Cost-effectiveness and budget impact of nivolumab plus ipilimumab versus platinum plus pemetrexed (with and without bevacizumab) in patients with unresectable malignant pleural mesothelioma in Switzerland

PharmacoEconomics

Michaela Carla Barbier[1], Alicia Fengler[2], Esther Pardo[2], Arjun Bhadhuri[1], Niklaus Meier[1], Oliver Gautschi[2,3]

[1] Institute of Pharmaceutical Medicine (ECPM) / Health Economics Facility, Department of Public Health, University of Basel, Switzerland

[2] Medical Oncology, Cantonal Hospital of Lucerne, Lucerne, Switzerland

[3] University of Bern, Bern, Switzerland

Corresponding Author:

Dr. Michaela Carla Barbier, Institute of Pharmaceutical Medicine (ECPM), University of Basel, Klingelbergstrasse 61, CH-4056 Basel, Switzerland. E-mail: michaela.barbier@unibas.ch

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Electronic Supplementary Appendix

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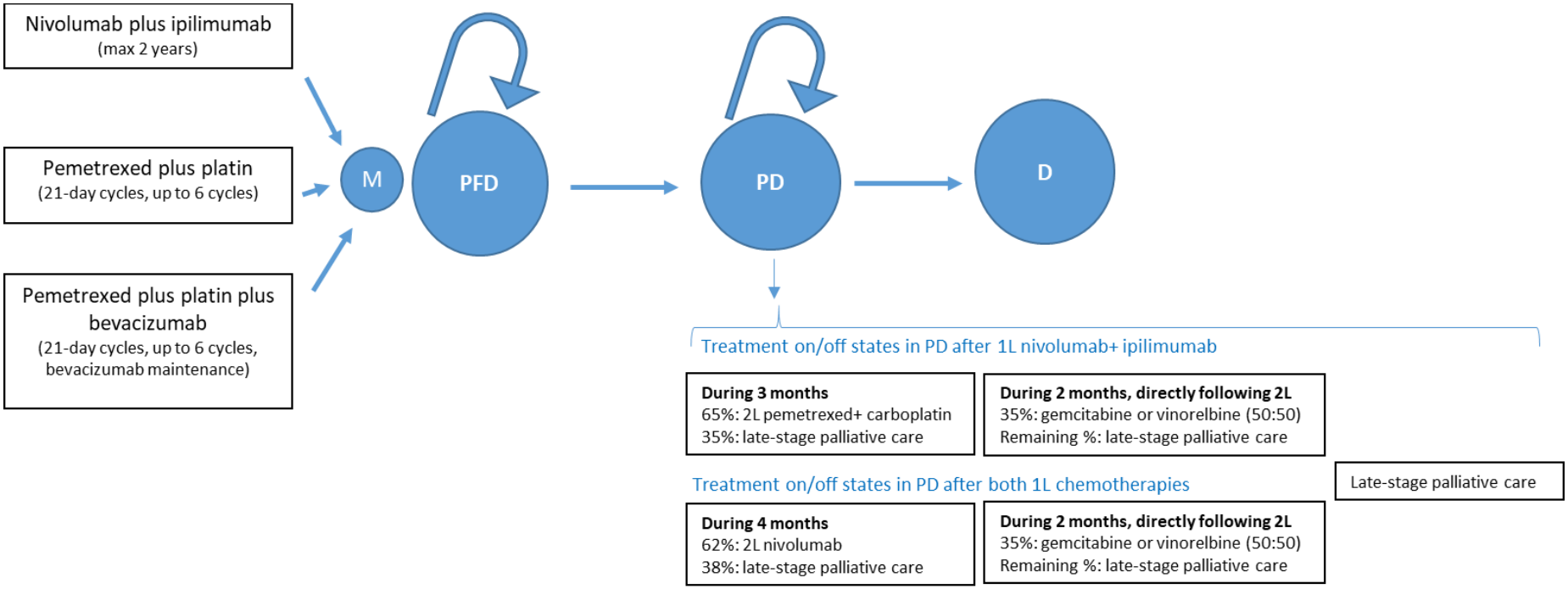
1 Model structure



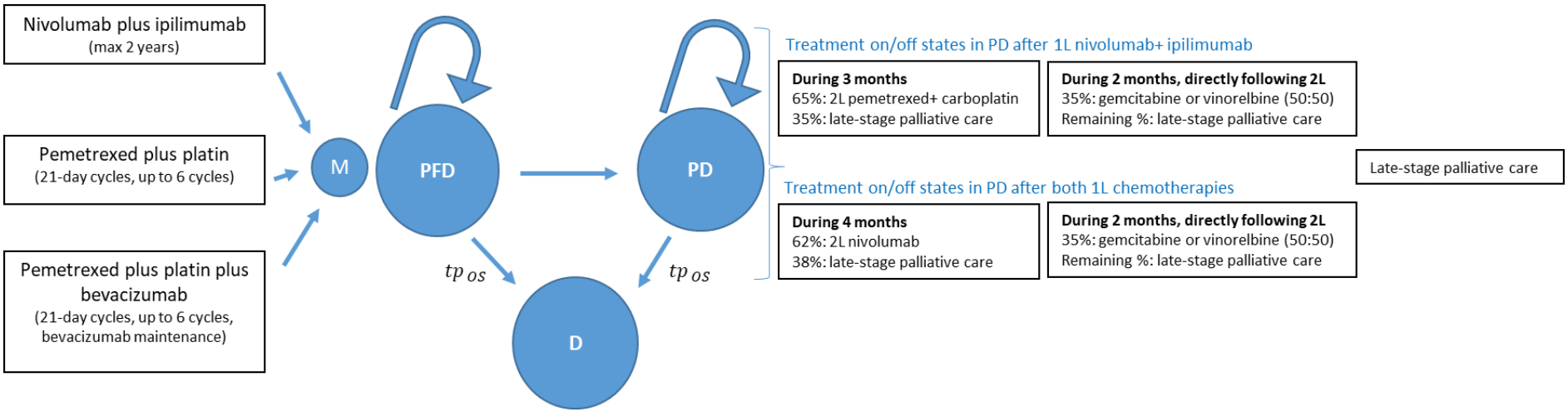
Supplementary Fig. 1 Base Case Markov State Transition Model

D death, *M* Markov node, *P* Probability, *PD* progressed disease, *PFD* Progression-free disease

Complementary note: In the base case, all patients were assumed to progress and no patient was assumed to die before progression, so the conditional probability P(death/PFD) was 0.

In the well-known conditional probability formula, P(death) simplifies in this case to P(death/PD)*P(PD), and hence P(death/PD) = $\frac{P(death)}{\mathrm{P(PD)}}$.

The transition probability of the event of interest $tp\,(t, t+1) = 1 - \frac{S(t+1)}{S(t)}$ [1] (with S(t) = P(T>t) at timepoint t) from PD to D cannot be calculated exactly only based on the overall survival (OS) and the progression-free survival (PFS) curve. Published OS curves are a weighted average of OS curves of the probability of death for both healthy and sick persons [2]. We approximated the transition probability from PD to D with the OS curve adjusted by the proportion of progressed patients among those still alive $(1 - (S_{PFS}(t) / S_{OS}(t)))$. In case parts of the fitted and extrapolated PFS curve were equal or above the OS curve, we replaced the probability of being progression-free at timepoints (t) with the probability of being alive at timepoints t+1. With this proceeding we kept the PFS curve below the OS curve.



Supplementary Fig. 2 First scenario Analysis Markov State Transition Model

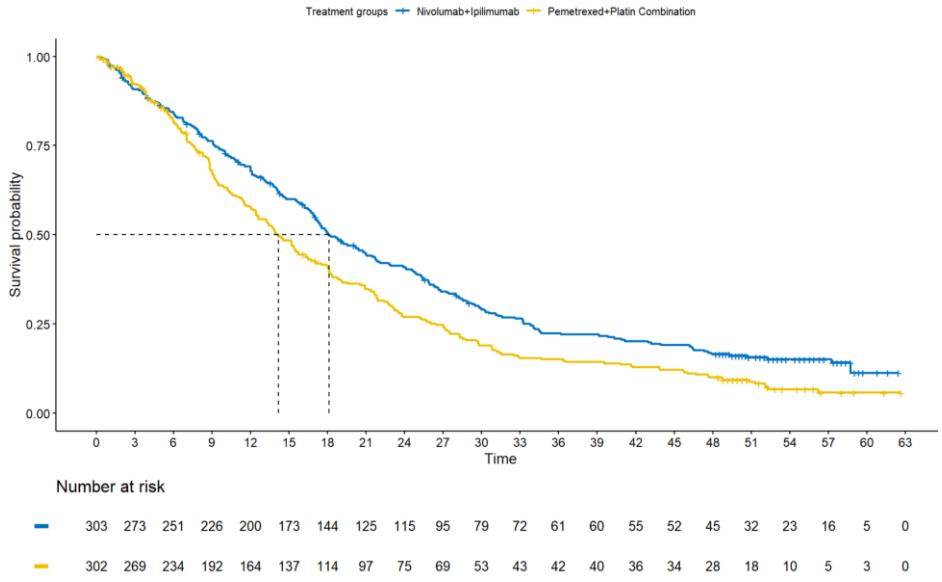
D death, *M* Markov node, *PD* progressed disease, *PFD* Progression-free disease, *tp* transition probability

Complementary notes:

In this first scenario, the probability of dying from the PFD state is assumed to be the same as from the PD state.

In case the PFS curve is equal or above the OS curve, no patient progresses and the transition probability from PFD to PD is set to 0.

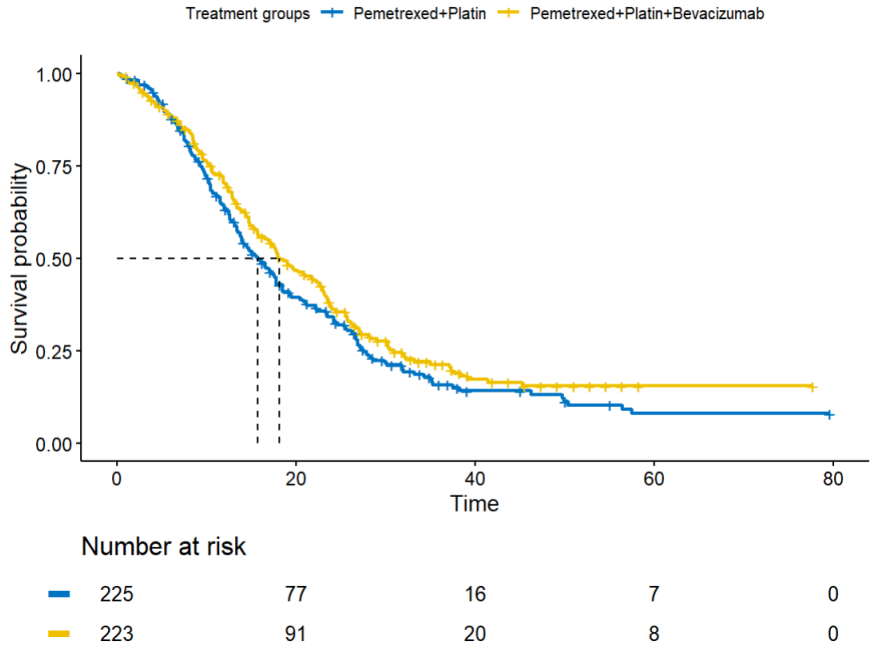
2 Kaplan-Meier OS and PFS re-construction



Supplementary Fig. 3 Re-construction of OS KM curves in CM-743 (4-year data)

	n	events	median	0.95LCL	0.95UCL	
Arm=Nivo+ipi	303	246	18.1	17.0	21.5	(median OS of original graph: 18.1[16.8, 21.0])
Arm=Pem+platin	302	263	14.2	12.6	16.5	(median OS of original graph: 14.1[12.4,16.3])

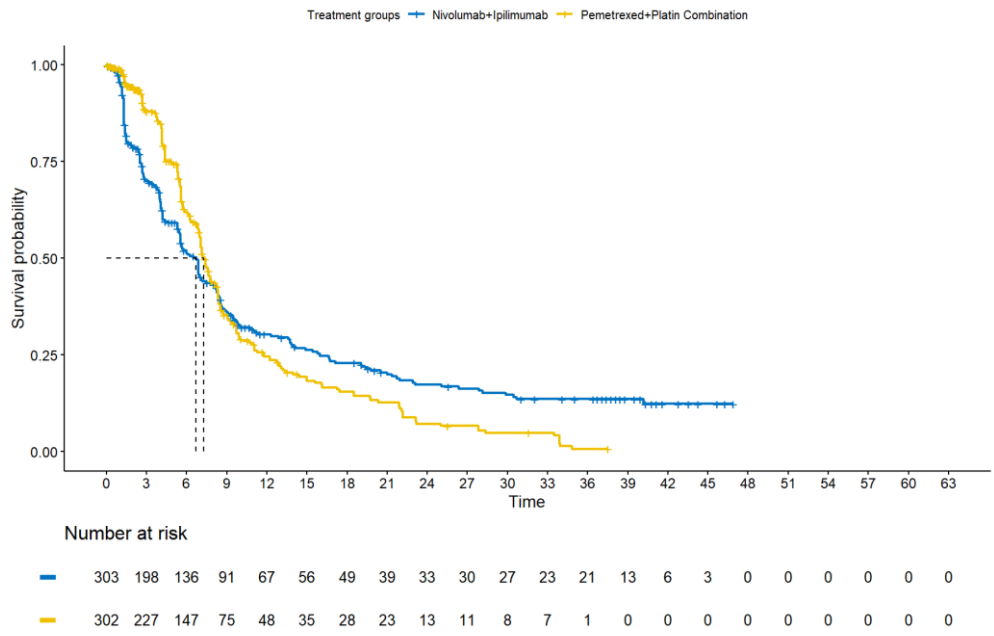
Unadjusted hazard ratio: 0.74 [0.62, 0.88] (adjusted HR of original graph: 0.73[0.61,0.87])



