric and spline-based survival functions to the observed PFS and OS data independently and projecting using the fitted functional forms.

The process for fitting parametric survival curves to patient-level data was based on methods guidance from the Danish Medicines Council and from the Decision Support Unit (DSU) at the National Institute for Health and Care Excellence (NICE) (Medicinrådet 2021, Latimer 2011). The following process was used to determine the most appropriate curve fits for OS, PFS and DoT in the model:

1. Testing of proportional effects assumption – the log cumulative hazards, log cumulative odds, and standardized normal curve plots were assessed to determine if the data from ATTRACTION-3 trial indicate proportional effects, in which case the curves for the two arms would be parallel; additionally, proportionality of the hazards between treatments are is further assessed by using the Grambsch and Therneau's correlation test and visual inspection of the Schoenfeld residuals plot
2. If the assumption of proportional effects held, a range of dependent parametric models were explored; otherwise, distributions were fitted to each arm independently
3. Within the various parametric survival distributions, the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) goodness-of-fit statistics were assessed to identify the best fitting survival models over the clinical trial period
4. The final choice of parametric survival distributions for the base case model was based on:
    a. the best fitting survival models measured by the lowest AIC statistic, measuring goodness-of-fit (compared with the KM data from ATTRACTION-3), with BIC as an alternative measure
    b. the visual inspection of the model's goodness-of-fit (compared with the KM data from ATTRACTION-3)
    c. the clinical plausibility of the extrapolated survival at 6 months, 1 year, 2 years, 3 years, 4 years, 5 years and 10 years

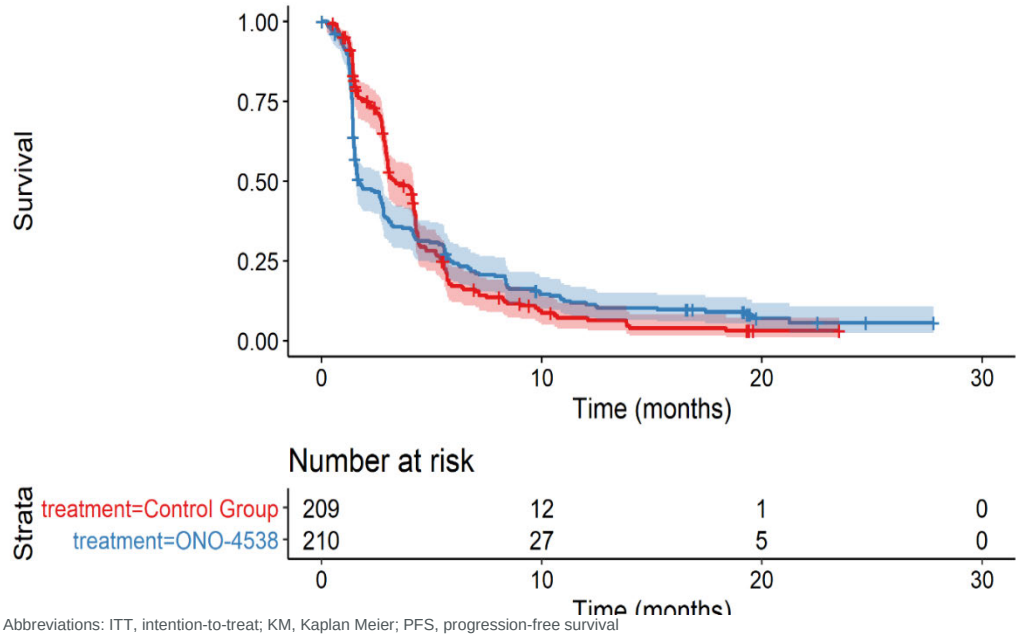
    It is important to consider goodness-of-fit as it measures the fit of the extrapolation against the available trial data; it is equally important to consider the clinical plausibility of the extrapolated portion of the curve as it is the area with the highest uncertainty due to lack of trial data

In the context of nivolumab, spline-based models can potentially provide better fits to the "plateau" flat tail observed towards the end of follow-up seen in both the OS and PFS curves, or the steep drop observed in the PFS curve within 9 weeks.

I.1 Extrapolation of progression-free survival

The KM curves for PFS in the nivolumab and taxane-based chemotherapy arms are shown in Figure 4. The PFS curve for nivolumab shows an initial drop; the KM curves are crossing around 4.4 months. The steep drop observed within the first 6 weeks of follow-up may be due to the delayed response seen for patients receiving immune-oncology therapy.

Figure 4: KM survival curve of PFS in the ITT population

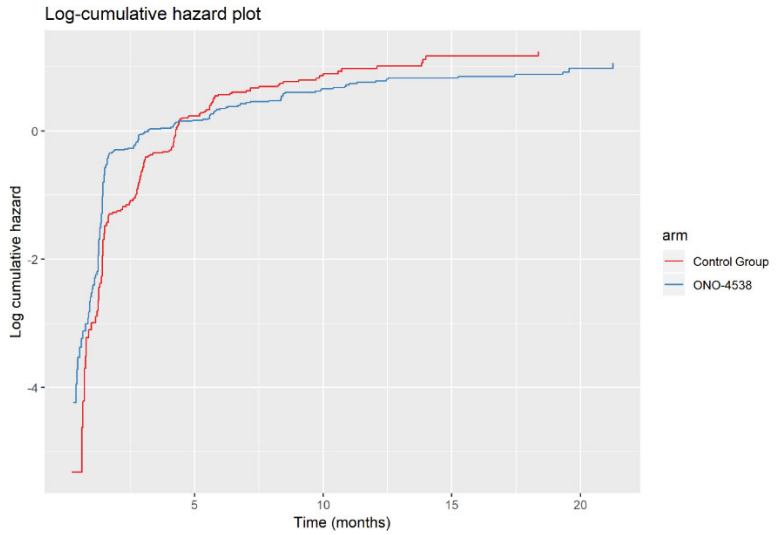


Abbreviations: ITT, intention-to-treat; KM, Kaplan Meier; PFS, progression-free survival

Testing of proportional hazards assumption

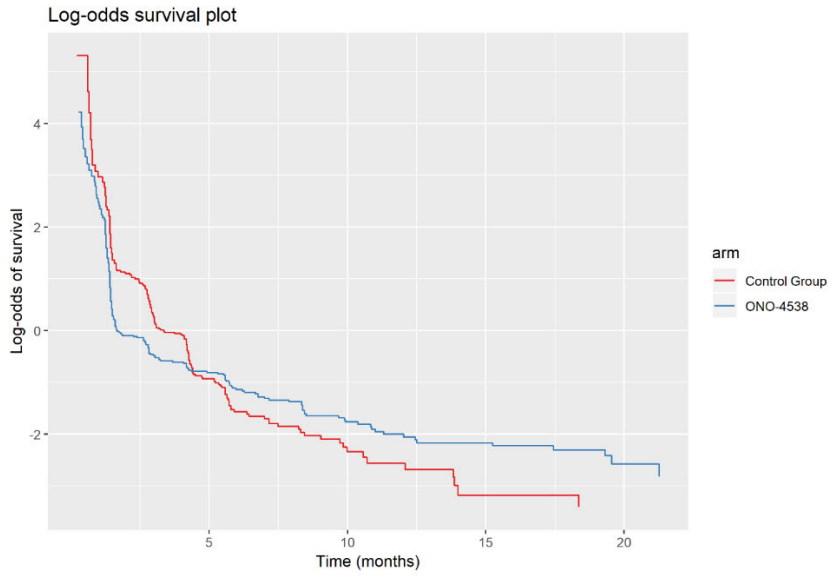
Proportional hazards were assessed by a visual inspection of the Schoenfeld residuals and log-cumulative hazards plots for PFS (see Figure 5, Figure 6 and Figure 7). Conducting the Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time confirmed the rejection of the null hypothesis of proportional hazards ($p < 0.001$). Therefore, independent parametric curves were used to model PFS in the base case.

Figure 5: Assessment of proportional hazards: log-cumulative hazard (PFS ITT population)



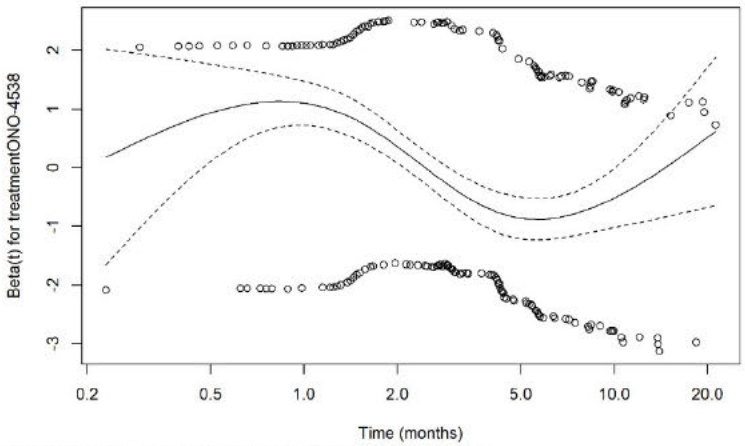
Abbreviations: ITT: Intention-to-treat; PFS: Progression-free survival

Figure 6: Assessment of proportional hazards: log-cumulative odds (PFS ITT population)



Abbreviations: ITT: Intention-to-treat; PFS: Progression-free survival

Figure 7: Assessment of proportional hazards: Schoenfeld residuals plot (PFS ITT population)



Abbreviations: ITT: Intention-to-treat; PFS: Progression-free survival

Assessing goodness-of-fit on independent parametric survival models

As the proportional hazard assumption does not hold for PFS, independent parametric survival curves were fitted separately to the nivolumab and control arm of the ATTRACTION-3 trial.

Table 22 and Table 23 refer to the AIC and BIC goodness-of-fit data for each distribution for nivolumab and taxane-based chemotherapy arms, respectively. The best fitting parametric distributions (as determined by the lowest AIC values) were the 2-knot spline hazards distribution for nivolumab and the log-logistic distribution for taxane-based chemotherapy.

Table 22: Summary of goodness of fit curves fitter to nivolumab PFS- independent survival models

Distribution	AIC	BIC
Spline hazards 2 knots (1)	**874.82**	**888.20**
Spline odds 2 knots (2)	+5.36	+5.36
Spline odds 1 knot (3)	+16.39	+13.04
Spline normal 1 knot (4)	+19.15	+15.80
Spline normal 2 knots	+21.77	+21.77
Spline hazards 1 knot (5)	+24.71	+21.37
Generalized gamma	+27.64	+24.29
Lognormal	+53.89	+47.19
Log-logistic	+53.91	+47.22
Gompertz	+86.01	+79.31
Weibull	+115.55	+108.85
Exponential	+118.32	+108.28
Gamma	+120.07	+113.38

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: Progression-free survival

Table 23: Summary of goodness-of-fit of curves fitted to taxane-based chemotherapy PFS – independent survival models

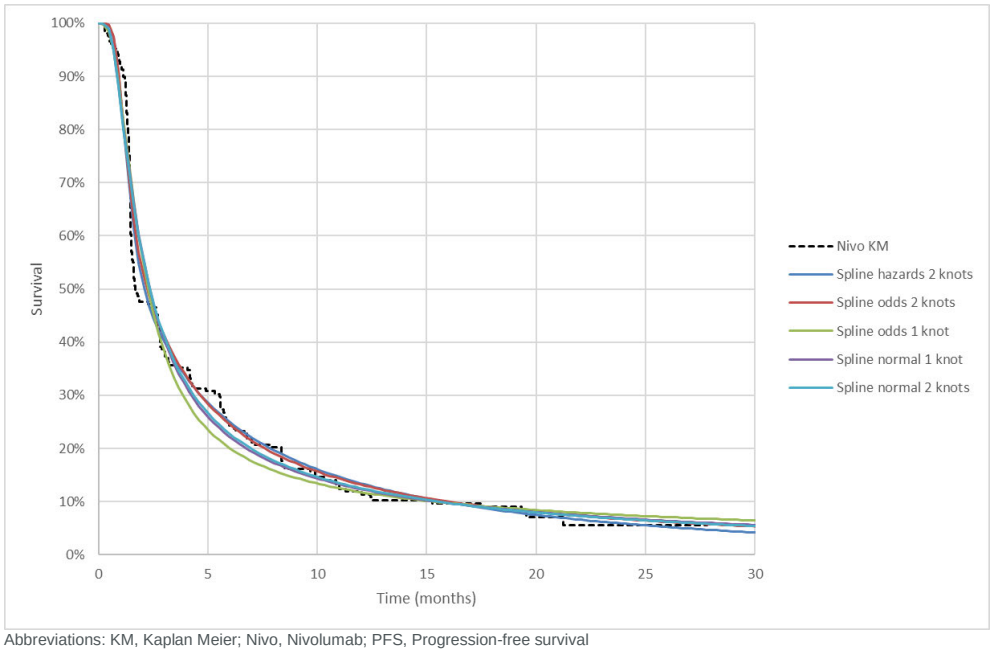
Distribution	AIC	BIC
Log-logistic (1)	**849.27**	**855.95**
Spline odds 1 knot (3)	+1.27	+4.61
Spline hazards 2 knots (5)	+1.71	+8.40
Spline normal 2 knots	+2.43	+9.12
Spline hazards 1 knot (4)	+2.44	+5.78
Spline odds 2 knots	+3.00	+9.69
Lognormal (2)	+3.60	+3.60
Generalized gamma	+5.08	+8.42
Spline normal 1 knot	+5.25	+8.59
Gamma	+27.42	+27.42
Weibull	+41.48	+41.48
Exponential	+59.31	+55.96
Gompertz	+60.99	+60.99

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: Progression-free survival

Landmark analysis was carried out to compare extrapolated survival and KM survival at different timepoints. For nivolumab, the range between survival models at 5 years was 0.3–4.1%. Figure 8 and Figure 9 provides a comparison of the KM PFS for nivolumab and the best fitting curves over the short (< 3 years) and long (10 year) time periods.