Supplementary Fig. 4 Re-construction of OS KM curves in MAPS

	n	events	median	0.95LCL	0.95UCL	
Arm=Pem+platin	225	178	15.8	13.8	18.5	(median OS of original graph: 16.1 [14.0, 17.9])
Arm=Triple arm	223	164	18.2	15.7	22.6	(median OS of original graph: 18.8 [15.9, 22.6])

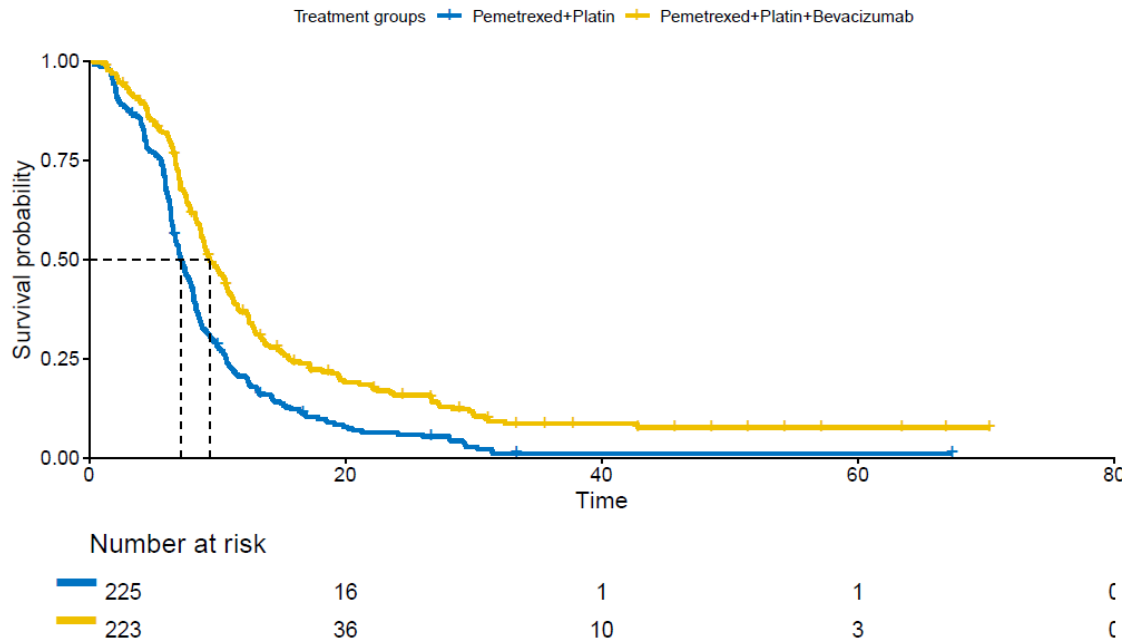
Unadjusted hazard ratio: 0.84 [0.68,1.04] (adjusted HR of original graph: 0.77 [0.62,0.95]; adjustment for minimisation variables)



Supplementary Fig. 5 Re-construction of PFS KM curves in CM-743 **(3-year data)**

	n	events	median	0.95LCL	0.95UCL	
Arm=Nivo+ipi	303	227	6.70	5.53	7.44	(median PFS 4-year original data: 6.8)
Arm=Pem+plating	302	221	7.28	6.94	8.21	(median PFS 4-year original data: 7.2)

Unadjusted hazard ratio: 0.94 [0.78, 1.13] (adjusted HR of 4-year original data: 0.93[0.77-1.13])
No 4-year PFS curve is currently published [3]. Only statistics were available as presented in the previous lines.



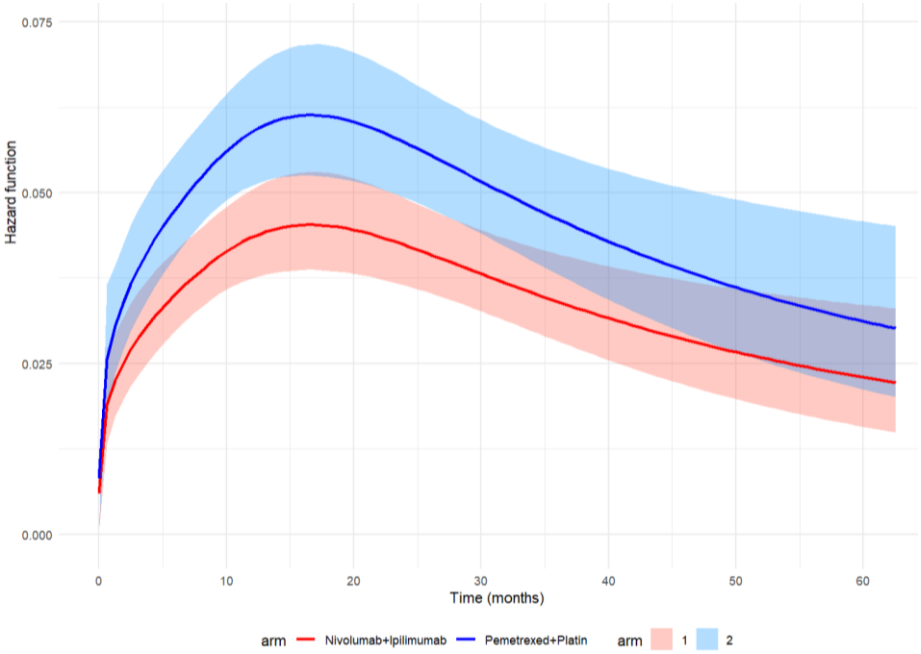
Supplementary Fig. 6 Re-construction of PFS KM curves in MAPS

	n	events	median	0.95LCL	0.95UCL	
Arm= Pem+Platin	225	217	7.18	6.72	8.05	(median PFS original data: 7.3 [6.7, 8.0])
Arm= Triple arm	223	192	9.40	8.76	10.77	(median PFS original data: 9.2 [8.5, 10.5])

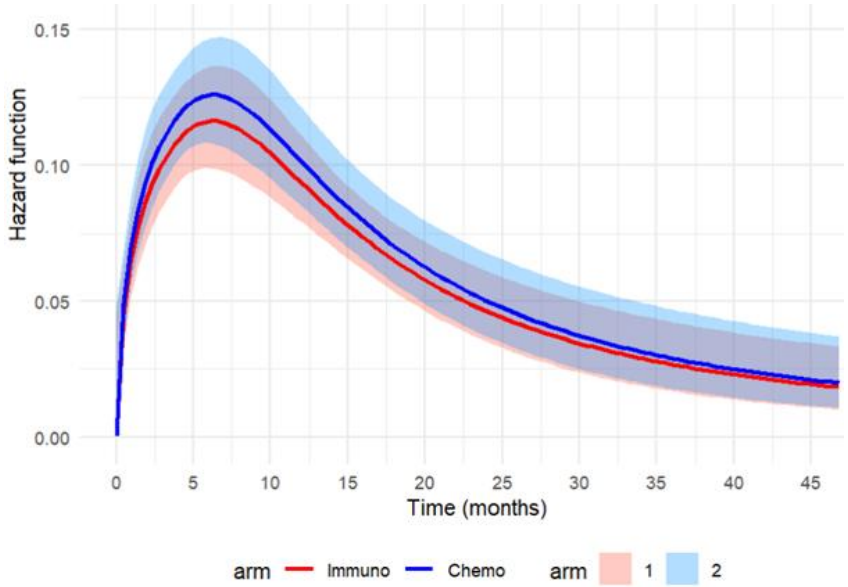
Unadjusted HR: 0.60 [0.49, 0.73] (adjusted HR of original graph: 0.61 [0.50,0.75]; adjustment for minimisation variables)

3 Survival curve fitting

3.1 Hazard functions CM-743



Supplementary Fig. 7 Smoothed hazard functions for CM-743 digitized overall survival data



Supplementary Fig. 8 Smoothed hazard functions for CM-743 digitized progression-free survival data

3.2 Suvival curve fitting OS CM-743

In a first step we verified that the hazard functions of possible distributions/functions are first increasing and then decreasing. Out of the ones with a hazard function in line with our criteria, we then selected distributions/functions that had lowest possible AIC and BIC and a long-term estimation at 10 years at 2% for nivolumab+ipilimumab and 0% for pemetrexed+platin. This was based on our clinical expection and in line with a UK expert group expecting 5-year survival at 5%, 7.5-year survival at 2%, and 10-year survival at 0-2% with current treatments in the UK [4].

3.2.1 Assessing goodness-of-fit of parametric and spline survival models within and outside the trial period

Supplementary Table 1. Goodness-of-fit for nivolumab+ipilimumab

Distributions/ Functions	Hazard function[a]	AIC	BIC	Long term estimation at 10 years[b]
Exponential	No	2126.634	2134.062	NA
Weibull	No	2124.491	2131.918	0.8%
Log-normal	Yes	2135.552	2142.98	5.5%
Log-logistic	Yes	2123.23	2130.657	5.6%
Gompertz	No	2126.634	2134.061	1.3%
Gamma	No	2123.417	2130.844	1.7%
GenGamma	No	2123.242	2134.383	0.8%
Spline Odds 1 knot	Yes	2120.637	2131.778	4.1%
Spline Odds 2 knots	Yes	2122.661	2137.516	3.4%
Spline Hazard 1 knot	No	2124.091	2135.232	1.3%
Spline Hazard 2 knots	Yes	2122.472	2137.327	2.5%
Spline Normal 1 knot	Yes	2121.397	2132.538	2.7%
Spline Normal 2 knots	Yes	2123.465	2138.32	2.9%

[a] First increasing and then decreasing

[b] Clinical expectation of 2% at 10-years (own clincial assumption and in line with [4] page 81/481)

AIC Akaike information criteria, *BIC* Bayesian information criteria, *NA* not applicable

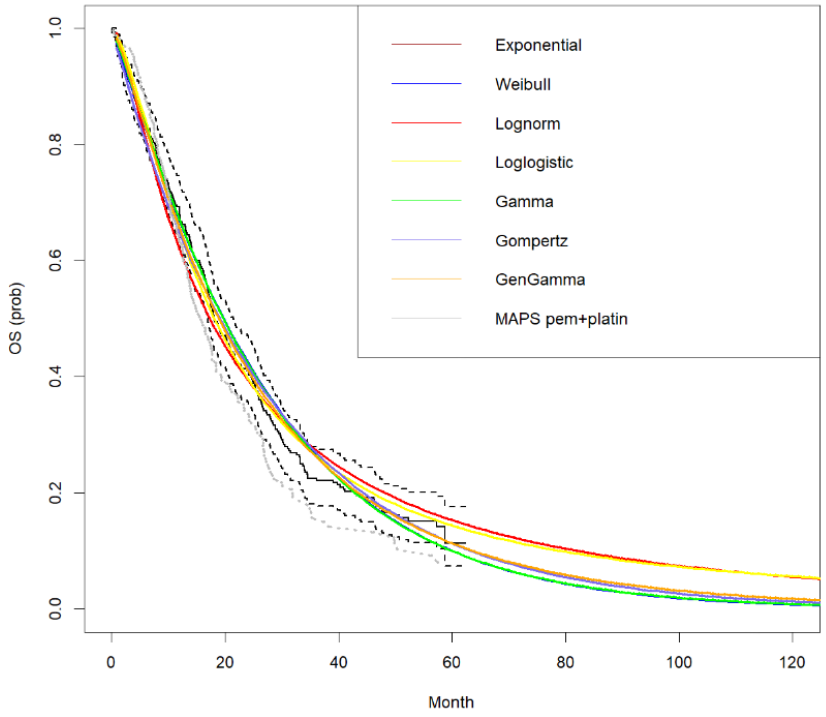
Supplementary Table 2. Goodness-of-fit for pemetrexed + platin

Distributions/ Functions	Hazard function[a]	AIC	BIC	Long term estimation at 10 years[b]
Exponential	No	2120.508	2124.218	0.3%
Weibull	No	2114.394	2121.815	0.1%
Log-normal	Yes	2121.658	2129.079	2%
Log-logistic	Yes	2106.009	2113.43	2.4%
Gompertz	No	2121.923	2129.344	0.1%
Gamma	No	2110.856	2118.277	0.1%
GenGamma	No	2108.412	2119.544	0.4%
Spline Odds 1 knot	Yes	2104.453	2115.584	1.7%
Spline Odds 2 knots	Yes	2106.425	2121.267	1.7%
Spline Hazard 1 knot	No	2108.519	2119.651	0.3%
Spline Hazard 2 knots	Yes	2106.568	2121.409	0.7%
Spline Normal 1 knot	**Yes**	**2106.222**	**2117.353**	**0.7%**
Spline Normal 2 knots	Yes	2106.341	2121.183	1.0%

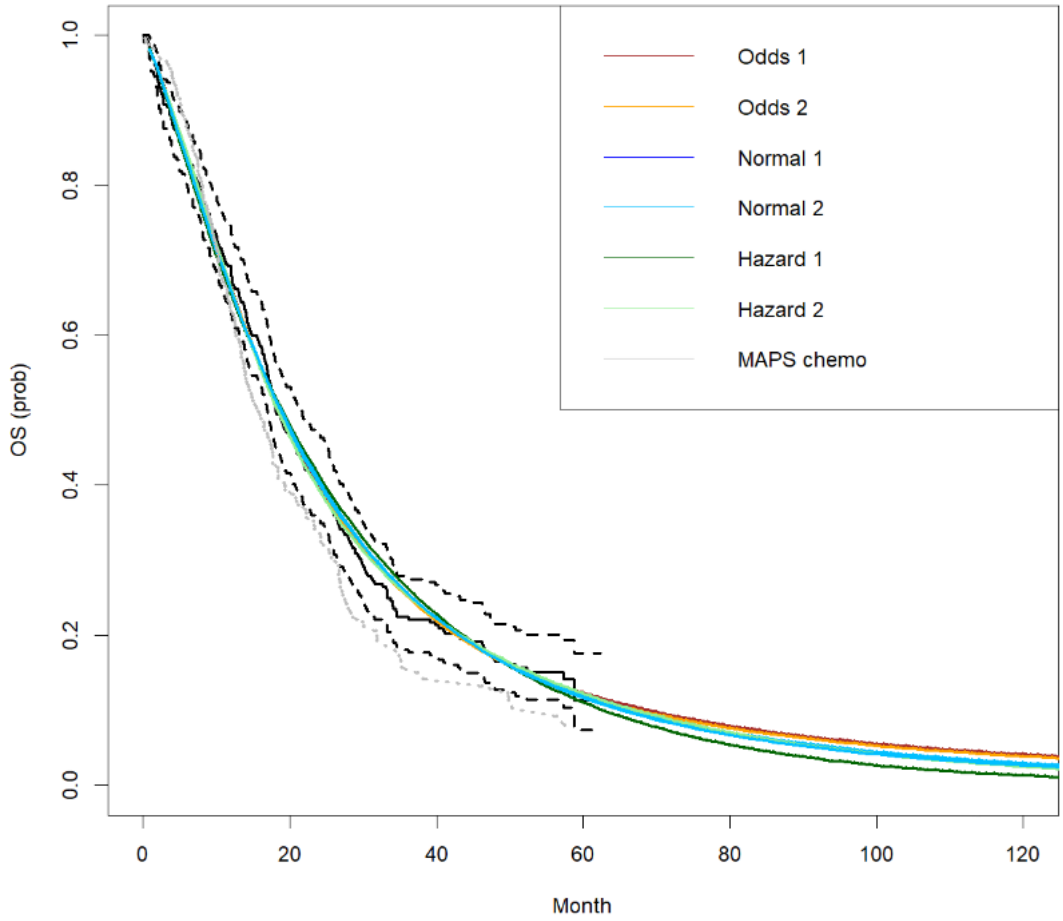
[a] First increasing and then decreasing

[b] Clinical expectation at10-year of 0%% (own clincial assumption and in line with [4])

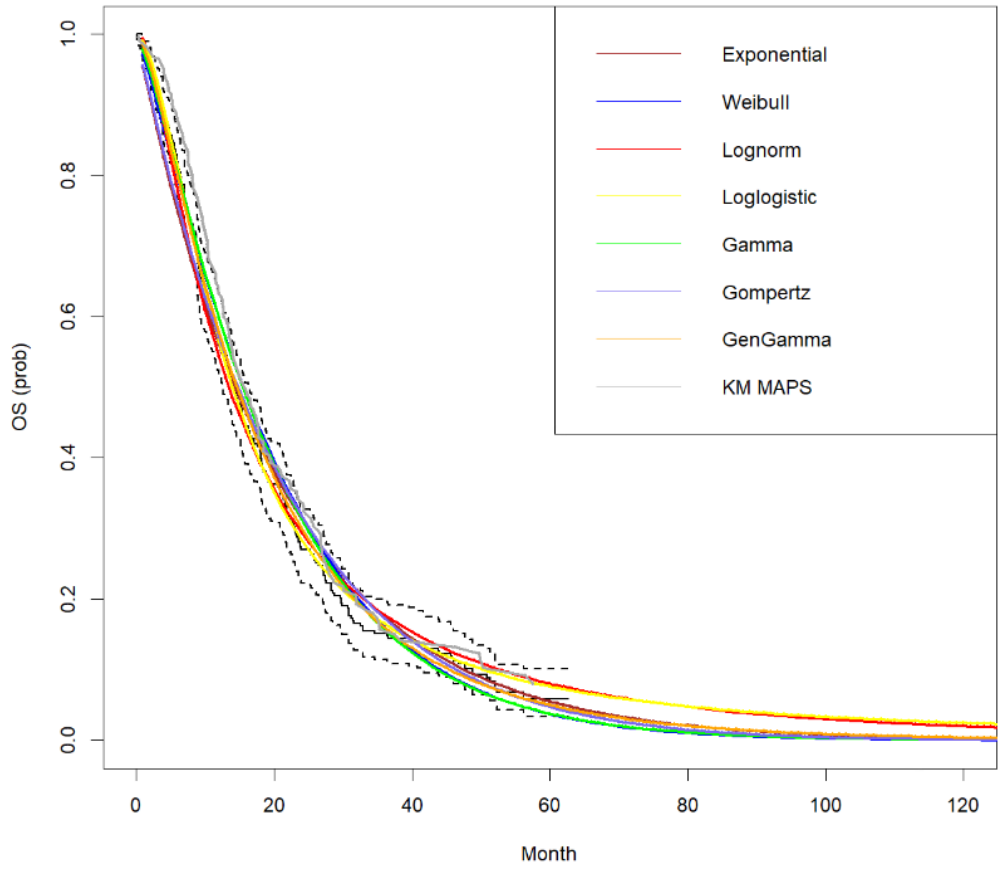
AIC Akaike information criteria, *BIC* Bayesian information criteria



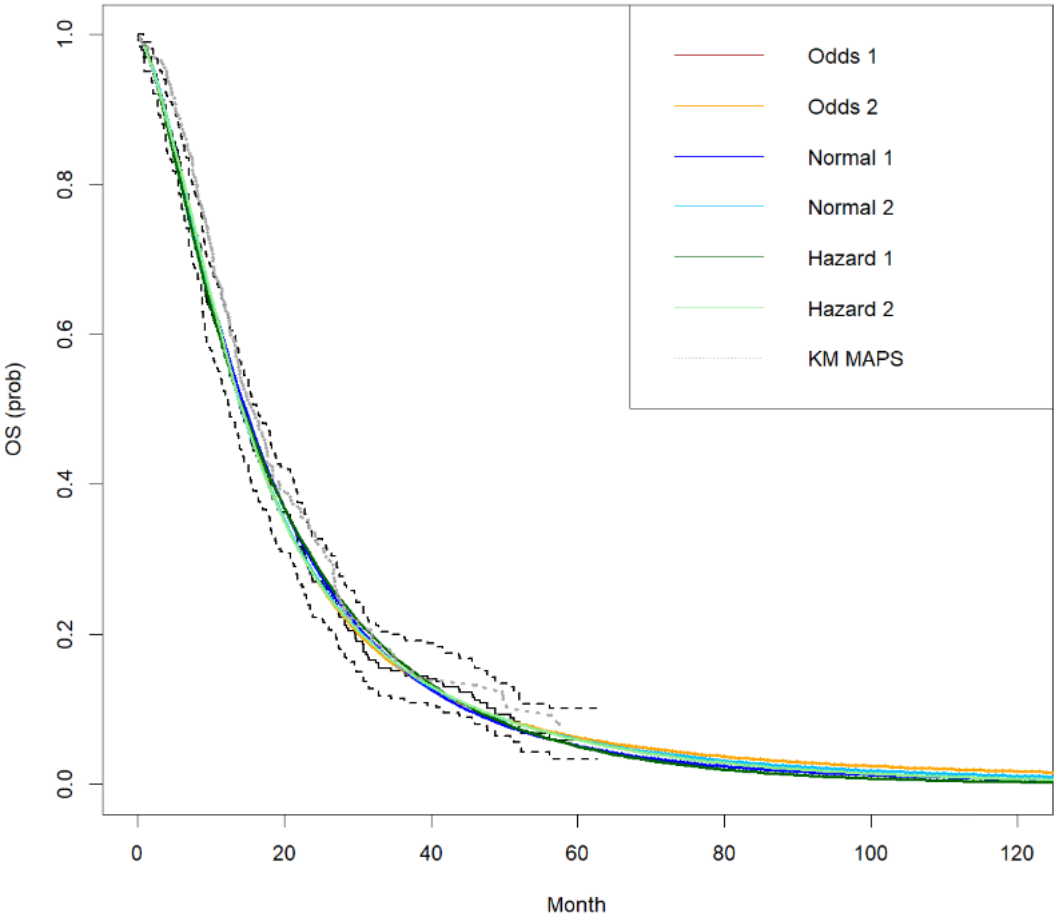
Supplementary Fig. 9 Parametric fit and extrapolation of OS under nivolumab+ipilimumab, digitized data of CM-743



Supplementary Fig. 10 Spline function fit and extrapolation of OS under nivolumab+ipilimumab, digitized data of CM-743



Supplementary Fig. 11 Parametric fit and extrapolation of OS under pemetrexed+platin, digitized data from CM-743

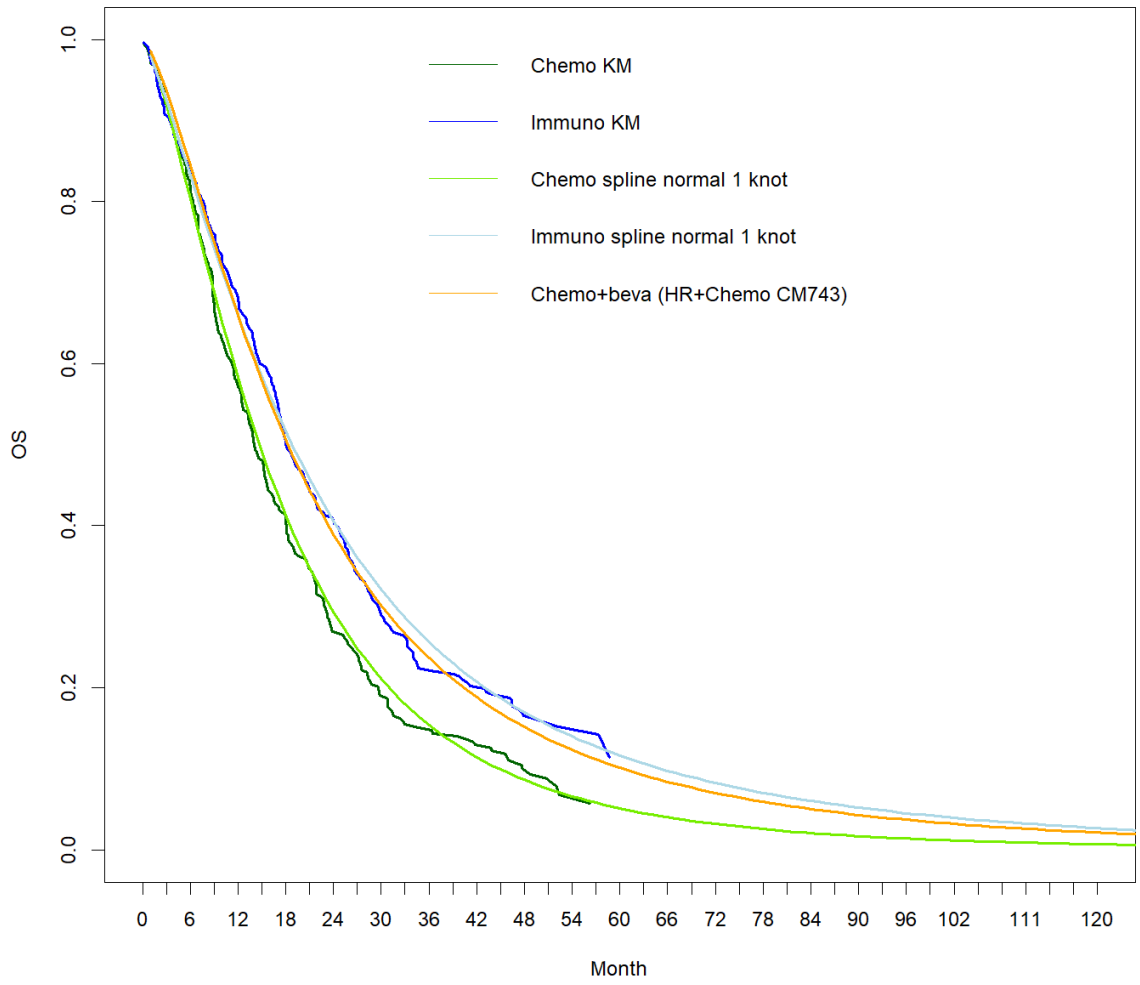


Supplementary Fig. 12 Spline function fit and extrapolation of OS under pemetrexed+platin, digitized data from CM-743

3.2.2 Selection of base-case distribution for OS CM-743

Taking all selection criteria into account, we selected a **spline normal 1 knot** function for the pemetrexed+platin arm of CM-743. We decided against a log-logistic distribution or spline odds functions since their predicted 10-year survival would have been higher than the clinical expectations for OS as outline in the NICE submission [5].

For the nivolumab+ipilimumab arm, all extrapolations with parametric distributions and spline functions led to a slightly lower OS during the first few months than the OS of the MAPS chemotherapy arm. An optimal selection was hence not possible. Taking all selection criteria into account and the fact that a normal 1 knot function had been selected for the chemotherapy arm, we also selected a **spline normal 1 knot** function to fit and extrapolate the KM OS curve for nivolumab+ipilimumab. Supplementary Fig. 13 visualizes the selected base-case distribution for OS CM-743.



Supplementary Fig. 13 Overall survival estimation (CM-743).

Beva bevacizumab, *chemo* chemotherapy, *CM743* Checkmate-743 trial, *HR* hazard ratio, *immuno* immunotherapy, *KM* Kaplan Meier, *OS* Overall survival

3.3 Survival curve ftting PFS CM-743

For the survival modelling of the PFS curves, we also verified in a first step that the hazard functions of possible distributions/functions are first increasing and then decreasing. Out of the ones with a hazard function in line with our criteria, we then selected distributions/functions that had lowest possible AIC and BIC, and a 4-year estimation at 9% for nivolumab+ipilimumab, and 0% for pemetrexed+platin. 4-year PFS estimates are published and are therefore available [3], but no PFS curves based on 4-year follow-up data.