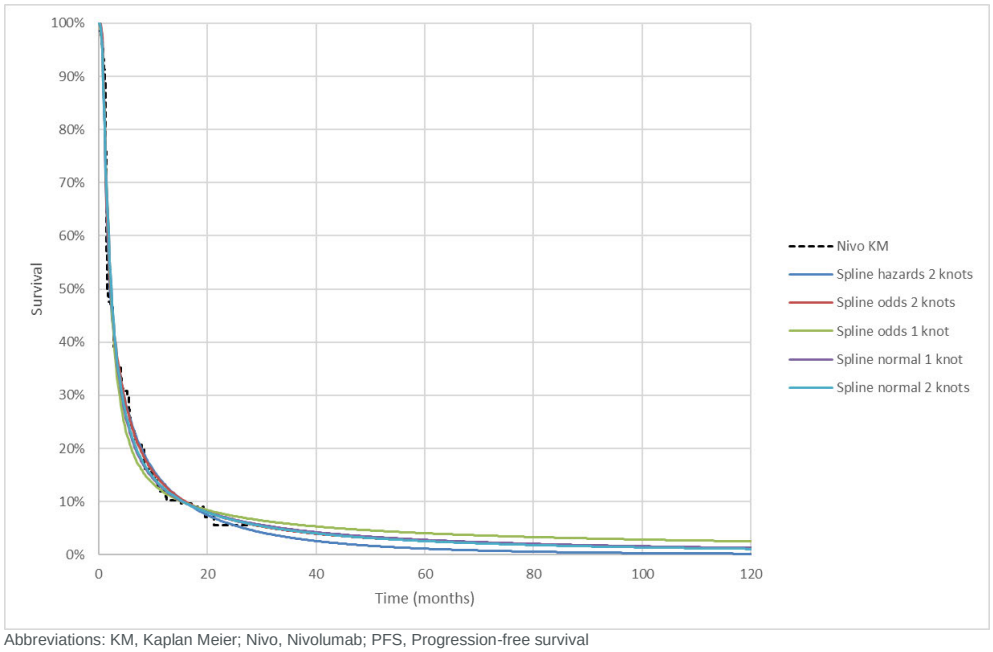
For taxane-based chemotherapy, the range between survival models at 5 years was 0.0–0.4%. Figure 10 and Figure 11 provides a comparison of the KM PFS for taxane-based chemotherapy and the best fitting curves over the short and long time periods.

Figure 8: Short-term graphical fit of top 5 ranked best fitting curves to KM PFS for the nivolumab arm



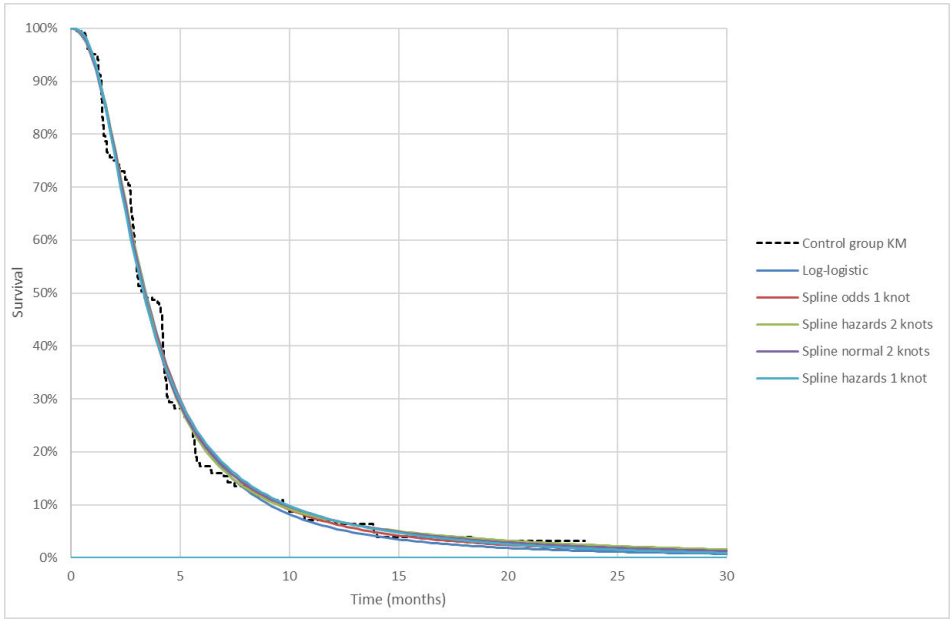
Abbreviations: KM, Kaplan Meier; Nivo, Nivolumab; PFS, Progression-free survival

Figure 9: Long-term graphical fit of top 5 ranked best fitting curves to KM PFS for the nivolumab arm



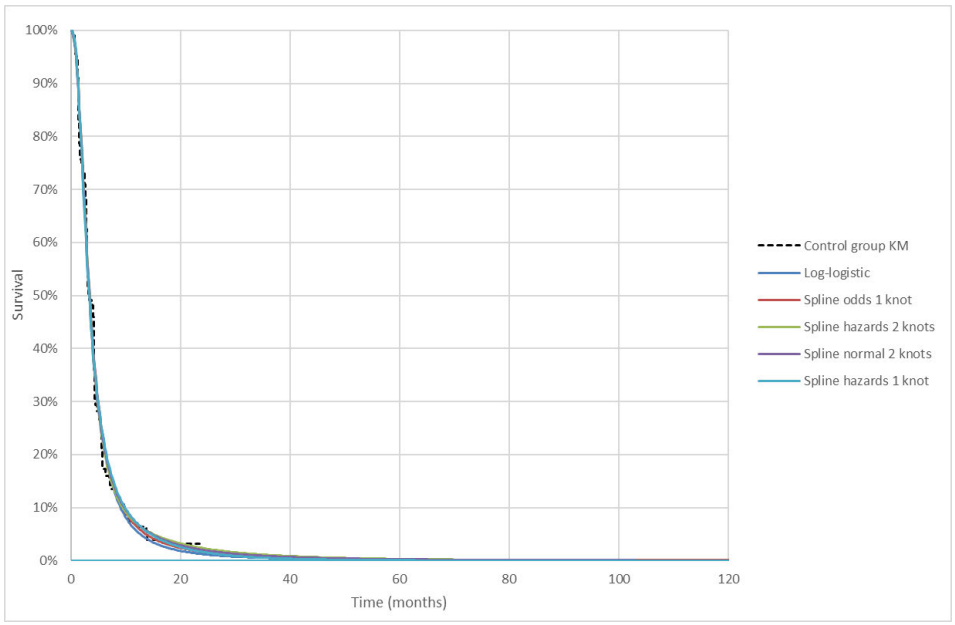
Abbreviations: KM, Kaplan Meier; Nivo, Nivolumab; PFS, Progression-free survival

Figure 10: Short-term graphical fit of top 5 ranked best fitting curves to KM PFS for the taxane-based chemotherapy arm



Abbreviations: KM, Kaplan Meier; PFS, Progression-free survival

Figure 11: Long term graphical fit of top 5 ranked best fitting curves to KM PFS for the taxane-based chemotherapy arm

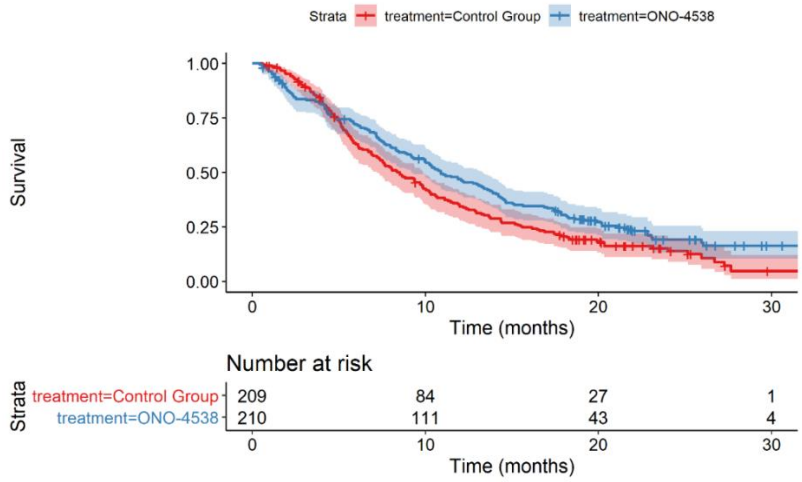


Abbreviations: KM, Kaplan Meier; PFS, Progression-free survival

I.2 Extrapolation of overall survival

The KM curves for OS in the nivolumab and taxane-based chemotherapy arms are shown in Figure 12. The OS curve for nivolumab shows an initial drop followed by a more stable survival plateau; the KM curves are crossing around 5 months.

Figure 12: KM survival curve of OS in the ITT population

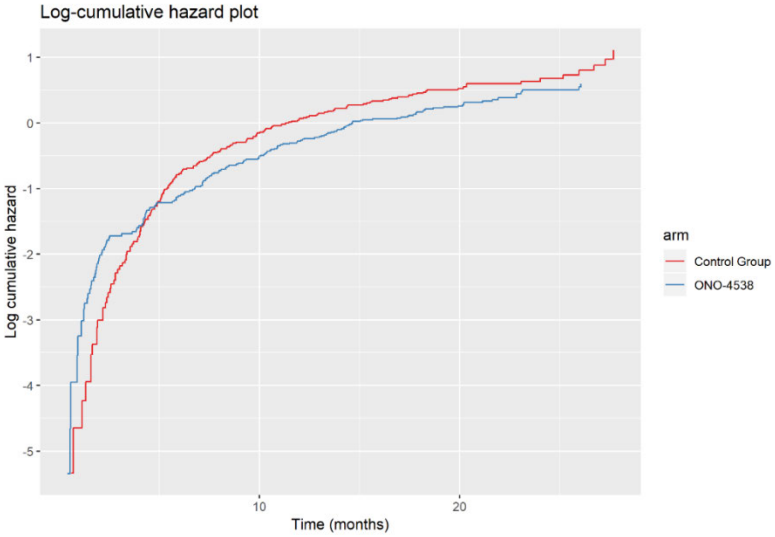


Abbreviations: KM, Kaplan Meier; ITT, Intention-to-treat; OS, Overall survival

Testing of proportional hazards assumption

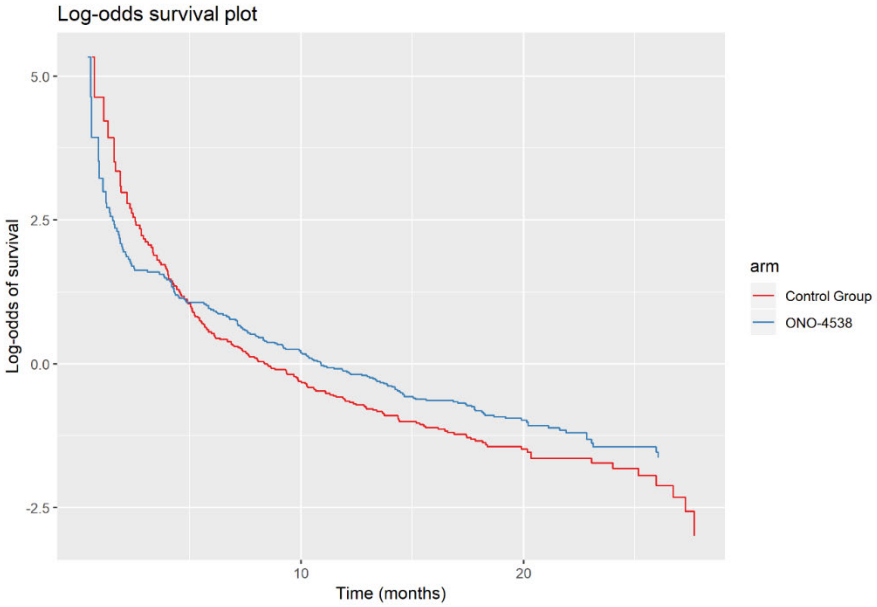
Visual inspection of the log-cumulative hazards, log-cumulative odds, and Schoenfeld residual plots was undertaken to assess proportionality of hazards between the treatment arms over time (see Figure 13, Figure 14 and Figure 15). There was a crossover in the log-cumulative hazard plot. A Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time confirmed the rejection of the null hypothesis of proportional hazards ($p < 0.05$). In these circumstances, a treatment covariate model (dependent model) may not be suitable. Individual survival models fitted to each arm of the study were therefore preferred.