3.3.1 Assessing goodness-of-fit of parametric and spline PFS models within and outside the trial period

Supplementary Table 3. Goodness-of-fit for nivolumab+ipilimumab

Distributions/ Functions	Hazard function[a]	AIC	BIC	Estimation at year 4[b]
Exponential	Not ok	1604.478	1611.906	2.15%
Weibull	Not ok	1590.351	1597.778	4.3%
Log-normal	Ok	1549.012	1556.439	7.2%
Log-logistic	Ok	1549.022	1556.449	7.1%
Gompertz	Not ok	1556.251	1563.678	11.4%
Gamma	Not ok	1598.381	1605.808	3.2%
GenGamma	Ok	1550.105	1561.246	8%
Spline Odds 1 knot	Ok	1542.043	1553.185	10.4%
Spline Odds 2 knots	Ok	1543.516	1558.371	10.0%
Spline Hazard 1 knot	Ok	1543.255	1554.396	10.2%
Spline Hazard 2 knots	Ok	1544.633	1559.487	10.4%
Spline Normal 1 knot	Ok	1549.24	1560.381	8.5%
Spline Normal 2 knots	Ok	1546.841	1561.696	10.4%

[a] Assumption: first sharply increasing and then decreasing over time

[b] Assumption: 9% at 4 years based on Zalcman et al. ESMO presentation [3]

AIC Akaike information criteria, *BIC* Bayesian information criteria, *y* year

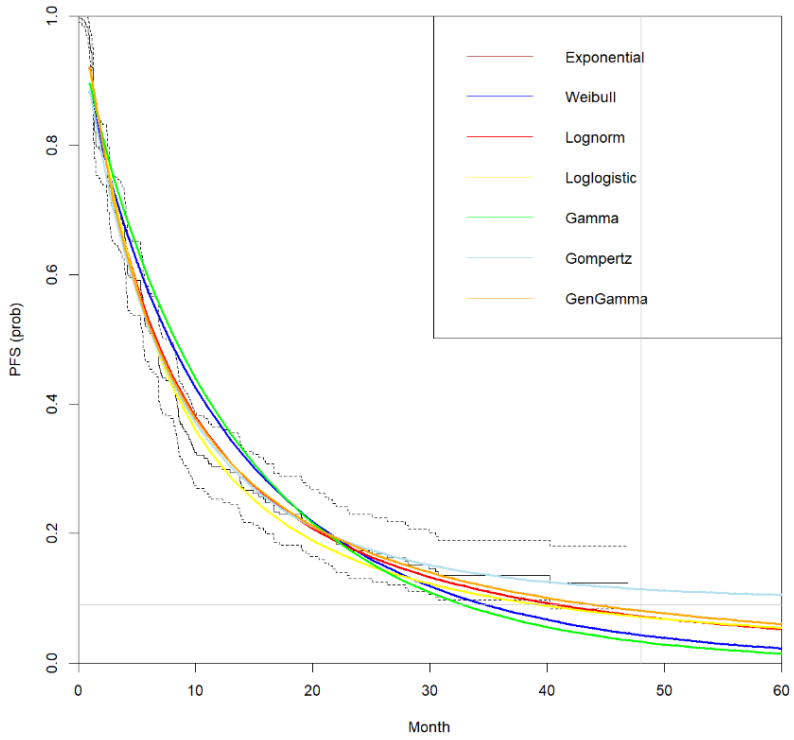
Supplementary Table 4. Goodness-of-fit for pemetrexed + platin

Distributions/ Functions	Hazard function*	AIC	BIC	Long term estimation at year 4**
Exponential	Not ok	1485.175	1488.886	1.1%
Weibull	Not ok	1449.803	1457.224	0%
Log-normal	ok	1446.413	1453.834	1.4%
Log-logistic	ok	1426.604	1434.024	1.6%
Gompertz	Not ok	1476.735	1484.156	0%
Gamma	Not ok	1439.06	1446.481	0.1%
GenGamma	Not ok	1435.971	1447.103	0.3%
Spline Odds 1 knot	ok	1426.7	1437.8	1.1%
Spline Odds 2 knots	ok	1423.9	1438.741	1.9%
Spline Hazard 1 knot	Not ok	1432.999	1444.13	0.5%
Spline Hazard 2 knots	ok	1423.13	1437.972	1.2%
Spline Normal 1 knot	Not ok	1433.164	1444.295	0.4%
Spline Normal 2 knots	ok	1422.879	1437.721	1.4%

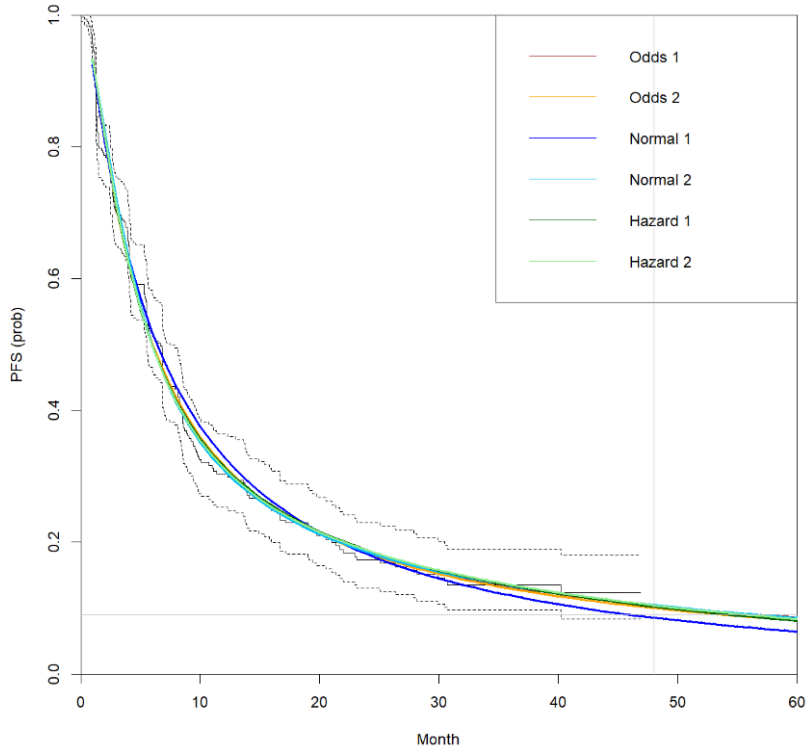
[a] Assumption: first sharply increasing and then decreasing over time

[b] Assumption: 0% at 4 years based on Zalcman et al. ESMO presentation [3]

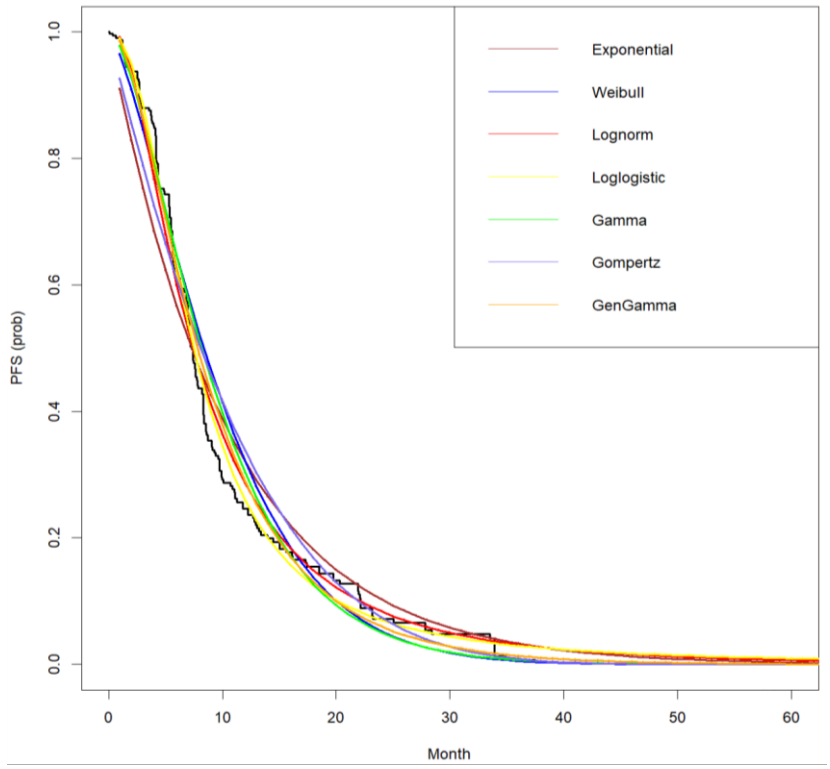
AIC Akaike information criteria, *BIC* Bayesian information criteria, *y* year



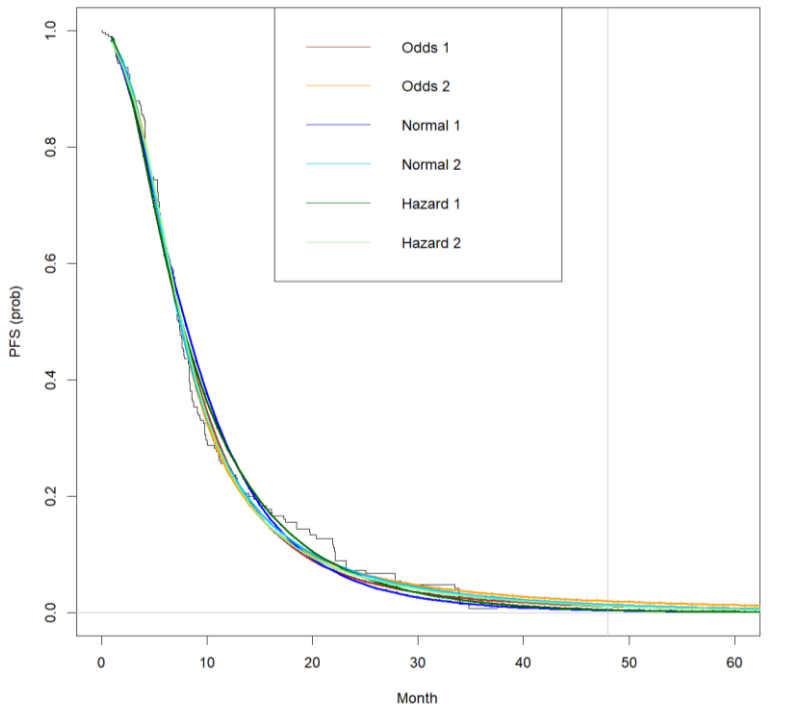
Supplementary Fig. 14 Parametric fit and extrapolation of PFS under nivolumab+ipilimumab, digitized data of CM-743



Supplementary Fig. 15 Spline function fit and extrapolation of PFS under nivolumab+ipilimumab, digitized data of CM-743



Supplementary Fig. 16 Parametric fit and extrapolation of PFS under pemetrexed+platin, digitized data of CM-743

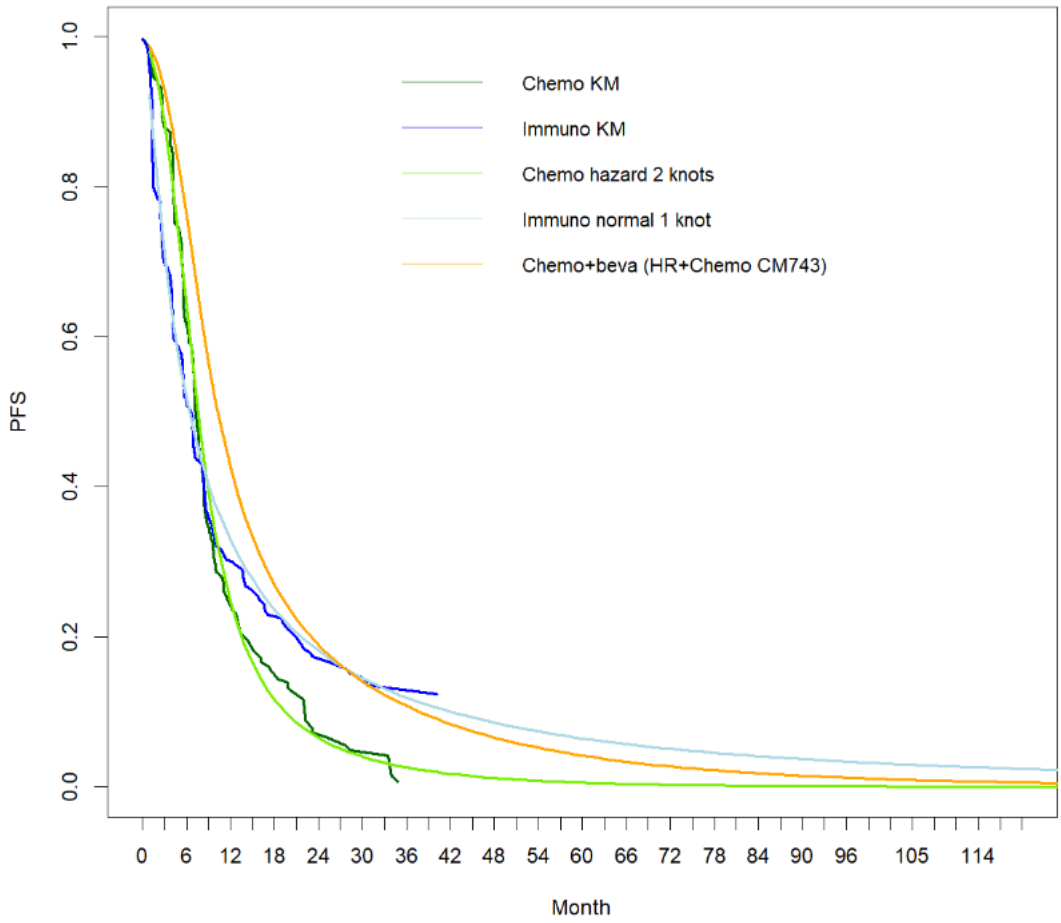


Supplementary Fig. 17 Spline function fit and extrapolation of PFS under pemetrexed+platin, digitized data of CM-743

3.3.2 Selection of base-case distribution for PFS CM-743

Taking all selection criteria into account, we selected a **spline hazard 2 knots** function for the pemetrexed+platin arm of CM-743 but several other functions were almost as good. The log-logistic and the spline normal 2 knots distributions obtained the lowest BIC and AIC values respectively, but higher 4-year PFS percentages of 1.6% and 1.4% (4-year PFS of 0% was reported by Zalcman et al. [3]). We did not select the spline odds 1 knot neither although it obtained the lowest 4-year PFS of 1.1%. Its predicted PFS was lower than the PFS in the MAPS chemotherapy arm in the range of 24 to 28 months.