Figure 13: Assessment of proportional hazards: log-cumulative hazard (OS ITT population)



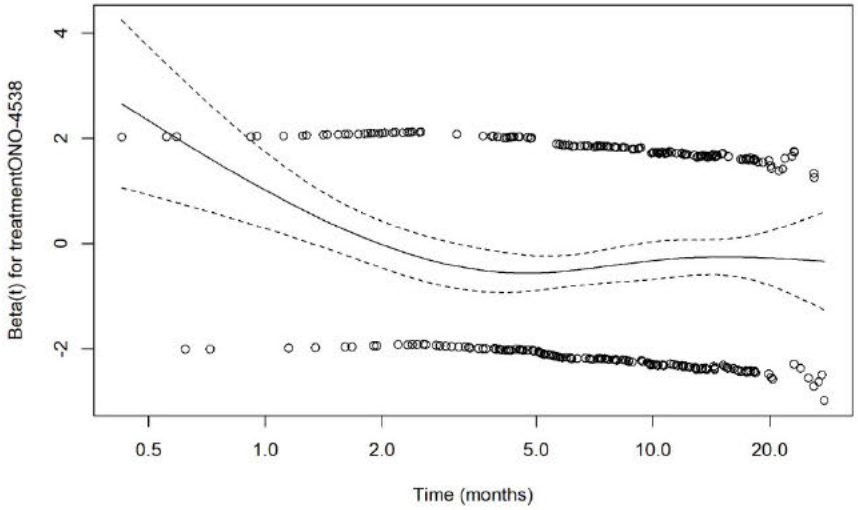
Abbreviations: ITT: Intention-to-treat; OS: Overall survival

Figure 14: Assessment of proportional hazards: log-cumulative odds (OS ITT population)



Abbreviations: ITT: Intention-to-treat; OS: Overall survival

Figure 15: Assessment of proportional hazards: Schoenfeld residuals plot (OS ITT population)



Abbreviations: ITT: Intention-to-treat; OS: Overall survival

Assessing goodness-of-fit on independent parametric survival models

As the proportional hazard assumption does not hold for OS, independent parametric survival curves were fitted separately to the nivolumab and control arm of the ATTRACTION-3 trial.

Table 24 and Table 25 provide a summary of the AIC and BIC goodness-of-fit statistics reported for each distribution for nivolumab and taxane-based chemotherapy arms, respectively. The best fitting parametric distributions (as determined by the lowest AIC values) were the 1-knot spline normal distribution for nivolumab and the log-normal for taxane-based chemotherapy.

Table 24: Summary of goodness-of-fit of curves fitted to nivolumab OS – independent survival models

Distribution	AIC	BIC
Spline normal 1 knot	**1,202.80**	+4.96
Gamma (2)	+0.55	+2.16
Spline normal 2 knots	+0.56	+8.87
Generalized gamma	+0.72	+5.68
Weibull (3)	+1.30	+2.92
Spline hazards 1 knot	+1.62	+6.58
Log-logistic (4)	+1.71	+3.33
Exponential (1)	+1.73	**1207.88**
Lognormal (5)	+1.97	+3.58
Spline odds 2 knots	+2.20	+10.50
Spline odds 1 knot	+2.67	+7.64
Gompertz	+3.32	+4.94
Spline hazards 2 knots	+3.43	+11.74

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: Overall survival

Table 25: Summary of goodness-of-fit of curves fitted to taxane-based chemotherapy OS – independent survival models

Distribution	AIC	BIC
Lognormal (1)	**1,181.52**	**1,188.21**
Spline hazards 1 knot (3)	+0.52	+3.86
Log-logistic (2)	+1.66	+1.66
Spline odds 1 knot (4)	+1.77	+5.11
Spline normal 1 knot (5)	+1.95	+5.29
Generalized gamma	+2.00	+5.34
Spline hazards 2 knots	+2.45	+9.14
Spline odds 2 knots	+3.40	+10.09
Spline normal 2 knots	+3.50	+10.18
Gamma	+3.60	+10.29
Weibull	+11.65	+11.65
Gompertz	+18.42	+18.42
Exponential	+33.00	+33.00

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: Overall survival

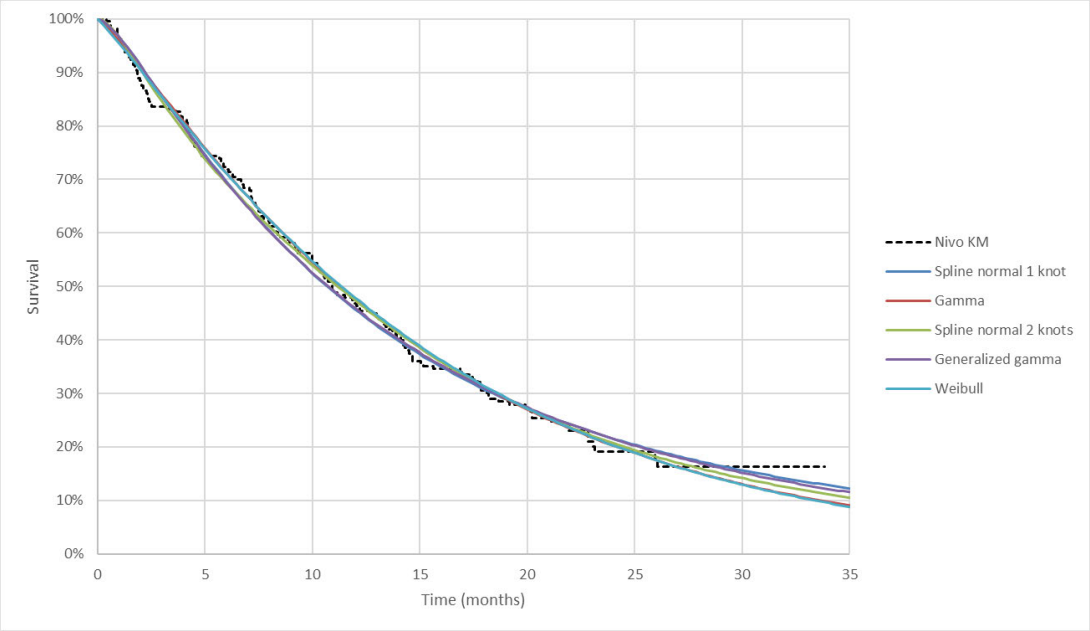
Due to the maturity of the ATTRACTION-3 trial KM curves, the distributions tested provided similar survival estimates in the short term, with most distributions fitting the data equally well.

Landmark OS at different time-points for the best fitting independent parametric survival models for each arm as determined by AIC values was explored. The landmark analysis showed that for each arm there were no substantial differences in predictions of long-term OS between the top fitting distributions.

This is also illustrated in Figure 16 and Figure 17 showing the nivolumab KM OS data and the best fitting curves over the short (< 3 years) and long (10 years) time periods of extrapolation, and Figure 18 and Figure 19 illustrating the taxane-based chemotherapy KM OS data with the best fitting curves over the short and long time period.

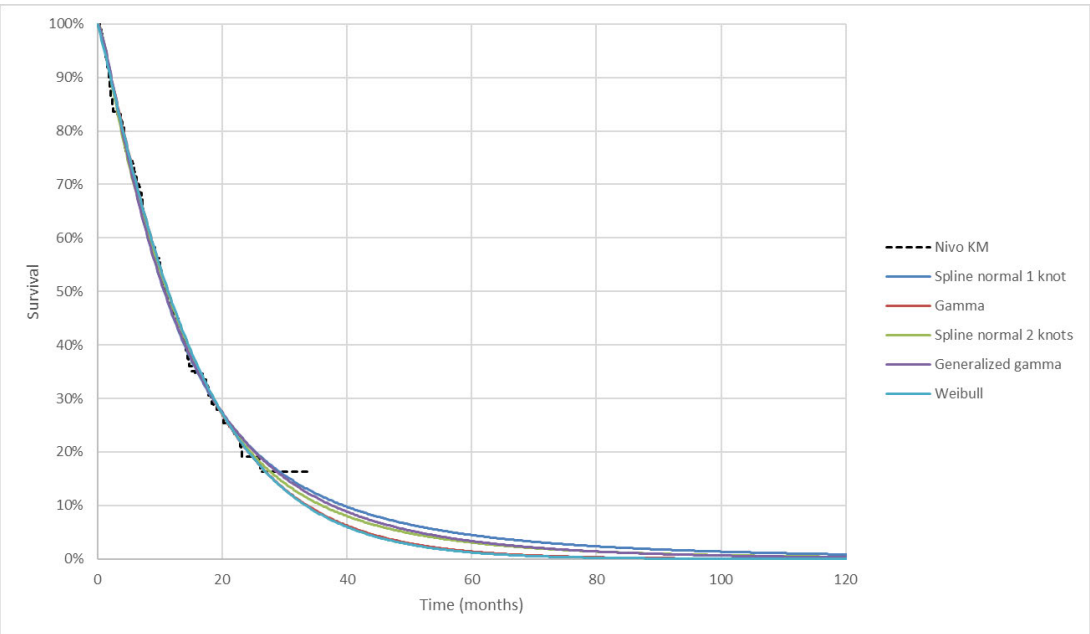
For nivolumab, the range between survival models at 10 years was 0.0–2.8%. For taxane-based chemotherapy, the range between survival models at 10 years was 0.0–1.0%.

Figure 16: Short-term graphical fit of top 5 ranked best fitting curves to KM OS for the nivolumab arm



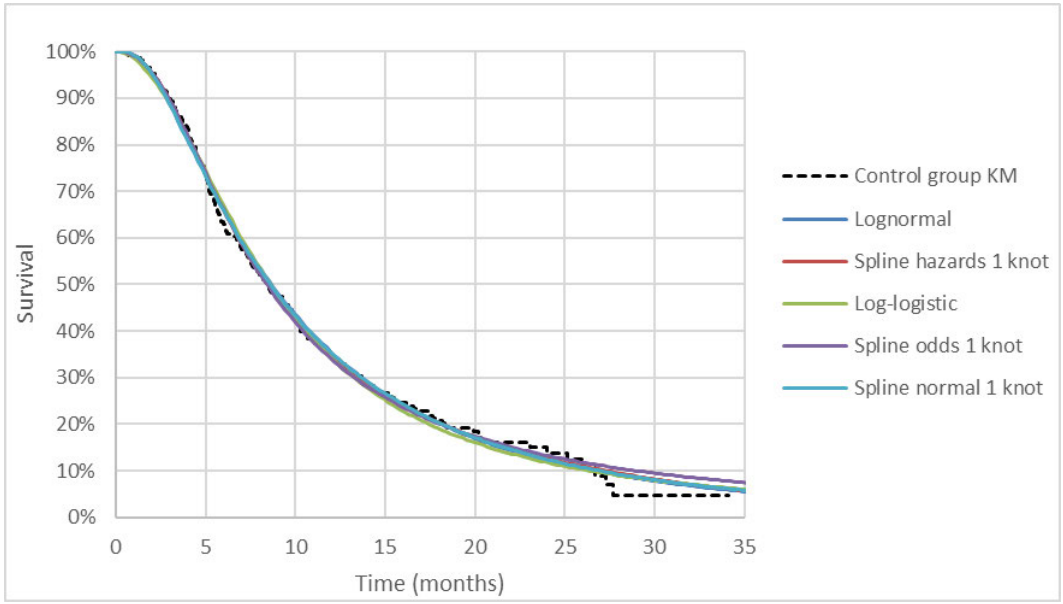
Abbreviations: KM, Kaplan Meier; Nivo, nivolumab; OS, Overall survival