For the nivolumab+ipilimumab arm, the spline odds 1 knot function achieved the lowest AIC and BIC values for the re-created KM data. All parametric distributions led to higher AIC/BIC values. All spline models and three parametric distributions (loglogistic, lognormal, generalised gamma) yielded hazard functions with a similar behaviour than the hazard function of the re-created individual patient data. The **spline normal 1 knot** obtained the closest predicted PFS of 8.5% at 4years (4y PFS rates of 9% reported [3]) and was in line with the selected distribution for OS under nivolumab+ipilimumab. Supplementary Fig. 18 visualizes the selected base-case distribution for PFS CM-743.

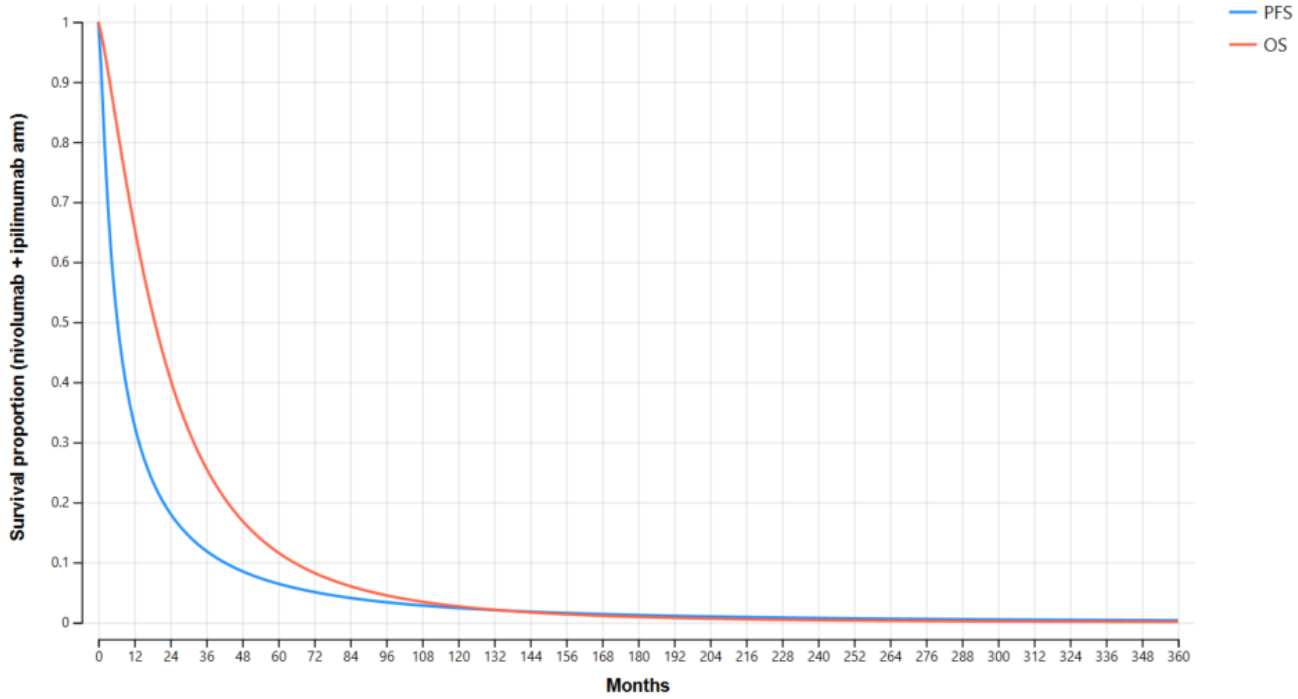


Supplementary Fig. 18 Progression-free survival estimation

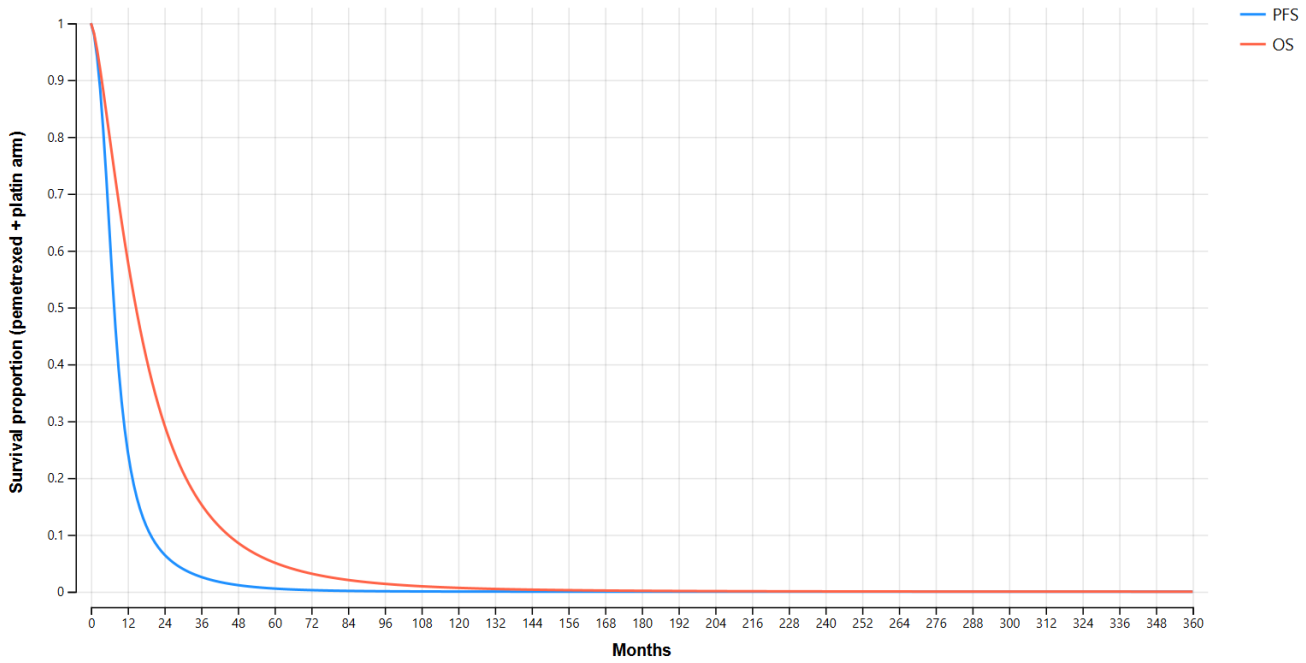
Beva bevacizumab, *chemo* chemotherapy, *CM743* Checkmate-743 trial, *HR* hazard ratio, *immuno* immunotherapy, *KM* Kaplan Meier, *PFS* progession-free survival

3.4 Fitted and extrapolated OS and PFS curves for each strategy

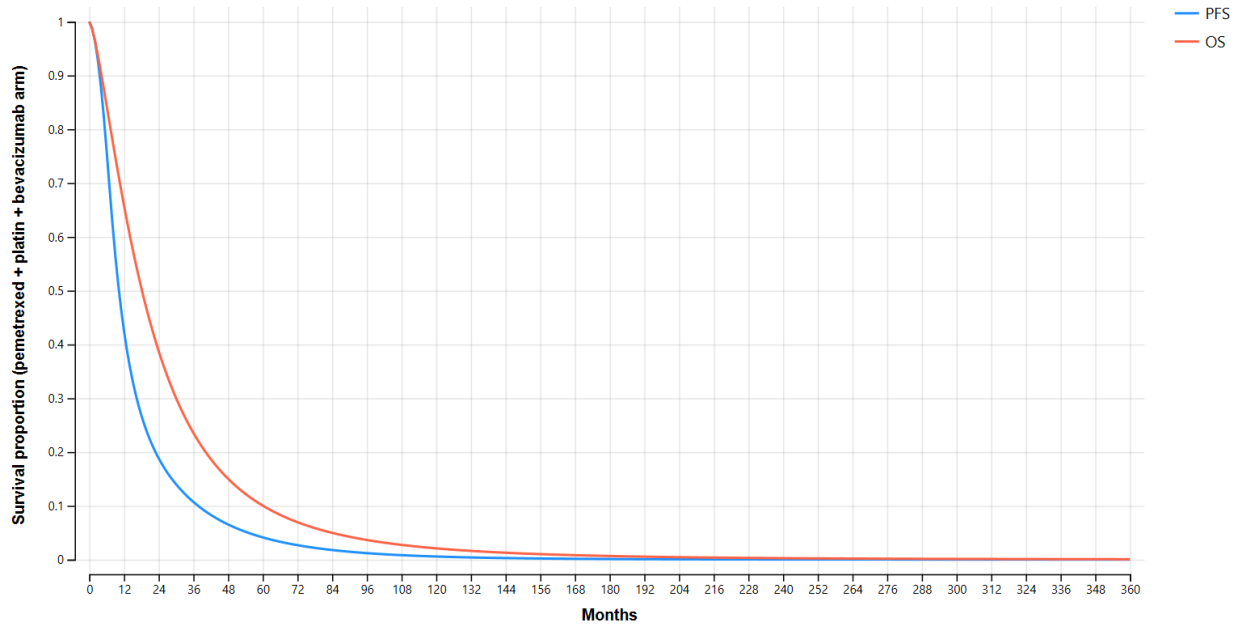
All three graphs have been created within the TreeAge partitioned survival model.



Supplementary Fig. 19 Fitted and extrapolated OS and PFS curves for nivolumab+ipilimumab strategy



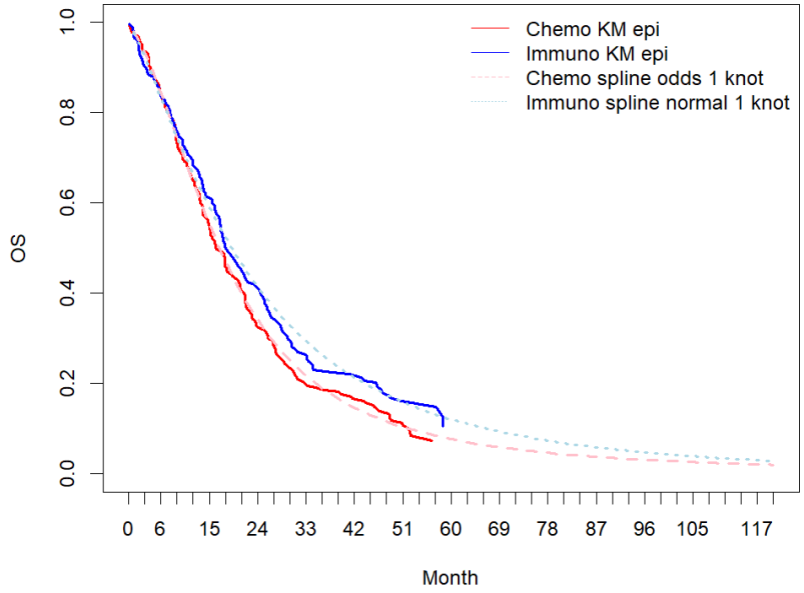
Supplementary Fig. 20 Fitted and extrapolated OS and PFS curves for pemetrexed+platin strategy



Supplementary Fig. 21 Fitted and extrapolated OS and PFS curves for pemetrexed+platin+bevacizumab strategy

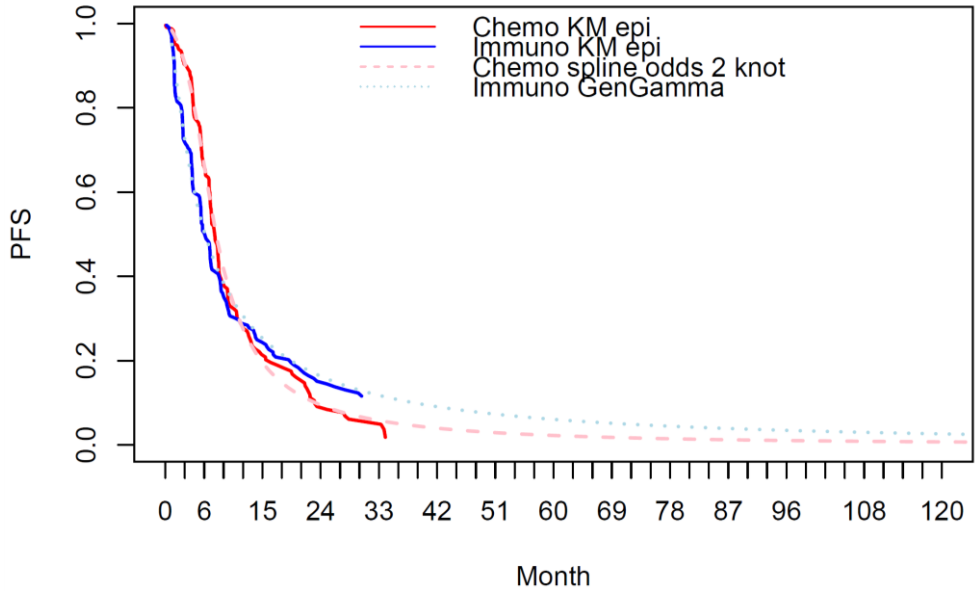
3.5 Survival curve fitting of CM-743 subgroups

3.5.1 Epithelioid subtype



Supplementary Fig. 22 Overall survival estimation, epithelioid subtype

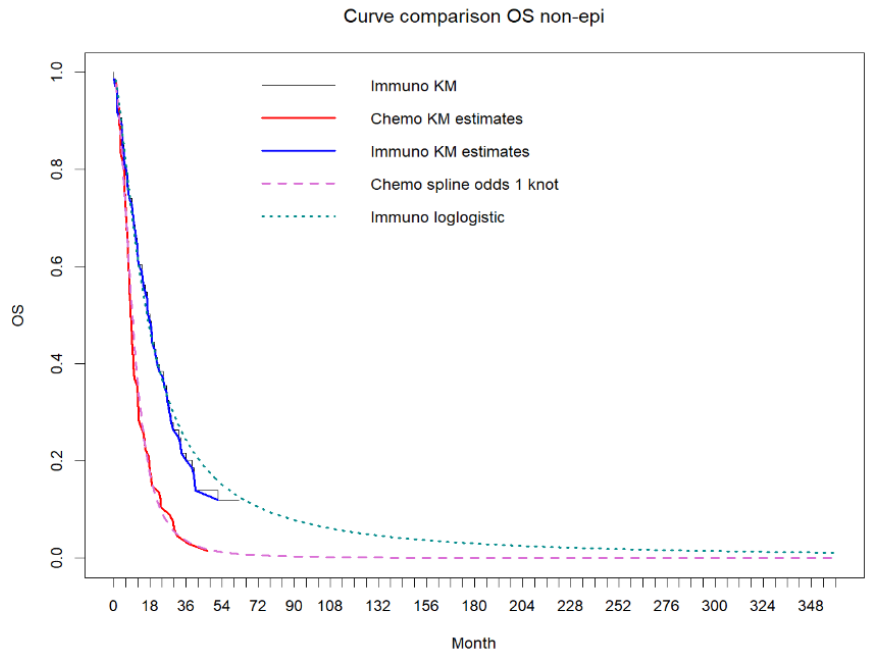
Chemo chemotherapy, *epi* epithelioid, *immuno* immunotherapy, *KM* Kaplan Meier, *OS* overall survival



Supplementary Fig. 23 Progression-fee survival estimation, epithelioid subtype

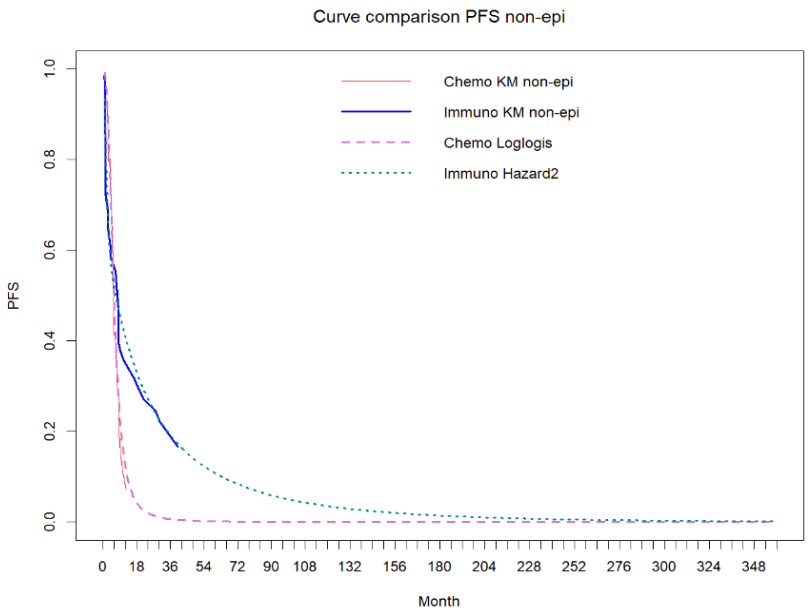
Chemo chemotherapy, *epi* epithelioid, *immuno* immunotherapy, *GenGamma* generalized gamma, *KM* Kaplan Meier, *PFS* progession-free survival

3.5.2 Non-epithelioid subtype



Supplementary Fig. 24 Overall survival estimation, non-epithelioid subtype

Chemo chemotherapy, *epi* epithelioid, *immuno* immunotherapy, *KM* Kaplan Meier, *OS* overall survival



Supplementary Fig. 25 Progression-fee survival estimation, non-epithelioid subtype

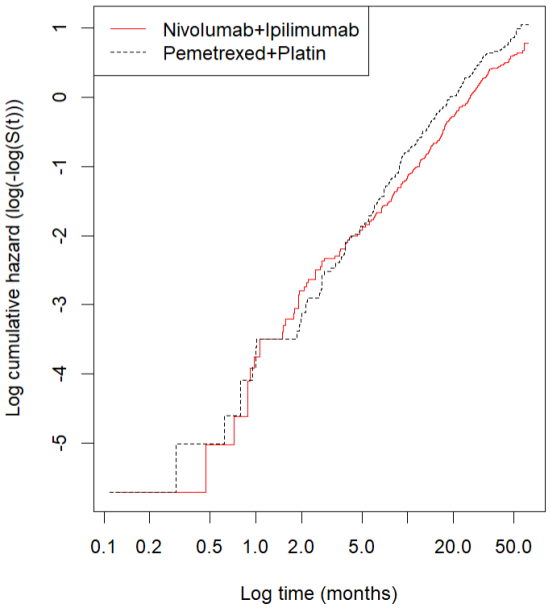
Chemo chemotherapy, *epi* epithelioid, *immuno* immunotherapy, *GenGamma* generalised gamma, *KM* Kaplan Meier, *loglogis* log-logistic, *PFS* progession-free survival

4 Testing of proportional hazards assumption

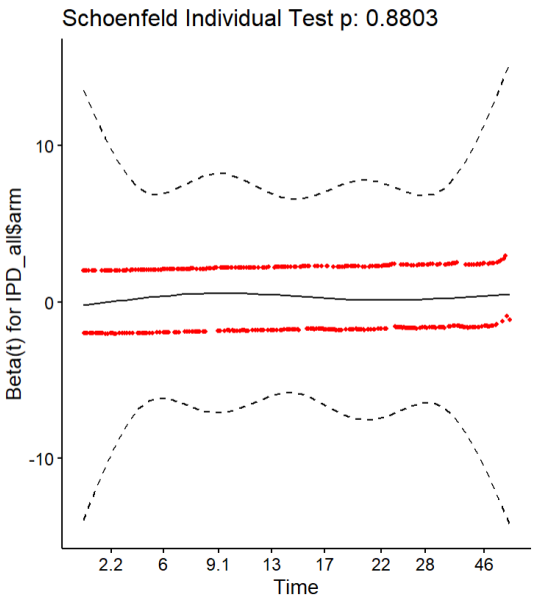
4.1 Testing of proportional hazards assumption OS CM-743

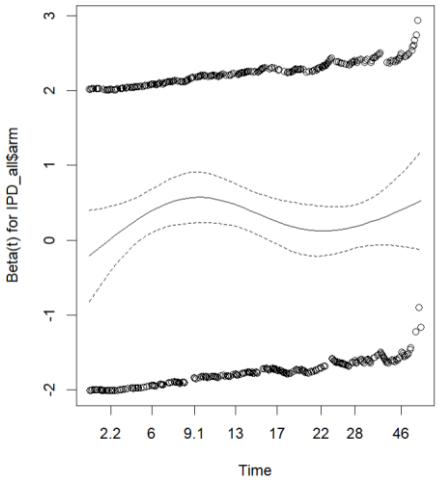
We performed a visual inspection of the log-cumulative hazards plots and the Schoenfeld residuals to assess proportionality of treatment effects over time.

Log-cumulative plot



Schönfeld residuals





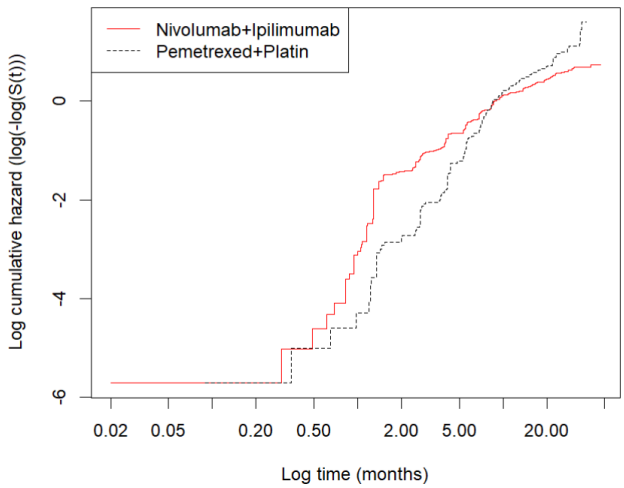
Supplementary Fig. 26 Proportional hazard plots OS CM-743

Schoenfeld residual plots showed an approximately linear pattern, and the test of the Schoenfeld residuals against log(time) did not reject the null hypothesis of proportional hazards (hence it can be assumed). However, inspection of the log-cumulative hazards plot revealed that the cumulative hazard for both arms crosses at multiple time points,

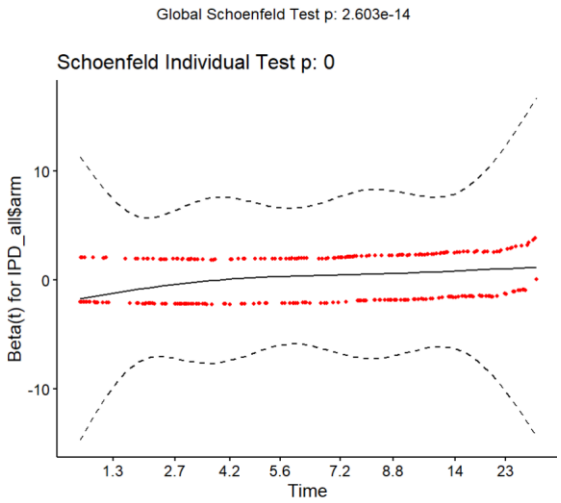
falsifying the assumption of proportional hazards (in line with 3-year data [4]). Therefore, we assumed non-proportional hazard for the 4y-OS data.

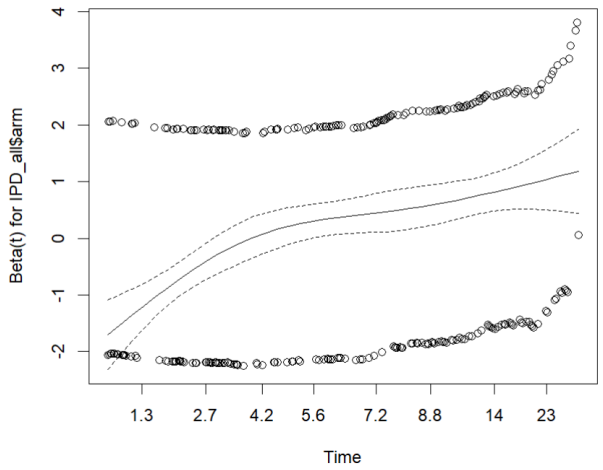
4.2 Testing of proportional hazards assumption PFS CM-743

Log-cumulative plot



Schönfeld residuals



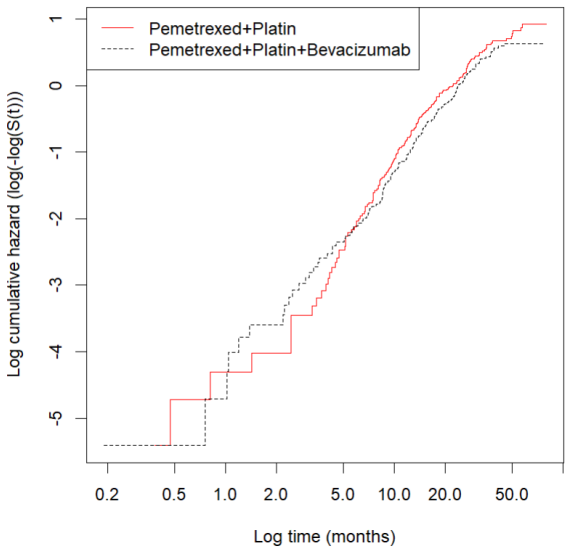


Supplementary Fig. 27 Proportional hazard plots PFS CM-743

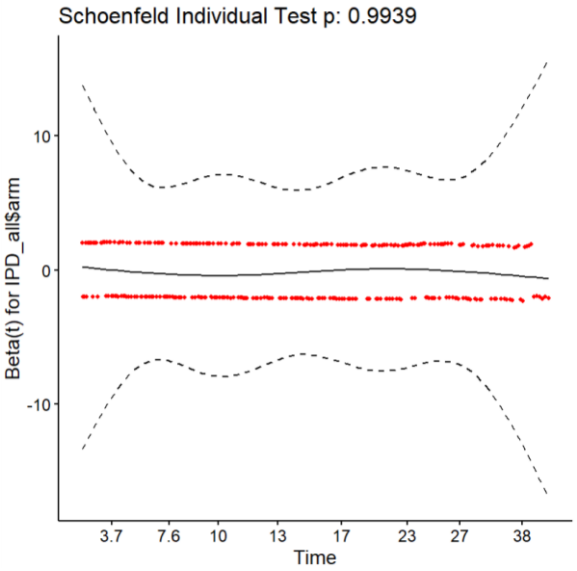
Schoenfeld residual plots did not show a linear pattern and the test of the Schoenfeld residuals against log(time) rejected the null hypothesis of proportional hazards (p-value <0.001). Also, inspection of the log-cumulative hazards plot revealed that the cumulative hazard for the two arms crosses (in line with [4]).