Figure 17: Long-term graphical fit of top 5 ranked best fitting curves to KM OS for the nivolumab arm



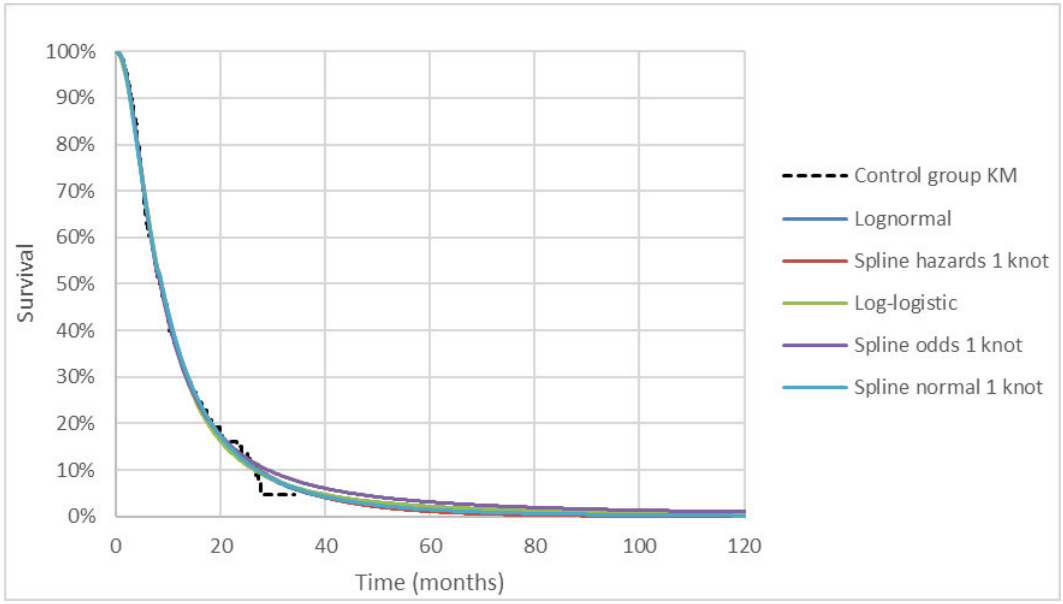
Abbreviations: KM, Kaplan Meier; Nivo, nivolumab; OS, Overall survival

Figure 18: Short-term graphical fit of top 5 ranked best fitting curves to KM OS for the taxane-based chemotherapy arm



Abbreviations: KM, Kaplan Meier; OS, Overall survival

Figure 19: Long-term graphical fit of top 5 ranked best fitting curves to KM OS for the taxane-based chemotherapy arm



Abbreviations: KM, Kaplan Meier; OS, Overall survival

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I.4 Validation of extrapolation

In the initial database lock for ATTRACTION-3, patient follow-up for PFS and OS outcomes were variable, with a median follow-up of 10.55 months and 8.02 months for the nivolumab and control arm, respectively. This follow-up period is shorter than the time horizon of the economic analysis. To estimate the cumulative PFS and OS in the model over the 10-year time horizon, parametric survival curves were fitted to ATTRACTION-3 patient-level data. Since around 15% of the patients in the nivolumab arm and around 5% in the control arm were alive at the end of the trial with the expectation of experiencing ongoing benefit from treatment, these curves were used to extrapolate survival beyond the study time horizon. Table 28 provides a comparison of mean and median OS, PFS and DoT reported in the clinical trial and extrapolated in the model (using the described base case settings).

There is a lack of real-world evidence in a comparable patient population with a longer follow-up than ATTRACTION-3. Therefore, no real-world evidence was used to validate curve choice selection.

Instead, landmark analysis comparing KM OS, PFS and DoT at different time-points with the best fitting independent parametric survival models were carried out. The intention was to eliminate any models that would predict clinically implausible outcomes.

Due to the maturity of the ATTRACTION-3 trial KM curves, the distributions tested provided similar survival estimates in the short term, with most distributions fitting the data equally well.

There were no substantial differences in predictions of long-term OS in nivolumab and taxane-based chemotherapy between the top fitting distributions.

- For nivolumab, the range between survival models at 10 years was 0.0–2.8%.

- For taxane-based chemotherapy, the range between survival models at 10 years was 0.0–1.0%.

There were no substantial differences in predictions of long-term PFS in nivolumab and taxane-based chemotherapy between the top fitting distributions.

- For nivolumab, the range between survival models at 5 years was 0.3–4.1%.
- For taxane-based chemotherapy, the range between survival models at 5 years was 0.0–0.4%.

There were no substantial differences in predictions of long-term DoT in nivolumab and taxane-based chemotherapy between the top fitting distributions.

- For nivolumab, the range between survival models at 2 years was 1.4–3.1%.
- For taxane-based chemotherapy, the range between survival models at 2 years was 0.0–0.5%.

Table 28: Comparison of mean and median OS, PFS and DoT in the model and in the ATTRACTION-3 trial

Clinical efficacy outcome	Used in the model (month)	Clinical documentation (month)
Mean PFS nivolumab	[redacted]	[redacted]
Mean PFS taxane-based chemotherapy	[redacted]	[redacted]
Mean OS nivolumab	[redacted]	[redacted]
Mean OS taxane-based chemotherapy	[redacted]	[redacted]
Mean DoT nivolumab	[redacted]	[redacted]
Mean DoT taxane-based chemotherapy	[redacted]	[redacted]
Median PFS nivolumab	[redacted]	[redacted]
Median PFS taxane-based chemotherapy	[redacted]	[redacted]
Median OS nivolumab	[redacted]	[redacted]
Median OS taxane-based chemotherapy	[redacted]	[redacted]
Median DoT nivolumab	[redacted]	[redacted]
Median DoT taxane-based chemotherapy	[redacted]	[redacted]

Abbreviations: PFS: Progression-free survival; OS: Overall survival; DoT: Duration of therapy; NR: Not reached

Appendix II Health related quality of life

Patient level quality of life data (EQ-5D-3L) from the ATTRACTION-3 trial are used for the progression-free (PF) and progressed disease (PD) health states in the model.

Patients on nivolumab within the PF health state experienced higher health state utility values in comparison with patients receiving taxane-based chemotherapy in the same health state. The treatment-specific and overall utility values are included in the model as a user-changeable option.

In the base case analysis, overall health state utilities are used, whereas treatment-specific utilities are investigated in a scenario analysis. Disutility values should only be applied when using the overall PF health state utility and not combined with treatment-specific PF utility values to avoid the risk of potential double-counting.

The health state utilities and adverse event disutility values applied in the model are presented in Table 29 below.

Table 29: Overall and treatment-specific utilities by health state, UK index

Health state	Mean utility (SE) 95% CI	Reference
Progression free		
Progression free	[redacted]	ATTRACTION-3
Nivolumab	[redacted]	ATTRACTION-3
Taxanes	[redacted]	ATTRACTION-3
Progressed disease		
Progressed disease	[redacted]	ATTRACTION-3
Death		
Death	0	Assumption
AE-related disutilities		
Anemia	-0.125	Lloyd *et al.*, 2008
Febrile neutropenia	-0.131	Tam VC *et al.*, 2013
Neutropenia	-0.0897	Nafees *et al.*, 2008
Lymphocyte count decreased	-0.0897	Assumed to be the same as neutropenia
Disutilities for the other AEs	No disutility	Assumption

Abbreviations: AE: Adverse event; CI, Confidence interval; PD, Progressive disease; PF, progression-free SE, standard error
Source: ATTRACT

Appendix III 36-month data from the ATTRACTION-3 trial

This section provides additional evidence from the ATTRACTION-3 trial. Compared to initial release of the results in 2019, this summary comes from an extended follow-up which is approximately 1.5 years longer than the previous one. More specifically, the survival data presented in this document belongs to minimum 3-year follow-up from the latest available database lock (DBL, 25-Aug-2020, data cut-off date, 25-May-2020; minimum follow-up, 36.04 months). Some of the data was published at ASCO GI (Table 30) (Chin 2021).

Table 30: Key Efficacy Results of ATTRACTION-3 based on the 25 Aug-2020 DBL

Efficacy Parameter	Nivolumab	Control
ITT Population (N)	210	209
Overall Survival (OS)		
Events, n (%)	[redacted]	[redacted]
Median, months (95% CI)[a]	10.9 (9.2, 13.3)	8.5 (7.3, 9.9)
HR (95% CI)[b]	0.79 (0.64, 0.97)	
p-value[c,d]	p = 0.0264*	
OS Rates (95% CI), %		
12-month	46.9 [redacted]	34.7 [redacted]
24-month	20.2 [redacted]	13.5 [redacted]
36-month	15.3 [redacted]	8.7 [redacted]
RES Population (N)[e]	171	158
Investigator-assessed Objective Response Rate (ORR)		
Responders, n (%)	33 (19.3)	34 (21.5)
95% CI[f]	[redacted]	[redacted]
Odds ratio (95% CI)[g]	[redacted]	
Difference (95% CI)[h]	[redacted]	
p-value[c,d]	[redacted]	
ITT Population (N)	210	209
Investigator-assessed Progression-free Survival (PFS)		
Events, n (%)	193 (91.9)	178 (85.2)
Median, months (95% CI)[a]	1.7 (1.5, 2.7)	3.4 (3.0, 4.2)
HR (95% CI)[c,d]	1.07 (0.87, 1.33)	

[redacted]

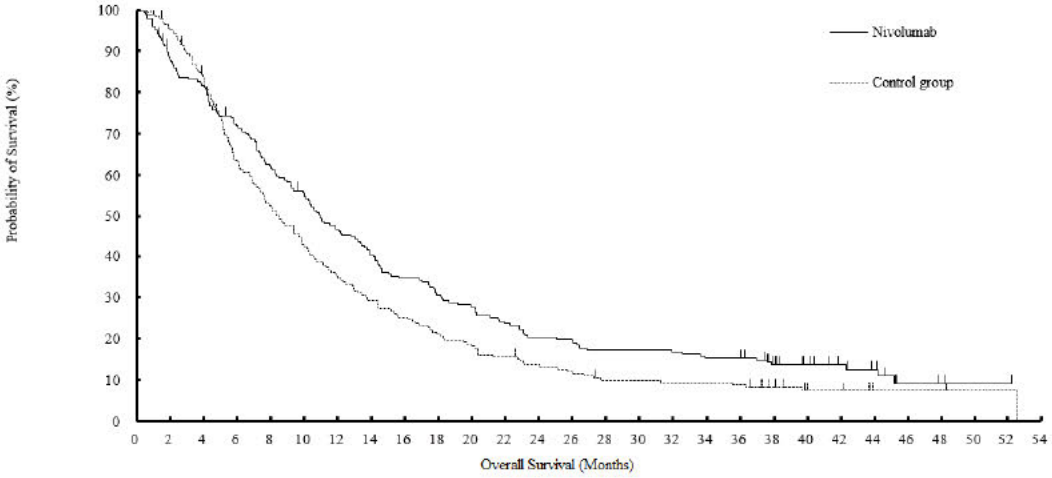
[h] Difference and the corresponding CI for the nivolumab group relative to the control group was calculated using Cochran-Mantel-Haenszel methodology with the 3 stratification factors as mentioned in footnote 'b'.

III.1 Overall survival (OS)

Overall, the updated OS results are consistent with those previously reported at the primary analysis and further elucidate the long-term benefit of nivolumab vs control in subjects with advanced ESCC.

- Nivolumab continued to show increased survival benefit over chemotherapy in patients with advanced ESCC. The upper boundary of the updated OS hazard ratio is still below 1. Updated OS hazard ratio (HR) for the nivolumab versus chemotherapy control was 0.79 (95% CI: 0.64, 0.97); descriptive p-value = 0.0264, which is similar to the OS HR previously reported at the primary analysis (HR = 0.77 [95% CI: 0.62, 0.96]; p = 0.0189).
- Updated median OS (mOS) was 10.9 months (95% CI: 9.2, 13.3) in the nivolumab group and 8.5 months (95% CI: 7.3, 9.9) in the control group. [redacted]
- Nivolumab continued to demonstrate improved OS rates at 24 months (20.2% vs 13.5%) and 36 months (15.3% vs 8.7%) compared with the chemotherapy control.
- Updated subgroup analyses of OS according to baseline demographics and disease characteristics continued to favour nivolumab over control (represented by a HR of < 1 or all pre-specified subgroups). See also Figure 30 and Figure 31, below, for forest plot representations.