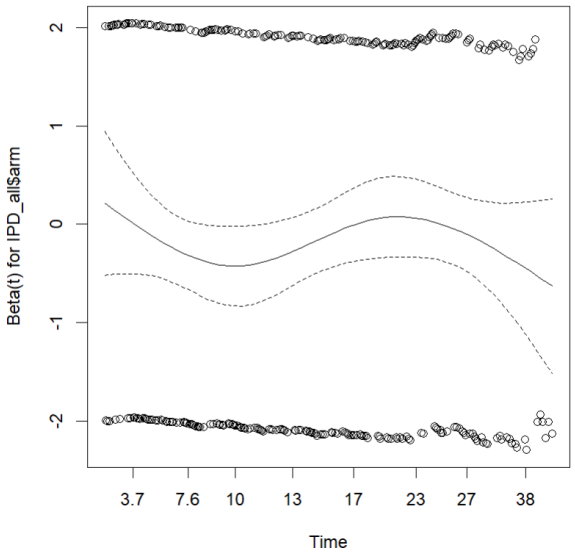
4.3 Testing of proportional hazards assumption OS MAPS

Log-cumulative plot



Schönfeld residuals





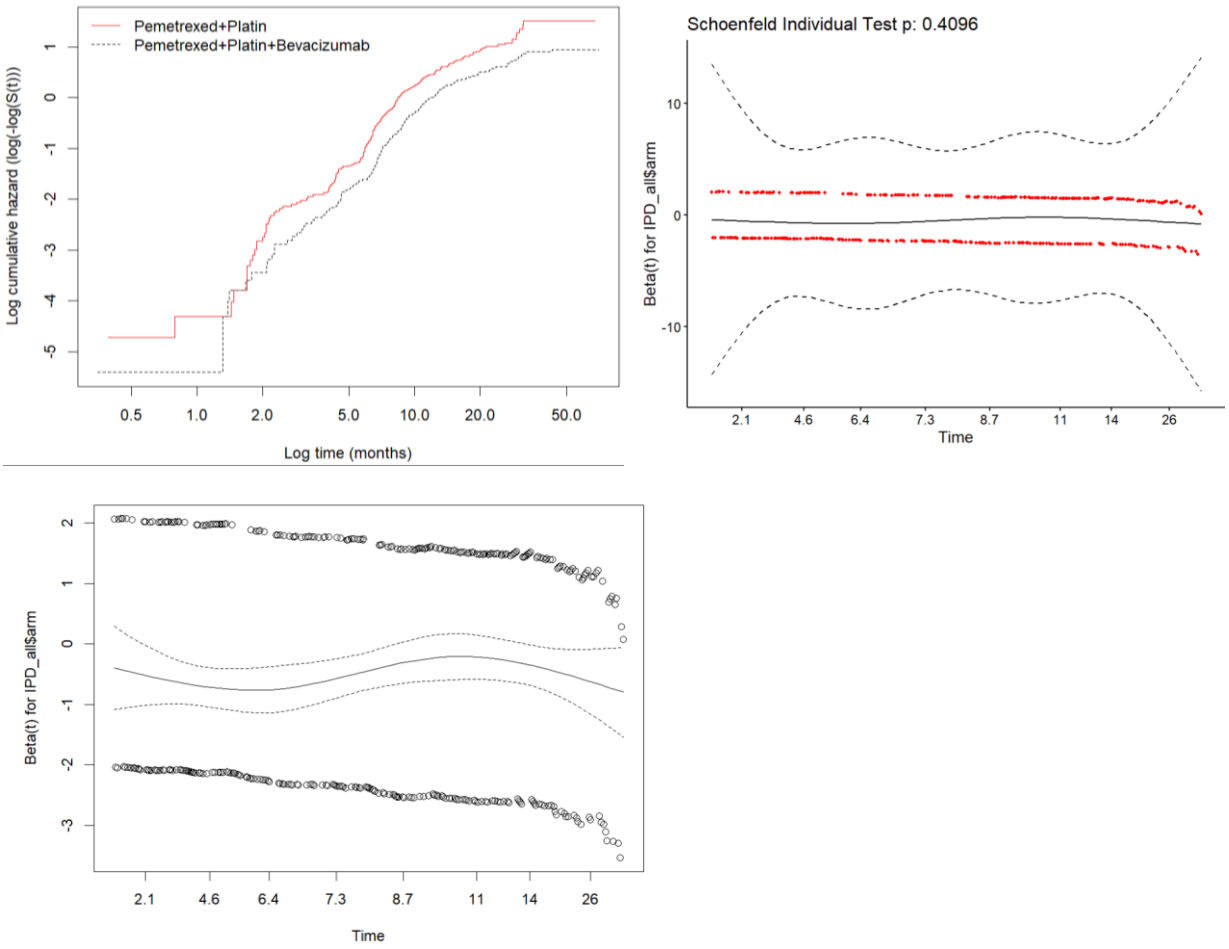
Supplementary Fig. 28 Proportional hazard plots OS MAPS

Schoenfeld residual plots showed an approximately linear pattern and the test of the Schoenfeld residuals against log(time) did not reject the null hypothesis of proportional hazards (hence it can be assumed). However, inspection of the log-cumulative hazards plot revealed that the cumulative hazard for both arms crossed.

4.4 Testing of proportional hazards assumption PFS MAPS

Log-cumulative plot

Schönfeld residuals

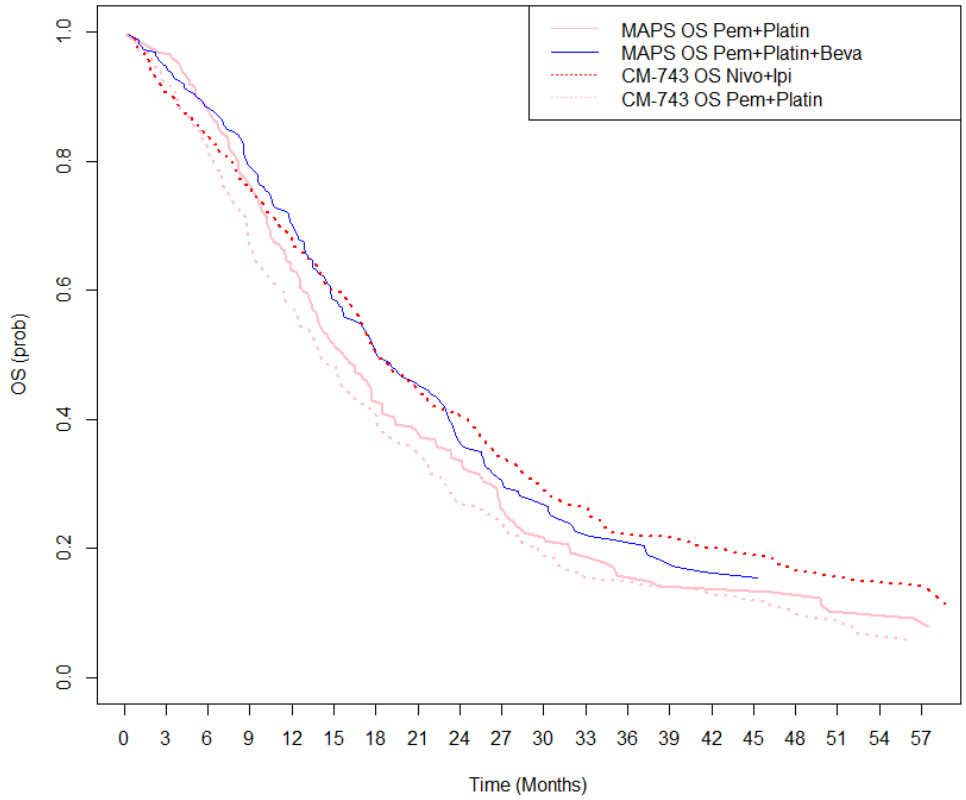


Supplementary Fig. 29 Proportional hazard plots PFS CM-743

Schoenfeld residual plots showed a linear pattern and the test of the Schoenfeld residuals against log(time) (p-value 0.41) did not reject the null hypothesis of proportional hazards. Inspection of the log-cumulative hazards plot revealed that the cumulative hazard for both arms touched early in time but otherwise stayed parallel.

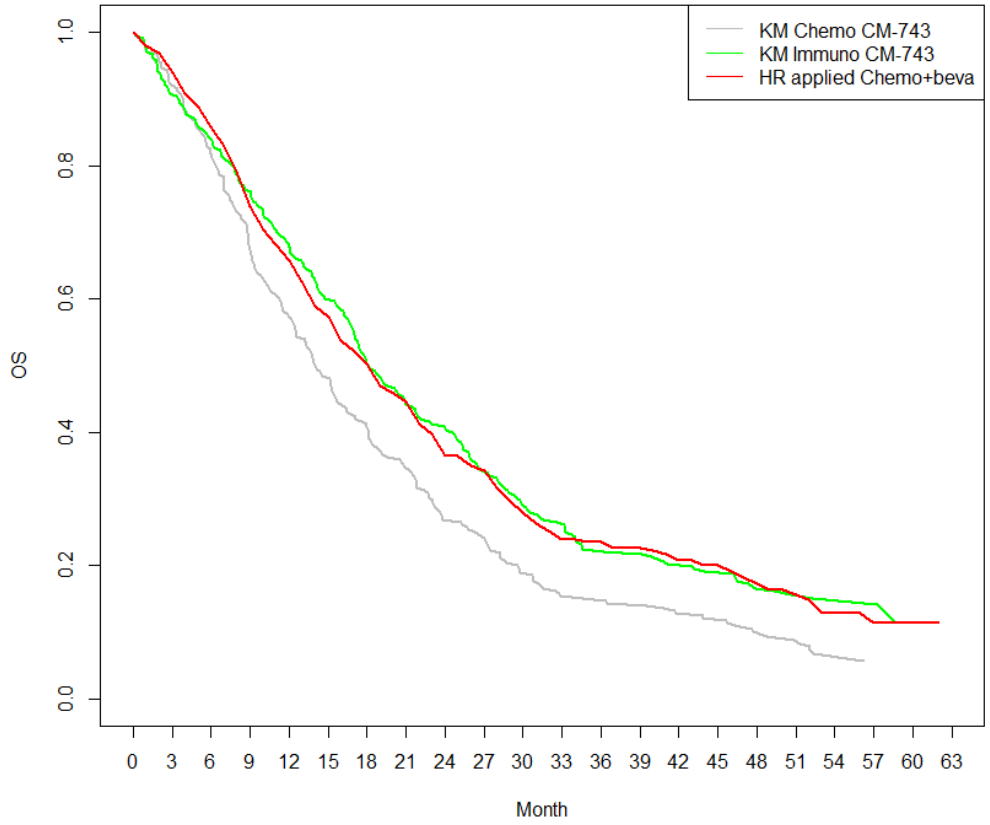
Although the log-cumulative hazard plots crossed for OS, we assumed the proportional hazards assumption to approximately hold for OS and PFS in MAPS since (1) the PFS curves of the MAPS study did not cross (in contrast to the PFS curves of CM-743), (2) the OS MAPS curves only crossed slightly at the beginning and stayed approximately constant over time, (3) the otherwise good results of the Schoenfeld residuals (graphs and statistical test). For this reason, we fitted the PFS pemetrexed+platin+bevacizumab curve with the MAPS HR adjusted to the pemetrexed+platin arm of the CM-743 study.

5 Comparison of Kaplan-Meier curves



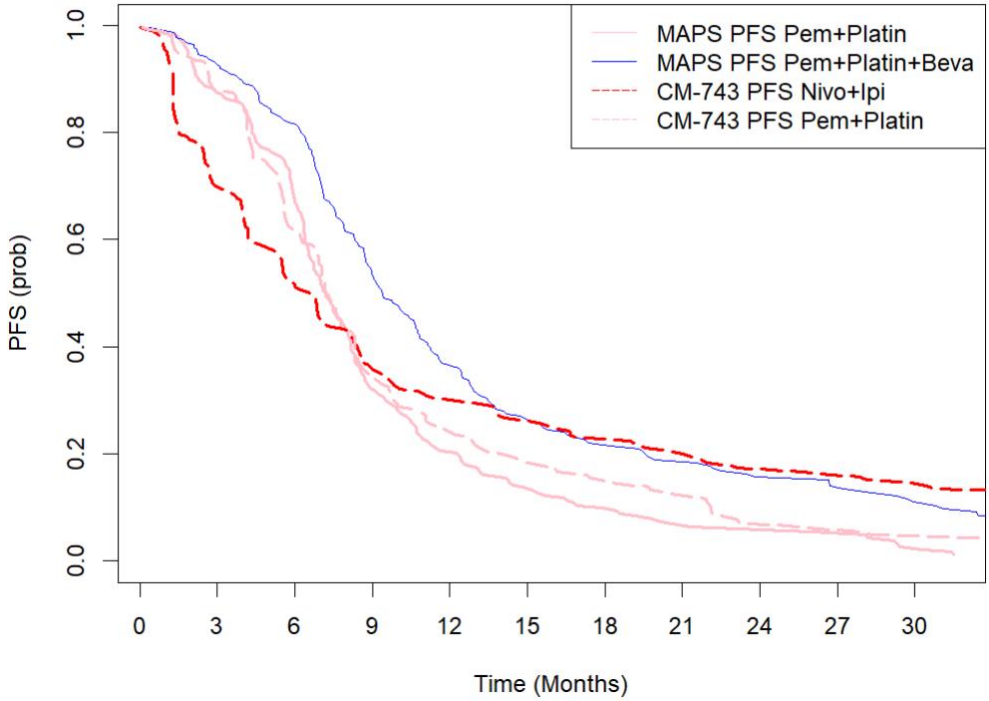
Supplementary Fig. 30 Recreated OS KM estimates of CM-743 and MAPS

Beva bevacizumab, *ipi* ipilimumab, *nivo* nivolumab, *OS* overall survival, *pem* pemetrexed



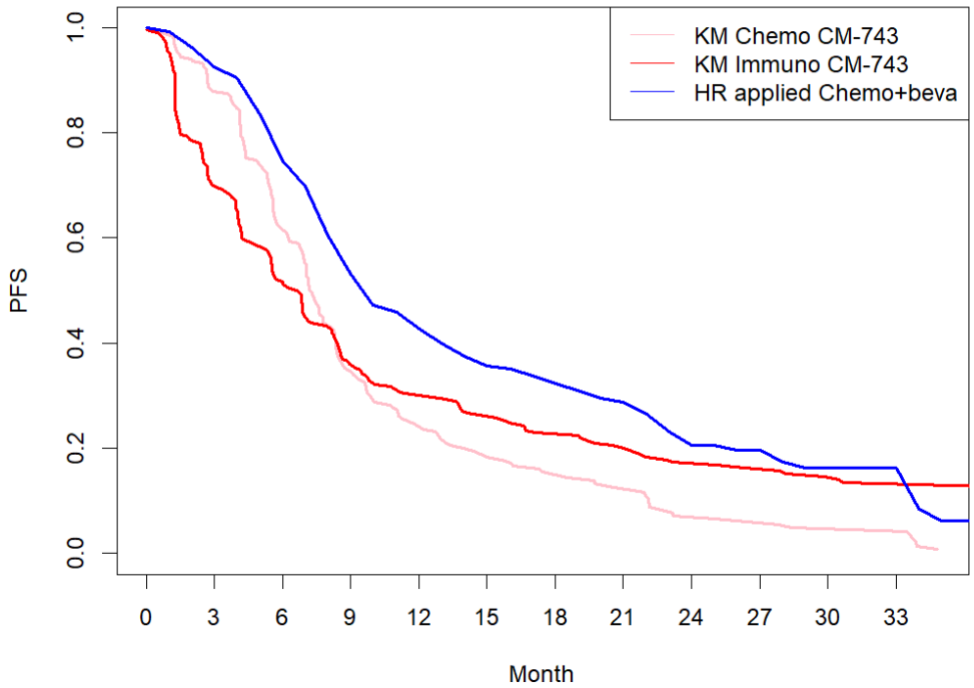
Supplementary Fig. 31 Recreated OS KM estimates of CM-743 and HR-based MAPS pem+platin+beva estimates