Figure 30: Kaplan-Meier Plot of Overall survival - All Randomized Subjects in ATTRACTION-3 - 25-Aug-2020 DBL



Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54
Nivolumab	210	182	167	147	126	111	95	82	70	62	56	48	41	39	35	35	34	31	31	22	17	12	9	3	2	1	1	0
Control group	209	196	170	127	106	85	69	58	50	42	36	31	26	22	18	18	17	17	16	11	7	6	2	2	2	1	1	0

III.2 Comparison with previously reported OS data

The efficacy results based on the additional 1.5 years of follow-up are consistent with the previously provided results.

In the submitted cost analysis a spline normal 1 knot function was used to estimate OS for the nivolumab arm which estimated the median OS to 10.58 months. The median OS in the latest data-cut is 10.91 months, i.e. unchanged compared to the previously reported median OS. The 3-year and 4-year OS was estimated to 11.8% and 7.0% respectively, slightly below, the 3-year and 4-year OS reported in the latest data-cut, which is 15.3% and 9.1%, respectively.

In the base case, a log-normal function was used to estimate OS of the taxane-based chemotherapy arm with an estimated median OS of 8.51 months. In the latest data-cut the median reported OS is 8.51 months which matches the extrapolated data. The 3-year and 4-year OS was estimated to 5.2% and 2.5% respectively, somewhat below the 3-year and 4-year OS reported in the latest data-cut, 8.7% and 7.4%, respectively.

To sum up, the suggested base case extrapolations based on the 18 month datacut somewhatunderestimated the OS when interpreted in light of the updated data cut, for both nivolumab and taxanes. The new information may motivate for the selection of standard parametric models such as lognormal or log logistic both for nivolumab and taxanes that captures the emerging plateau. It is worth noticing that the subsequent treatment percentages in the trial are similar, but that the patients in the taxanes arm more frequently received immunotherapy (6% of patients in the chemotherapy arm vs <1% in the nivolumab arm) (Kato et al. Suppl, appendix table S4)[1].

[redacted]

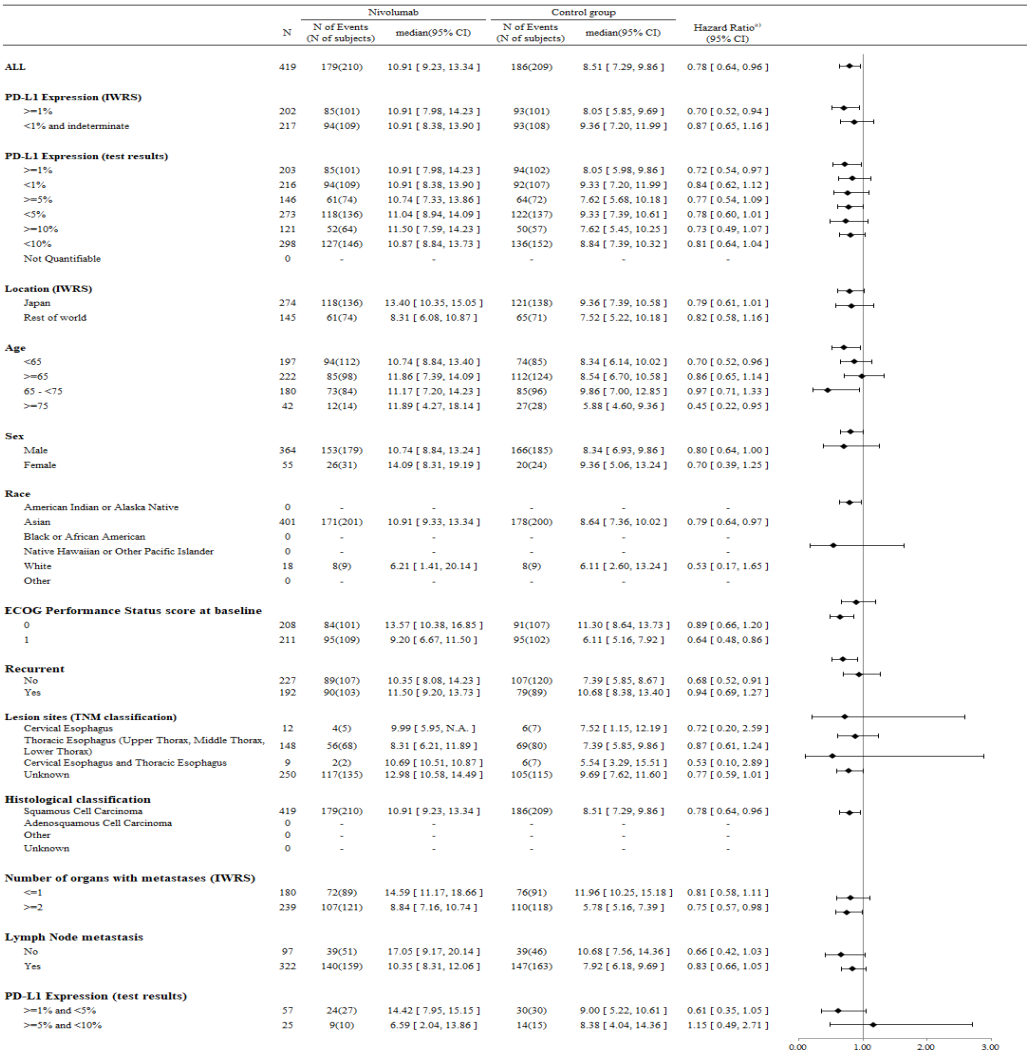
[1] Supplement to: Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019; published online Sept 30. http://dx.doi.org/10.1016/ S1470-2045(19)30626-6.

III.3 Overall survival in subgroups

Figure 32 and

Figure *33* below presents the forest plots of the subgroups.

Figure 32: Forest Plot of Subgroup Analyses for Overall Survival - All randomized patients in ATTRACTION-3



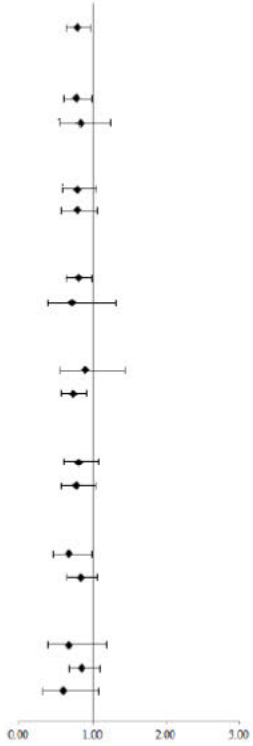
	N	Nivolumab: N of Events (N of subjects)	Nivolumab: median(95% CI)	Control group: N of Events (N of subjects)	Control group: median(95% CI)	Hazard Ratio[a)] (95% CI)
ALL	419	179(210)	10.91 [9.23, 13.34]	186(209)	8.51 [7.29, 9.86]	0.78 [0.64, 0.96]
PD-L1 Expression (IWRS)						
>=1%	202	85(101)	10.91 [7.98, 14.23]	93(101)	8.05 [5.85, 9.69]	0.70 [0.52, 0.94]
<1% and indeterminate	217	94(109)	10.91 [8.38, 13.90]	93(108)	9.36 [7.20, 11.99]	0.87 [0.65, 1.16]
PD-L1 Expression (test results)						
>=1%	203	85(101)	10.91 [7.98, 14.23]	94(102)	8.05 [5.98, 9.86]	0.72 [0.54, 0.97]
<1%	216	94(109)	10.91 [8.38, 13.90]	92(107)	9.33 [7.20, 11.99]	0.84 [0.62, 1.12]
>=5%	146	61(74)	10.74 [7.33, 13.86]	64(72)	7.62 [5.68, 10.18]	0.77 [0.54, 1.09]
<5%	273	118(136)	11.04 [8.94, 14.09]	122(137)	9.33 [7.39, 10.61]	0.78 [0.60, 1.01]
>=10%	121	52(64)	11.50 [7.59, 14.23]	50(57)	7.62 [5.45, 10.25]	0.73 [0.49, 1.07]
<10%	298	127(146)	10.87 [8.84, 13.73]	136(152)	8.84 [7.39, 10.32]	0.81 [0.64, 1.04]
Not Quantifiable	0	-	-	-	-	-
Location (IWRS)						
Japan	274	118(136)	13.40 [10.35, 15.05]	121(138)	9.36 [7.39, 10.58]	0.79 [0.61, 1.01]
Rest of world	145	61(74)	8.31 [6.08, 10.87]	65(71)	7.52 [5.22, 10.18]	0.82 [0.58, 1.16]
Age						
<65	197	94(112)	10.74 [8.84, 13.40]	74(85)	8.34 [6.14, 10.02]	0.70 [0.52, 0.96]
>=65	222	85(98)	11.86 [7.39, 14.09]	112(124)	8.54 [6.70, 10.58]	0.86 [0.65, 1.14]
65 - <75	180	73(84)	11.17 [7.20, 14.23]	85(96)	9.86 [7.00, 12.85]	0.97 [0.71, 1.33]
>=75	42	12(14)	11.89 [4.27, 18.14]	27(28)	5.88 [4.60, 9.36]	0.45 [0.22, 0.95]
Sex						
Male	364	153(179)	10.74 [8.84, 13.24]	166(185)	8.34 [6.93, 9.86]	0.80 [0.64, 1.00]
Female	55	26(31)	14.09 [8.31, 19.19]	20(24)	9.36 [5.06, 13.24]	0.70 [0.39, 1.25]
Race						
American Indian or Alaska Native	0	-	-	-	-	-
Asian	401	171(201)	10.91 [9.33, 13.34]	178(200)	8.64 [7.36, 10.02]	0.79 [0.64, 0.97]
Black or African American	0	-	-	-	-	-
Native Hawaiian or Other Pacific Islander	0	-	-	-	-	-
White	18	8(9)	6.21 [1.41, 20.14]	8(9)	6.11 [2.60, 13.24]	0.53 [0.17, 1.65]
Other	0	-	-	-	-	-
ECOG Performance Status score at baseline						
0	208	84(101)	13.57 [10.38, 16.85]	91(107)	11.30 [8.64, 13.73]	0.89 [0.66, 1.20]
1	211	95(109)	9.20 [6.67, 11.50]	95(102)	6.11 [5.16, 7.92]	0.64 [0.48, 0.86]
Recurrent						
No	227	89(107)	10.35 [8.08, 14.23]	107(120)	7.39 [5.85, 8.67]	0.68 [0.52, 0.91]
Yes	192	90(103)	11.50 [9.20, 13.73]	79(89)	10.68 [8.38, 13.40]	0.94 [0.69, 1.27]
Lesion sites (TNM classification)						
Cervical Esophagus	12	4(5)	9.99 [5.95, N.A.]	6(7)	7.52 [1.15, 12.19]	0.72 [0.20, 2.59]
Thoracic Esophagus (Upper Thorax, Middle Thorax, Lower Thorax)	148	56(68)	8.31 [6.21, 11.89]	69(80)	7.39 [5.85, 9.86]	0.87 [0.61, 1.24]
Cervical Esophagus and Thoracic Esophagus	9	2(2)	10.69 [10.51, 10.87]	6(7)	5.54 [3.29, 15.51]	0.53 [0.10, 2.89]
Unknown	250	117(135)	12.98 [10.58, 14.49]	105(115)	9.69 [7.62, 11.60]	0.77 [0.59, 1.01]
Histological classification						
Squamous Cell Carcinoma	419	179(210)	10.91 [9.23, 13.34]	186(209)	8.51 [7.29, 9.86]	0.78 [0.64, 0.96]
Adenosquamous Cell Carcinoma	0	-	-	-	-	-
Other	0	-	-	-	-	-
Unknown	0	-	-	-	-	-
Number of organs with metastases (IWRS)						
<=1	180	72(89)	14.59 [11.17, 18.66]	76(91)	11.96 [10.25, 15.18]	0.81 [0.58, 1.11]
>=2	239	107(121)	8.84 [7.16, 10.74]	110(118)	5.78 [5.16, 7.39]	0.75 [0.57, 0.98]
Lymph Node metastasis						
No	97	39(51)	17.05 [9.17, 20.14]	39(46)	10.68 [7.56, 14.36]	0.66 [0.42, 1.03]
Yes	322	140(159)	10.35 [8.31, 12.06]	147(163)	7.92 [6.18, 9.69]	0.83 [0.66, 1.05]
PD-L1 Expression (test results)						
>=1% and <5%	57	24(27)	14.42 [7.95, 15.15]	30(30)	9.00 [5.22, 10.61]	0.61 [0.35, 1.05]
>=5% and <10%	25	9(10)	6.59 [2.04, 13.86]	14(15)	8.38 [4.04, 14.36]	1.15 [0.49, 2.71]

Analysis Set : ITT

a) Hazard ratio was estimated by using unstratified Cox proportional hazards model.

Figure 33: Forest Plot of Subgroup Analyses for Overall Survival - All randomized patients in ATTRACTION-3

	N	Nivolumab: N of Events (N of subjects)	Nivolumab: median(95% CI)	Control group: N of Events (N of subjects)	Control group: median(95% CI)	Hazard Ratio[a] (95% CI)
ALL	419	179(210)	10.91 [9.23, 13.34]	186(209)	8.51 [7.29, 9.86]	0.78 [0.64, 0.96]
Liver metastasis						
No	308	130(153)	13.08 [10.74, 14.59]	138(155)	9.89 [8.51, 11.47]	0.77 [0.61, 0.98]
Yes	111	49(57)	5.65 [3.88, 9.17]	48(54)	5.13 [4.24, 6.70]	0.83 [0.55, 1.24]
Lung metastasis						
No	229	95(112)	10.58 [8.31, 13.40]	103(117)	8.34 [6.87, 9.89]	0.79 [0.60, 1.04]
Yes	190	84(98)	11.86 [8.38, 14.65]	83(92)	8.51 [6.14, 11.10]	0.78 [0.58, 1.06]
Bone metastasis						
No	371	159(187)	11.04 [9.92, 13.57]	163(184)	9.36 [7.52, 10.32]	0.80 [0.64, 0.99]
Yes	48	20(23)	7.33 [4.34, 14.09]	23(25)	5.13 [3.91, 7.92]	0.71 [0.39, 1.31]
Target lesion						
No	88	32(38)	11.56 [7.95, 20.30]	40(50)	11.99 [7.56, 16.16]	0.89 [0.56, 1.43]
Yes	331	147(172)	10.87 [8.84, 13.24]	146(159)	7.69 [6.70, 9.69]	0.73 [0.58, 0.92]
Past treatments for cancer (surgery)						
No	214	82(99)	10.22 [7.39, 12.22]	99(115)	7.52 [5.85, 9.69]	0.81 [0.60, 1.08]
Yes	205	97(111)	12.75 [9.23, 14.49]	87(94)	9.69 [7.56, 11.60]	0.77 [0.58, 1.04]
Past treatments for cancer (radiotherapy)						
No	124	47(57)	11.50 [9.23, 17.45]	59(67)	7.20 [5.75, 9.69]	0.67 [0.45, 0.98]
Yes	295	132(153)	10.74 [8.31, 13.24]	127(142)	9.33 [7.39, 10.68]	0.84 [0.65, 1.07]
History of smoking						
Never	62	25(30)	12.98 [6.67, 17.45]	26(32)	8.54 [5.22, 12.91]	0.68 [0.39, 1.18]
Former	306	135(159)	10.87 [9.17, 13.24]	131(147)	9.33 [7.56, 10.61]	0.86 [0.67, 1.09]
Current	51	19(21)	9.92 [6.08, 25.95]	29(30)	5.80 [4.07, 9.89]	0.59 [0.33, 1.08]



Analysis Set : ITT

a) Hazard ratio was estimated by using unstratified Cox proportional hazards model.

III.4 Objective Response Rate (ORR)

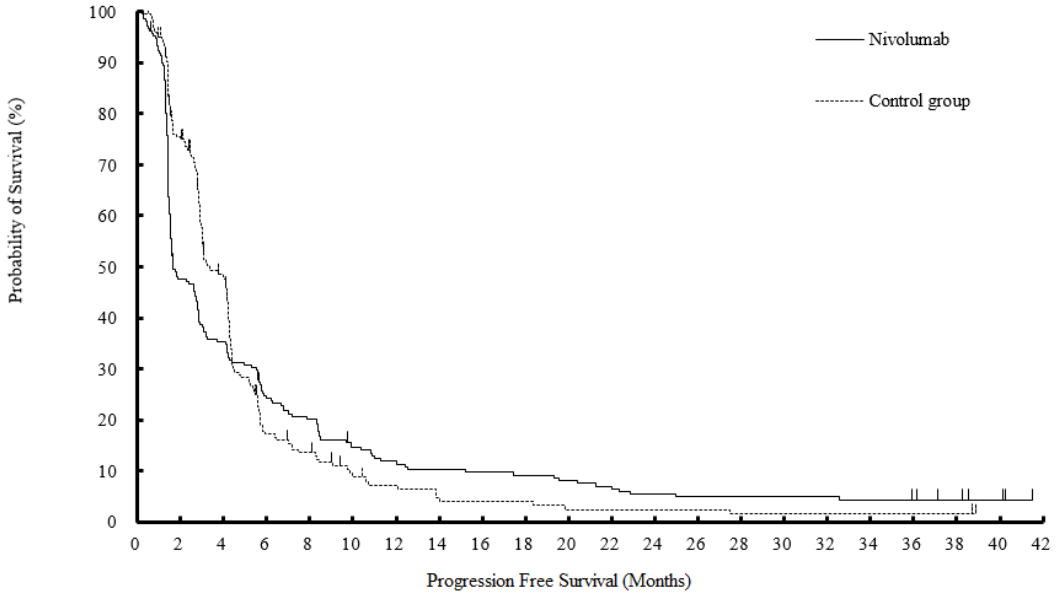
The updated ORR for the response evaluable set (RES) remain unchanged from what was previously reported at the primary analysis: 19.3% [redacted]) in the nivolumab group vs 21.5% [redacted]) in the control group.

III.5 Progression-free Survival (PFS)

The updated PFS results are consistent with those previously reported at the primary analysis. Updated median PFS was 1.7 months (95% CI: 1.5, 2.7) in the nivolumab group and 3.4 months (95% CI: 3.0, 4.2) in the control group, with the HR of 1.07 (95% CI: 0.87, 1.34) (Figure 34).

Not presented here, but the stability in the PFS profile is expected to translate into stability in Duration of Treatment (DoT), meaning that the incremental drug acquisition costs should not change much with new data.

Figure 34: Kaplan-Meier Plot of Progression-free Survival - All randomized patients in ATTRACTION-3



Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42
Nivolumab	210	96	71	48	40	27	22	19	18	17	15	12	10	9	9	9	9	8	7	5	3	0
Control group	209	147	89	29	22	12	9	5	5	5	3	3	3	3	2	2	2	2	2	2	0	0

Medicinrådet

Medicinrådets protokol for vurdering af nivolumab til behandling af planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi

Version 1.1

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, Medicinrådet undersøger, den behandling, Medicinrådet sammenligner med, og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil den ansøgende virksomhed få besked.

Dokumentoplysninger	
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Indholdsfortegnelse

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1. Begreber og forkortelser

5FU: 5-Fluoropyrimidin

CI: Konfidensinterval

CPS: *Combined Positive Score*

EMA: Det Europæiske Lægemiddelagentur (*European Medicines Agency*)

EORTC: *European Organisation for Research and Treatment of Cancer*

EPAR: European Public Assessment Report

ESMO: European Society for Medical Oncology

EUnetHTA: European Network for Health Technology Assessment

FDA: The Food and Drug Administration

FINOSE: Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger

GRADE: System til at vurdere evidens *(Grading of Recommendations, Assessment, Development and Evaluation)*

HTA: Medicinsk teknologivurdering (*Health Technology Assessment)*

IQWiG: The Institute for Quality and Efficiency in Healthcare

ITT: *Intention-to-treat*

I.V. Intravenøst

MKRF: Mindste klinisk relevante forskel

NCCN: National Comprehensive Cancer Network

NICE: The National Institute for Health and Care Excellence

OS: Overall survival

PD-1: Programmed cell death-1

PICO: Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*

S1: *Dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine (DIF) based on a biochemical modulation of 5-fluorouracil (5FU); S-1 contains tegafur (FF) and two types of enzyme inhibitor, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) in a molar ratio of 1:0.4:1.*

SMD: *Standardized Mean Difference*

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Bristol Myers Squibb (BMS), som ønsker, at Medicinrådet vurderer nivolumab til planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi. Medicinrådet modtog den foreløbige ansøgning den 27. oktober 2020. Nivolumab fik forhåndsgodkendelse (positive opinion) i EMA den 16. oktober 2020 og den endelige EC-godkendelse til indikationen den 23. november 2020.

2.1 Spiserørskræft

Kræft i eosophagus (spiserør), ventrikel (mavesæk) og gastroesophageal overgang (mavemund) hører samlet til den 8. hyppigste kræftform i Danmark. Medianalderen for diagnosetidspunktet er for alle tre kræftformer omkring 70 år. En stor del af patienterne kan ikke tilbydes helbredende behandling, da de på diagnosetidspunktet enten har spredt sygdom eller er i for dårlig almen tilstand til at gennemgå behandling.

I Danmark håndteres patientgruppen samlet via et multidisciplinært øsofagus- og ventrikelcancerteam på fire afdelinger (Rigshospitalet, Odense Universitetshospital, Aalborg Universitetshospital og Aarhus Universitetshospital).

Spiserørskræft forekommer dobbelt så hyppigt hos mænd som hos kvinder. Rygning og alkohol øger risikoen for kræft i spiserøret. Den hyppigste form for kræft i spiserøret er planocellulært karcinom, som overvejende er lokaliseret højt og/eller midt i spiserøret. Planocellulære karcinomer, der involverer mavemunden, betragtes også som spiserørskræft. En lille andel af karcinomerne i spiserøret udgøres af adenokarcinomer. Forekomsten af adenokarcinom i mavemunden er steget i de senere år og er nu hyppigere end både planocellulære karcinomer i spiserøret og adenokarcinomer i den distale del af mavesækken.

Symptomer

Det første symptom på kræft i spiserøret eller mavemunden er som regel synkebesvær og eventuelt opkastninger. Ofte ses ledsagende betydende vægttab og kvalme. Der kan være trykken eller en brændende fornemmelse bag brystbenet eller højt i maveregionen, og mange patienter føler sig unormalt trætte, eventuelt med lav blodprocent på grund af blødning fra kræftknuden. Smerter er et hyppigt symptom, der ofte kræver smertestillende medicin.

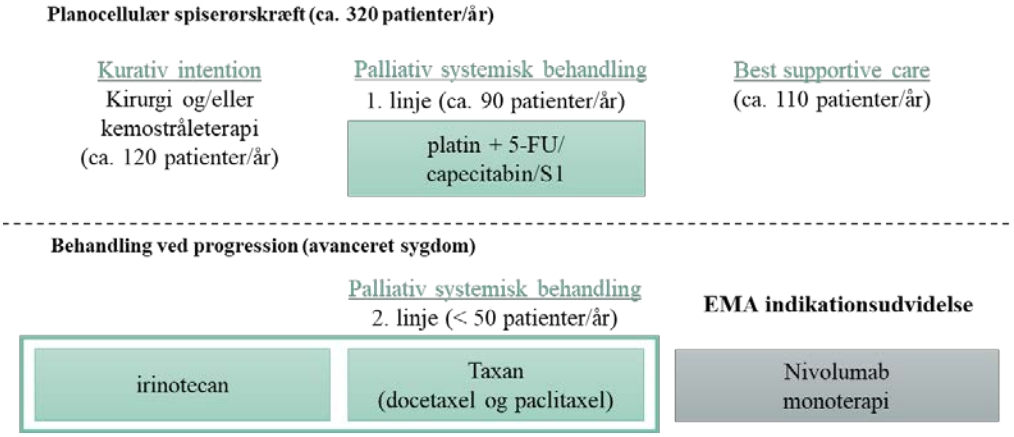
Forekomst

I 2019 blev der i Danmark registreret 1.167 nye tilfælde af patienter med kræft i spiserør, mavesæk eller mavemund ifølge Dansk EsophagoGastrisk Cancer Gruppe (DEGC) database [1]. Af disse var der 626 tilfælde af adenokarcinom i mavemunden, 221 tilfælde af adenokarcinom i mavesækken og 320 tilfælde af planocellulær spiserørskræft. Behandlingen med nivolumab vil være relevant for de af disse 320 patienter med planocellulær spiserørskræft, der er kandidater til 2. linjebehandling.

2.2 Nuværende behandling

De kliniske retningslinjer er beskrevet af Danske Multidisciplinære Cancer Grupper (DMCG) [1]. Behandlingsmulighederne er i al væsentlighed de samme for planocellulært karcinom og adenokarcinom. Datagrundlaget for behandling af planocelllulær spiserørskræft er dog sparsomt, og retningslinjerne baserer sig overvejende på undersøgelser af patienter med adenocarcinom i mavesæk og mavemund [1].

Patienter, der diagnosticeres med kræft i spiserøret, vil, afhængig af udbredelsen af sygdommen, kunne behandles med enten kurativ intention ved kirurgi og/eller kemostråleterapi eller palliativ kemoterapi, eventuelt palliativ stråleterapi, se figur 1. Patienter, der ikke er kandidater til disse behandlinger på grund af dårlig almentilstand, modtager symptomlindrende behandling (best supportive care).



Figur 1: Oversigt over behandling for patienter med spiserørskræft.

Af de 320 nydiagnosticerede tilfælde af planocellulær kræft i spiserøret anslår fagudvalget, at ca. 120 blev behandlet med kurativ intention. Heraf fik ca. 40 patienter foretaget kurativt kirurgisk indgreb, og ca. 80 patienter modtog behandling med kurativt intenderet kemoradioterapi. Ca. 110 patienter havde for dårlig almen tilstand til at være kandidater til kemoterapi og fik derfor best supportive care.

Samlet anslår fagudvalget derfor, at der årligt er ca. 90 patienter med planocellulær spiserørskræft, der påbegynder palliativ systemisk 1. linjebehandling, og færre end 50 patienter årligt, der påbegynder palliativ, systemisk 2. linjebehandling og dermed vil være kandidater til nivolumab.

1. linjebehandling

Der er sparsom evidens for effekten af palliativ systemisk behandling til planocellulær spiserørskræft [2]. Europæiske guidelines [3] foreslår derfor, at best supportive care eller monoterapi som 1. linje palliativ systemisk behandling bør overvejes. Der er dog generel konsensus om, at palliativ kemoterapi til tidligere ubehandlede patienter eller patienter med recidiverende uhelbredelig kræft i spiserøret består af en kombination af et platinholdigt kemoterapeutikum (cis-, oxali- eller carboplatin) og en antimetabolit (5-Fluoropyrimidin (5FU), capecitabine eller S1), eventuelt med tillæg af taxan.

Ved avanceret kræft i mavesækken er kemoterapi forbundet med en median overlevelsesgevinst på 7 måneder (fra 4 til ca. 11 måneder), sammenlignet med best supportive care [4]. Det er vist, at kombinationsbehandling er mere effektiv end enkeltstofbehandling [4]. Andelen af patienter, der overlever 1 år efter start på 1. linjebehandling er i Danmark 34 % [1]. Efter 1. linjebehandling er behandlingsmulighederne begrænsede. Uden behandling er den forventede progressionsfri overlevelse (PFS) mindre end 2 måneder og overlevelse (OS) 2-4 måneder [5–8].

2. linjebehandling

Indikationen, der ligger til grund for denne protokol, er patienter, som tidligere har modtaget kemoterapi og er kandidater til 2.-linje systemisk behandling af spiserørskræft. Som 2. linjebehandling anbefaler både europæiske (ESMO [6]) og amerikanske (NCCN [7]) guidelines et taxan eller irinotecan ved progression under eller efter 1. linjebehandling med platinholdigt kemoterapeutikum og antimetabolit.

I Danmark følges disse anbefalinger med brugen af de to taxaner, paclitaxel og docetaxel, og irinotecan. Disse lægemidler er ikke godkendt til behandling af kræft i spiserøret i 2. linje (off-label anvendelse). Dog er docetaxel godkendt i 1. linje til adenocarcinom i mavesæk/mavemund i kombination med platin/5FU. Desuden har alle tre lægemidler den tidligere anvendte danske indikation ”visse maligne lidelser” og har været anvendt i Danmark i en årrække.

Brugen af lægemidlerne understøttes af studier, som viser effekt i 2. linje for patienter med adenokarcinom i mavesæk eller mavemund. Tabel 1 viser en oversigt over resultater på OS og PFS i kliniske studier for de forskellige 2. linjebehandlinger til patienter med adenocarcinom i spiserør, mavemund og mavesæk. Ved behandling med et taxan er den mediane OS 5-6 måneder, i nyere, randomiserede studier dog 7-8 måneder [9–11]. Ved behandling med irinotecan er den mediane OS 4-6,5 måneder og median PFS 2,5 måneder. Etårsoverlevelse efter start på 2. linjebehandling er i randomiserede studier mellem 20-30 % [5–11]. Af ovenstående årsager er 2.-linje kemoterapi standard til patienter i god almen tilstand og normalt eller let nedsat funktionsniveau [5,7,8,11,12].

Paclitaxel, docetaxel og irinotecan anses som ligeværdige behandlinger til 2. linjebehandling af kræft i spiserøret. Da der er betydelig toksicitet ved behandling med irinotecan, opstartes behandling hermed ofte i en lavere dosis (80 % af anbefalet dosis), som øges, hvis patienten har et acceptabelt niveau af bivirkninger ved kontrol efter 1. cyklus af behandlingen. De typiske akutte bivirkninger til kemoterapi er træthed, der påvirker patienternes funktionsniveau. Kemoterapi medfører ofte kvalme, opkastninger, nedsat appetit, mundhulegener, mavesmerter eller diarré, hvilket yderligere øger risikoen for vægttab, som er et kardinalsymptom hos denne patientgruppe. Påvirkning af knoglemarven kan give nedsat immunforsvar, blodmangel og risiko for blødninger. Af mere kronisk karakter kan være risikoen for påvirkning af hørelse, nedsat nyrefunktion, nervebetændelse samt påvirkning af hjerte- og lungefunktion.

Tabel 1: PFS og OS ved 2. linjebehandling hos patienter med adenokarcinom i mavesæk eller mavemund

	Best supportive care [5–8]	**Thuss-Patience 2011** [7]	**Kang 2012** [8]		**Ford 2014** [5]	**Wilke 2014** [9]	**Thuss-Patience 2017** [10]	**Shitara 2018** [11]
		Irinotecan	Irinotecan	Taxan	Taxan	Taxan	Taxan	Taxan
Antal patienter		21	133		84	335	117	296
Median PFS, måneder	1-2	2,5				2,9	2,9	4,1
median OS, måneder	2-4	4,0	6,5	5,2	5,2	7,4	8,6	8,3
OS rate	23-32 %* v. 6 mdr. 12 % v. 12 mdr.	-	-	-	39 % v. 6 mdr.	30 % v. 12 mdr.	-	27 % v. 12 mdr.

* OS-raterne v. 6 måneder er kun rapporteret i to af studierne: Ford 2014 [5] og Fuchs 2013 [6]. Ford 2014 er et relativt lille studie med højere andel af patienter med kræft i spiserør/mavemund (84 patienter sv.t. 54 %) end i Fuchs 2013 (238 patienter sv.t. 25 %). Der er generelt bedre prognose ved kræft i mavesækken sammenlignet med kræft i spiserør/mavemund, hvilket forklarer forskellen i overlevelsesraten ved 6 måneder (henholdsvis 23 og 32 %), da studierne omhandler forskellige populationer.

2.3 Nivolumab

Nivolumab, som markedsføres under handelsnavnet Opdivo®, er et monoklonalt antistof, som bindes til PD-1-receptorerne og derigennem øger immunsystemets antineoplastiske respons. Nivolumab tilhører den nye behandlingsmodalitet indenfor immunterapi, som også kaldes ”check-point inhibition”. Baggrunden for denne behandlingstype er, at tumorceller gennem binding af overfladeproteinet PD-L1 til en receptor på immunforsvarets celler, kaldet *Programmed Cell Death Protein 1 (PD-1),* kan nedregulere/hæmme immunforsvarets angreb [13]. Specifikke antistoffer, som blokerer PD-1 eller PD-L1, kan derfor reaktivere immunforsvarets cytotoksiske T-cellers mulighed for at angribe tumorceller. Udtryk af PD-L1 kan vurderes ved immunohistokemisk undersøgelse på histologisk materiale, hvor det opgøres, hvor mange celler i tumor, der udtrykker PD-L1 i forhold til det samlede antal tumorceller. Hvis udtrykket vurderes på tumorceller, kaldes undersøgelsen Tumor Proportion Score (TPS). Hvis udtrykket vurderes på både tumorceller og associerede immunceller, kaldes undersøgelsen Combined Positive Score (CPS).

Nivolumab har indikation til en række forskellige kræftformer, hvoraf nogle har været vurderet af Medicinrådet (angivet i kursiv):

- Inoperabel eller metastatisk melanom som monoterapi eller i kombination med ipilimumab.

- Efter komplet resektion af melanom med lymfeknudeinvolvering eller metastase(r) som monoterapi (adjuverende behandling). *Anbefalet af Medicinrådet til patienter med komplet reseceret modermærkekræft stadium III og IV*.
- Lokalt fremskreden eller metastatisk planocellulært ikke-småcellet lungecancer efter tidligere kemoterapi.
- Fremskredent renalcellekarcinom (nyrekræft) som 1. linjebehandling i kombination med ipilimumab eller som monoterapi efter tidligere kemoterapi. *Anbefalet af Medicinrådet i kombination med ipilimumab til patienter med lokalavanceret inoperabel eller metastaserende nyrekræft (mRCC) i intermediær eller dårlig prognosegruppe, der ikke tidligere har modtaget behandling.*
- Recidiverende eller refraktært klassisk Hodgkins lymfom efter autolog stamcelletransplantation og behandling med brentuximab vedotin.
- Recidiverende eller metastatisk planocellulær hoved-hals-cancer under eller efter platinbaseret kemoterapi.
- Lokalt fremskredent inoperabelt eller metastatisk urothelkarcinom (kræft i blære og urinveje) efter tidligere platinbaseret kemoterapi. *Anbefalet af Medicinrådet til patienter i performancestatus 0-1 med sygdomsprogression efter platinbaseret kemoterapi.*

Den aktuelle indikationsudvidelse gælder planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi. Nivolumab administreres intravenøst (i.v.) og doseres med 240 mg hver 2. uge. Behandlingen fortsættes indtil sygdomsprogression eller uacceptable bivirkninger.

Nivolumab har ikke status af Orphan drug til behandling af planocellulært karcinom i spiserøret og har ikke været igennem Accelerated assessment i EMA i forbindelse med denne indikation.

Check-point inhibitorer

Behandling med check-point inhibitorer er undersøgt i flere studier til patienter med planocellulær spiserørskræft. I et fase II enkeltarm-studie med pembrolizumab i 3. eller senere linje viste subgruppeanalyser lovende responsrater hos patienter med planocellulært carcinom og hos patienter med PD-L1-positive tumorer [14]. I et fase III-studie blev 628 patienter randomiseret til pembrolizumab eller standard kemoterapi (taxan eller irinotecan) i 2. linje [15]. Den største effekt sås i gruppen af patienter med planocellulært carcinom og CPS > 10, svarende til højt PD-L1 udtryk. Her blev overlevelsen forlænget fra 6,7 til 10,3 måneder (HR 0,64 [95 % CI 0,46; 0,90]) samt i gruppen af asiatiske patienter uanset PD-L1-udtryk (HR 0,66 [95 % CI 0,50; 0,87]) [15]. Tilsvarende viser de foreløbige data fra et randomiseret fase III-studie i 1.linje til patienter med spiserørskræft især overlevelsesgevinst i gruppen af patienter med planocellulært karcinom og et højt PD-L1-udtryk (HR 0,57 [95 % CI 0,43; 0,75] samt i en asiatisk subpopulation (HR 0,64 [95 % CI 0,51; 0,81]) [16].

Pembrolizumab er godkendt af FDA til behandling af planocellulært karcinom i spiserøret. I forbindelse med den europæiske ansøgning fandt European Medicines Agency ikke tilstrækkelig dokumentation for overlevelsesgevinst i en europæisk

population, idet resultaterne var drevet af en asiatisk subpopulation. Herefter trak firmaet (Merck) ansøgningen tilbage [17].

3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel, Medicinrådet undersøger (interventionen), af den behandling, Medicinrådet sammenligner med (komparator(er)), og af effektmålene.

3.1 Klinisk spørgsmål 1

Hvilken værdi har nivolumab sammenlignet med paclitaxel, docetaxel eller irinotecan for patienter med planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi?

Population

Voksne patienter med planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi.

Intervention

Nivolumab 240 mg i.v. hver 2. uge indtil sygdomsprogression eller uacceptable bivirkninger.

Komparator

Følgende lægemidler betragtes som ligeværdige, derfor kan alle lægemidlerne anvendes som komparator, og det er tilstrækkeligt med et af lægemidlerne som komparator. Alle lægemidlerne gives til progression eller uacceptable bivirkninger.

Paclitaxel: 80 mg/m^2 i.v. på dag 1, 8 og 15 hver 4. uge

Docetaxel: 75 mg/m^2 i.v. hver 3. uge

Irinotecan: 180 mg/m^2 i.v. hver 2. uge

Effektmål

De valgte effektmål fremgår af tabel 2.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 2. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). Den mindste klinisk relevante forskel er den forskel mellem intervention og komparator, der som minimum skal opnås for at

effektforskellen vurderes at være klinisk relevant. I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

Tabel 2: Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Samlet overlevelse (overall survival, OS)	*Kritisk*	Dødelighed	Median-overlevelse	3 måneder
			Andel der fortsat er i live efter 12 måneder	5 procentpoint
Bivirkninger	*Kritisk*	Livskvalitet samt alvorlige symptomer og bivirkninger	Andel af patienter der oplever grad 3-5 bivirkninger	10 procentpoint
			Kvalitativ gennemgang af bivirkninger	-
Livskvalitet	*Vigtigt*	Livskvalitet samt alvorlige symptomer og bivirkninger	EORTC-QOL-C30	10 point
			EORTC-QOL-OES18	10 point
Progressionsfri overlevelse (PFS)	*Vigtigt*	Livskvalitet samt alvorlige symptomer og bivirkninger	Median PFS	3 måneder
			Andel der fortsat er i PFS efter 12 måneder	5 procentpoint

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
** Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.

3.2.1 Kritiske effektmål

Samlet overlevelse

Forbedret samlet overlevelse med mindst mulig toksicitet er det optimale mål for kræftbehandling. Samlet overlevelse defineres som tiden fra randomisering eller behandlingsstart til død uanset årsag. Medicinrådet betragter overlevelse som et kritisk effektmål, da spiserørskræft er en livstruende sygdom. Overlevelse ønskes opgjort, i prioriteret rækkefølge, som både mediane antal måneder samt i overlevelsesrate efter 12 måneder. Begge ønskes opgjort, fordi den mediane overlevelse kan være øget, uden at der er øget overlevelse efter 12 måneder. Det er væsentligt at have begge informationer for at have et fyldestgørende grundlag for vurderingen.

Den nuværende standardbehandling i 2. linje giver en median overlevelse på 5-8 måneder og en etårsoverlevelse på 20 - 30 %. Derfor vurderer fagudvalget, at den

mindste klinisk relevante forskel sammenlignet med komparator er 3 måneders median overlevelse og 5 procentpoint i overlevelsesraten efter 12 måneder.

Bivirkninger

En bivirkning er en uønsket hændelse, som er vurderet at være relateret til lægemidlet. Bivirkninger ved behandling af spiserørskræft i 2. linje kan være meget alvorlige og kan i nogle tilfælde medføre døden. Behandlingen er ikke kurativ, og det er derfor afgørende for valg af behandling, at patienterne ikke er påvirket af bivirkninger i deres resterende levetid. Derfor er bivirkninger valgt som et kritisk effektmål.

Medicinrådet ønsker en fyldestgørende oversigt over bivirkninger med det formål at foretage en kvalitativ gennemgang af disse. Herunder ønskes en opgørelse af andel af patienter, der oplever grad 3-4 bivirkninger, samt en sammenlignende analyse af forekomsten ved behandlingen med henholdsvis nivolumab og komparator. Baseret på studier omhandlende komparatorerne er andelen af patienter, der oplever grad 3-4 bivirkninger, op til 30 %. Fagudvalget vurderer, at den mindste klinisk relevante forskel er 10 procentpoint.

Medicinrådet vil lægge vægt på den kvalitative gennemgang af bivirkninger, herunder alvorlighed og håndterbarhed, idet der er stor forskel på bivirkningsprofilen af henholdsvis nivolumab og komparator, og det kan være vanskeligt at sammenligne betydningen af de forskellige bivirkninger. Såfremt der ikke findes opgørelser over bivirkninger, kan Medicinrådet acceptere opgørelser over uønskede hændelser.

3.2.2 Vigtige effektmål

Livskvalitet

Påvirkning af livskvaliteten som følge af behandling og grundsygdom betyder meget for den enkelte patient. Den potentielle negative effekt på livskvaliteten vil ofte være afgørende for valg af behandling, særligt i en population med kort restlevetid. Det er vanskeligt at måle effekten på livskvalitet af en behandling i 2. linje, idet behandlingen forventes at medføre betydelige bivirkninger og desuden gives til progression. Dermed er patientens livskvalitet sandsynligvis påvirket af enten bivirkninger eller af sygdomsprogression uanset hvilket tidspunkt, det opgøres på. Medicinrådet ønsker livskvalitet opgjort som et mål for bivirkningsbyrden under behandlingen. Derfor er livskvalitet valgt som et vigtigt effektmål.

I sammenligningen mellem en immunterapi som nivolumab og kemoterapi vil der være forskel på, hvornår effekten indsætter, hvilket påvirker målingen af livskvalitet tidligt i behandlingsforløbet. På grund af patienternes korte forventede levetid bør der derfor heller ikke gå for lang tid, før effekten på livskvalitet måles. Derfor ønskes livskvalitet opgjort som ændring fra baseline til 1 måned efter afsluttet behandling. Livskvalitet ønskes opgjort ved to spørgeskemaer: EORTC-QOL-C30, der giver information om overordnet helbredsrelateret livskvalitet og EORTC-QOL-OES18, der omhandler livskvalitet relateret til symptomer og gener ved spiserørskræft.

EORTC QLQ-C30
EORTC QLQ-C30 er udviklet til at måle livskvaliteten hos patienter med kræft. EORTC QLQ-C30 er et spørgeskema med 30 spørgsmål og i alt 15 domæner, herunder fem funktionsskalaer, tre symptomskalaer, seks enkeltstående symptomer/omstændigheder og en global livskvalitetsscore [18]. Der anvendes en scoringsskala fra 0-100 (en høj score angiver et højt funktionsniveau). Resultatet af to af de 30 spørgsmål udgør den globale livskvalitetscore. En ændring i 10 point fra baseline anses for klinisk relevant for patienter med fremskreden kræft [19][20][21]. Den mindste klinisk relevante forskel er derfor sat til 10 points forskel for nivolumab sammenlignet med komparator.

EORTC QLQ-OES18
EORTC QLQ-OES18 er udviklet som et supplement til EORTC QLQ-C30. Spørgeskemaet indeholder 18 spørgsmål omhandlende spisefunktion samt relaterede smerter. Der anvendes en scoringsskala fra 0-100 (en høj score angiver et højt niveau af symptomer). Da dette spørgeskema er et supplement til EORTC QLQ-C30, og der anvendes samme scoringsskala, defineres den mindste klinisk relevante forskel også som 10 point for dette spørgeskema.

Hvis der ikke findes data opgjort ved et af de ovennævnte spørgeskemaer, kan fagudvalget acceptere data fra et andet spørgeskema, såfremt ansøger kan begrunde relevansen og den mindste klinisk relevante forskel heraf.

Progressionsfri overlevelse

Medicinrådet anser PFS som et vigtigt effektmål til vurdering af den periode hvor patienterne har det bedre efter de har modtaget 2. linjebehandling. PFS kan således give en anden information end overlevelse. Den tid, der går uden sygdomsprogression, vil typisk være præget af stabilitet eller bedring i symptomerne, herunder færre smerter og gener og bedre spisefunktion, hvilket har stor indflydelse på patientens dagligdag og livskvalitet. PFS afspejler således byrden af symptomer samt varigheden af denne periode og kan dermed anses som et surrogatmål for respons. PFS inddrager dog også tidsaspektet.

PFS ønskes opgjort som median i antal måneder. Fagudvalget anslår, at median PFS med nuværende standardbehandling er mindre end 4 måneder. Derfor vurderer fagudvalget, at den mindste klinisk relevante forskel sammenlignet med komparator er 3 måneders median PFS.

4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMAs) European Public Assessment Reports (EPAR). Herudover kan data fra Food and Drug Administration (FDA) og internationalt anerkendte HTA-agenturer (fx NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Hvis disse data er tilstrækkelige til at kunne vurdere lægemidlet, vil

Medicinrådet som hovedregel ikke anvende andre data[1]. Data skal derudover stemme overens med protokollens beskrivelser. Hvis ansøger har kendskab til upublicerede data, der kan belyse eventuelle angivne mangler, kan de indgå/indsendes, jf. Medicinrådets kriteriepapir.

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der findes et studie, hvor nivolumab er sammenlignet direkte med investigators valg af kemoterapi (paclitaxel eller docetaxel). Der er tale om følgende studie:

- ATTRACTION-3 (NCT02569242)

Det er tilstrækkeligt datagrundlag til at besvare de(t) kliniske spørgsmål. Ansøger skal derfor ikke søge efter yderligere data, men skal konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator(er).

5. Den endelige ansøgning

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO (population, intervention, komparator og effektmål) mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.

[1] For yderligere detaljer se Medicinrådets kriteriepapir om anvendelse af upublicerede data

- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (fx intention to treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier, og vurdér, hvorvidt resultaterne er sammenlignelige.

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

Sundhedsøkonomiske analyser

En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundhedsøkonomisk model og et teknisk dokument, hvor modellen og de antagelser, der er bygget ind i modellen, beskrives, og hvor ansøgers sundhedsøkonomiske analyse fremgår. Ved dynamisk forstås, at en variabel kun skal ændres ét sted for at være gennemgående for hele modellen. Anvend eventuelt Medicinrådets metodevejledning og tjekliste til sundhedsøkonomiske modeller til at teste modellens dynamik, og at modellen overholder formelle krav.

En sundhedsøkonomisk analyse er ikke et resultat, men er en bred analyse af modellens dynamik, hvilke parametre der har indflydelse på resultaterne, samt hvorfor og hvordan

disse parametre indgår. Derfor skal det tekniske dokument som minimum indeholde følgende:

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.
- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, fx behandlingslængde eller lægemiddelomkostninger.
- Ekstrapoleret data skal beskrives.
- Udfør følsomhedsanalyser, som belyser, hvilke parametre i modellen der har størst indflydelse på resultatet.
- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.

6. Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad man kan have tiltro til den evidens, Medicinrådet baserer vurderingen af lægemidlets værdi på.

7. Andre overvejelser

Det kliniske spørgsmål baserer sig på EMAs indikation, som er uafhængig af PDL1-ekspression. Fagudvalget ønsker dog data for, hvorvidt behandlingseffekten af nivolumab er afhængig af tumors ekspression af PD-L1 vurderet ved immunhistokemisk undersøgelse, herunder hvorvidt PD-L1-status kan relateres til de valgte effektmål. Fagudvalget ønsker i denne forbindelse oplyst, hvilket set-up som er anvendt for at teste ekspression af PD-L1, herunder platform, antistof (clon) og scoringsprincipper.

Fagudvalget har bemærket, at studiepopulationen i ATTRACTION-3 har en meget lille andel af vestlige patienter og en meget høj andel af asiatiske patienter. Derfor ønsker fagudvalget, at ansøger redegør for overførbarheden til den danske patientpopulation, herunder hvorvidt der er forskel på effektstørrelsen mellem etniske grupper.

Medicinrådet ønsker at forholde sig til, om der som alternativ til 240 mg nivolumab hver 2. uge kan anvendes 480 mg hver 4. uge eller en vægtbaseret dosis (f.eks. 3 mg/kg hver 2. uge eller 6 mg/kg hver 4. uge). Derfor bedes ansøger fremsende eventuelle data, som kan understøtte brugen af fast versus vægtjusteret dosis. Hvis der ikke findes erfaringer/data med de forskellige doseringer hos patienter med spiserørskræft, ønsker Medicinrådet, at ansøger fremsender data fra andre indikationer. Ansøger bedes beskrive, om de forventer, at der er forskel på at give fast eller vægtjusteret dosis for effektmålene i denne protokol samt eventuelle årsager hertil.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning fra Medicinrådet.

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kræft i mavesæk og mavemund

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Lene Bæksgaard Jensen *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Mette Karen Nytoft Yilmaz *Overlæge*	Region Nordjylland
Marianne Nordsmark *Overlæge*	Region Midtjylland
Helle Anita Jensen *Overlæge*	Region Syddanmark
Kenneth Hofland *Overlæge*	Region Sjælland
Jon Kroll Bjerregaard *Overlæge*	Region Hovedstaden
Natalia Marta Luczak *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Zandra Ennis *Læge*	Dansk Selskab for Klinisk Farmakologi
Mikkel Eld *Overlæge*	Dansk Patologiselskab
En patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

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11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	6. januar 2021	Godkendt af Medicinrådet
1.1	14. januar 2021	Dosering er ændret fra: *Nivolumab 240 mg i.v. hver 2. uge indtil sygdomsprogression, uacceptable bivirkninger eller op til 24 måneder hos patienter uden sygdomsprogression.* til: *Nivolumab 240 mg i.v. hver 2. uge indtil sygdomsprogression eller uacceptable bivirkninger.*