Beva bevacizumab, *chemo* chemotherapy, *HR* hazard ratio, *immuno* immunotherapy, *KM* Kaplan Meier, *OS* overall survival



Supplementary Fig. 32 Recreated PFS KM estimates of CM-743 and MAPS

Beva bevacizumab, *ipi* ipilimumab, *nivo* nivolumab, *pem* pemetrexed, *PFS* progression-free survival



Supplementary Fig. 33 Recreated PFS KM estimates of CM-743 and HR-based MAPS pem+platin+beva estimates

Beva bevacizumab, *chemo* chemotherapy, *HR* hazard ratio, *immuno* immunotherapy, *KM* Kaplan Meier, *PFS* progression-free survival

6 Follow-up treatments

CM-743 reported patient progression of 86% in the immuno- and of almost 100% in the chemo-arm for the 3-year data [6]. However, only the number and percentages of patients with systemic further line treatment of all patients at baseline for nivolumab+ipilimumab (n=136/303, 44.9%) and pemetrexed+platin (n=128/302, 42.4%) were reported [6]. The number of patients who were still alive and received further line treatment at the start of their progression was not shown. Also, patients may have received more than one type of subsequent therapy. In general, all possible further line treatments are (equally) limited in efficacy and it is currently unclear which one is best to use in clinical practise. For all of these reasons, we rather used a realistic (currently applied) mix of further line treatments in Switzerland after discussion of these within our medical expert group. In the UK company model for the NICE submission, all non-National Health Service second-line treatment costs from both arms had been removed after questioning by the evidence review group [7].

Supplementary Table 5. Follow-up treatments

1L	2L treatments		Source	3L treatments		Source
Nivolumab + ipilimumab	65%	carboplatin + pemetrexed for 3 months in Markov model (2 months in PartSA)	% derived from Peters (44.9%) and own assumptions. Durations from Baas first-line (mean of 3 months) [8]	35%	17.5% Gemcitabin for 2 months in Markov model (1 month in PartSA)	Durations derived from Popat 2020 PROMISE-meso trial [9] % own assumption
					17.5% vinorelbin for 2 months (1 month in PartSA)	
				30%	late-stage palliative	
	35%	late-stage palliative		difference to 100%	continuation of late-stage palliative	
Platin + pemetrexed (+bevacizumab)	62%	nivolumab monotherapy for 4 months in Markov model (3 months in PartSA)	nivolumab [10]	35%	17.5% gemcitabin for 2 months (1 month in PartSA)	Durations derived from Popat 2020 PROMISE-meso trial [9]
					17.5% vinorelbin for 2 months (1 month in PartSA)	
				27%	new new late-stage palliative	
	38%	late-stage palliative		difference to 100%	continuation of late-stage palliative	

[a] In the probabilistic sensitivity analysis, the parameter was varied with a beta distribution (mean, mean*0.2). In deterministic sensitivity analysis we used the 2.5% and 97.5% percentiles of the beta distribution.

Carbo carboplatin, *PartSA* partitioned survival analysis, *2L* second-line, *3L* third-line

Overall, we consider the estimated percentages of 2L and 3L treatments only as approximative and varied them in sensitivity analyses. The percentages of further lines of treatment of the triple treatment with bevacizumab were varied independently of the percentages of the chemotherapy arm without bevacizumab.

During the period of further lines of treatment in the progressed state, drug, administration, physician visits, and laboratory costs were included in the analysis. Treatment-unspecific imaging costs were also incorporated (Supplementary Table 10).

7 Utilities

Supplementary Table 6. Utility input parameters, Markov state transition model

Health State	On/Off Treatment	Nivolumab+ ipilimumab	Pemetrexed + platin	Pemetrexed + platin + bevacizmab	Source
PFD	On	0.736 (0.012)	0.734 (0.012)	Assume the same as under chemo but never off	NICE 2021 p.200 [5]
	Off	0.733 (0.021)	0.719 (0.017)		
PD	On	0.708 (0.016)	0.638 (0.030)	Assume the same as under chemo but never off	
	Off	0.607 (0.015)	0.572 (0.015)		

PD progressed disease, *PFD* Progression-free disease

Supplementary Table 7. Utility input parameters of PD state, partitioned survival model

Health State	On/Off Treatment	Nivolumab+ ipilimumab	Pemetrexed + platin	Pemetrexed + platin + bevacizmab	Source
PD	NA	0.65 (0.01)	0.58 (0.02)	Assume the same as under chemo but never off	NICE 2021 p.99/481 [5]

NA Not applicable*, PD* progressed disease

8 Overview input parameters

Supplementary Table 8. Input parameters

Input parameter	Estimate	DA Min	DA Max	PA distribution	Description / Comment	Source
Drug Costs 2022	Monthly costs (in CHF)	--	--	--		Swiss Specialty list (SL) [11]
Nivolumab monthly	7,422.72	4,813	10,594	--	DA limits are 95% Cs based on 10,000 simulations runs from a gamma distribution (mean, 0.2*mean)	
Ipilimumab monthly	6,559.32	4,246	9,370	--		
Bevacizumab monthly	4,869.11	3,147	6,966	--		
	Pack costs					
Nivolumab	3,407.15	--	--	--	Pack Size 240 mg	Can be varied with a certain %
Ipilimumab	4,516.25	--	--	--	Pack Size 50 mg	Can be varied with a certain %
Pemetrexed	1,274.70	--	--	--	1000 mg/40ml	
Vitamin B9 Folic Acid	7.20	--	--	--	28 pieces	
	14.20				100 pieces	
Vitamin B12 supplement	17.80	--	--	--	1000µg, BL for immunotherapy 1L; BL, 3. and 6. cycle for chemotherapy arms 1L	
Carboplatin	47.05	--	--	--	150 mg	
Bevacizumab	1,117.50	--	--	--	400 mg i.v. for 90 (60, 30) minutes for the 1st (2nd, all subsequent) infusion(s)	
Palonosetron	68.45	--	--	--	0.25mg i.v. D0 Q3W during chemotherapy	
Dexamethasone	20.80	--	--	--	Tablets 4 mg 20 pieces, costs added during 1. cycle	
Gemcitabine	624.23	--	--	--		
Vinorelbine	847.61	--	--	--		Swiss SL
	DRG one-off costs					
Cisplatin inpatient stay	4,221.57	--	--	--		SwissDRG [12]
Pemetrexed “Zusatzentgelt”	2,417.28	1,566	3,453	Gamma(mean, 0.2*mean)		SwissDRG “Zusatzentgelte”
Bevacizumab “Zusatzentgelt”	3,084.09	1,996	4,413	No PA		SwissDRG “Zusatzentgelte”

Input parameter	Estimate	DA Min	DA Max	PA distribution	Description / Comment	Source
I.V. outpatient administration	Costs per visit (in CHF)	Varied costs per strategy *0.7	Varied costs per strategy *1.3	Varied overall costs per strategy with gamma distribution (mean=1, SE=0.153)		TARMED 1.09 [13]
Nivolumab, bevacizumab, gemcitabine or vinorelbine	186.66					
Nivolumab+ipilimumab	315.53					
Pemetrexed+carboplatin	294.24					
Pemetrexed+carboplatin+ bevacizumab						
1st infusion	600.35					
2nd infusion	557.77					
>=3. infusion	515.19					
Physician visit costs	Costs per visit(in CHF)	Monthly total varied *0.7	Monthly total varied *1.3	Monthly total costs varied with gamma distribution (mean=1, SE=0.153)		TARMED 1.09 [13]
1L Screening visit	428.16					
Regular oncologist visit (during and after treatment duration end)						
- without report	186.59				For 2L nivolumab monotherapy, 3L gemcitabine/vinorelbine (on days 1 and 8)	
- with report	220.20				Report at BL visit and 1L visits with CT.	
Intermediate visit (week 2 out of 3 week cycle) or late palliative care visit	169.40				For intermediate chemotherapy 1L and 2L carboplatin visits	
Laboratory costs	Costs per laboratory visit (in CHF)	Monthly total varied *0.7	Monthly total varied *1.3	Monthly total costs varied with gamma distribution (mean=1, SE=0.153)		Analysis list (AL) [14]
Full blood count	70.50				Haematogram V + chemistry 1+2; for chemotherapy arms amylase and lipase costs (CHF 6.80) were subtracted. Also used for nivolumab monotherapy 2L	

Input parameter	Estimate	DA Min	DA Max	PA distribution	Description / Comment	Source
TSH, free T3 and T4 test	25.60				For nivolumab+ipilimumab arm only	
Hepatitis B+C test	31.40				Once at BL for all arms	
Small lab	13.10				Contains Haematogram V only. For intermediate chemotherapy arm visits	
Imaging costs	Costs per visit	Monthly total varied *0.7	Monthly total varied *1.3	Monthly total costs varied with gamma distribution (mean=1, SE=0.153)	All imaging costs also assumed for cisplatin arms since performed in separate visits	
Screening Biopsy	13,439				One-off costs	SwissDRG (E02C)
CT Scan chest + abdomen	811				Every 6 weeks during 1. year, every 3 months afterwards	TARMED, “Real-world” data of the cantonal hospital of Lucerne
First-line (1L) AE costs	One-off costs (in CHF)					See Supplementary Table 9 for more details
Nivolumab+ipilimumab	1,042	682.81	1,500.47	Gamma(mean=1, SE=0.153)		
Pemetrexed+carboplatin	677	437.26	966.11			
Pemetrexed+cisplatin	1,221	791.09	1,752.33			
Pemetrexed+cisplatin + bevacizumab	3,608	2,344.69	5,156.21			
Maximum first line treatment durations						
1L Nivolumab+ipilimumab	14	--	--	--		Baas Table S1 Mean=7.9 months, Median=5.6 months [8]
1L Pemetrexed+carboplatin	3	--	--	--		Baas Mean=3 months Median= 3.5 Months [8]
Treatment durations of further lines in Markov models						
2L Nivolumab	4	2.607	5.674	Gamma(mean, 0.2*mean)	3 month in partitioned survival analysis model	
2L Pemetrexed+carboplatin	3	1.917	4.253	Gamma(mean, 0.2*mean)	2 month in partitioned survival analysis model	Baas Mean 1L duration 3 months [8]
3L Gemcitabine/ Vinorelbine	2	1.295	2.863	Gamma(mean, 0.2*mean)	1 month in partitioned survival analysis model	

Input parameter	Estimate	DA Min	DA Max	PA distribution	Description / Comment	Source
Proportion of patients with further line treatments						Own assumptions
2L Pemetrexed+carboplatin after 1L Immunotherapy	0.65	0.372	0.878	Beta(mean, 0.2*mean)		
2L Nivolumab after 1L Chemotherapy	0.62	0.366	0.840	Beta(mean, 0.2*mean)		
3L Gem or Vino after 1L Immunotherapy	0.35	0.221	0.494	Beta(mean, 0.2*mean)		
3L Gem or Vino after 1L Chemotherapy	0.35	0.221	0.494	Beta(mean, 0.2*mean)		
Late-stage palliative care	Monthly costs (in CHF)					
Monthly visit + laboratory tests + pain medication	159.26	103.17	228.50	Gamma(mean, 0.2*mean)		AL, SL, TARMED
	One-off costs (in CHF)					
Inpatient terminal/EOL costs	27,427	17,829	39,080	Gamma(mean, 0.2*mean)		"Real-world" data of the cantonal hospital of Lucerne
Utilities					>=10000 simulations	NICE 2021 HTA [5] (page 200)
PFS Immunotherapy on treatment mean (SE)	0.736	0.712	0.759	Beta(mean, SE=(0.012))		
PFS Immunotherapy on treatment SE				not varied		
PFS Immunotherapy off mean (SE)	0.733	0.692	0.773	Beta(mean, SE=(0.021))		
PFS Immunotherapy off SE				not varied		
PFS Pemetrexed+carboplatin on	0.734	0.710	0.757	Beta(mean, SE=0.012)		
PFS Pemetrexed+carboplatin on SE				not varied		
PFS Pemetrexed+carboplatin off	0.719	0.685	0.752	Beta(mean, SE=0.017)		
PFS Pemetrexed+carboplatin off SE				not varied		
PFS Pem+platin+bevacizumab	= PFS Chemotherapy on	0.710	0.757	Beta(mean, SE)		
PFS Pem+platin+bevacizumab SE	= PFS Chemotherapy on SE	-	-	-		

Input parameter	Estimate	DA Min	DA Max	PA distribution	Description / Comment	Source
For Markov state transition model						
PD Immunotherapy on	0.708	0.676	0.739	Beta(mean, SE=0.016)		
PD Immunotherapy on SE				-		
PD Immunotherapy off	0.607	0.577	0.636	Beta(mean, SE=0.015)		
PD Immunotherapy off SE				-		
PD Pem+platin on	0.638	0.578	0.676	Beta(mean, SE=0.030)		
PD Pem+platin on SE				-		
PD Pem+platin off	0.572	0.514	0.630	Beta(mean, SE=0.015)		
PD Pem+platin off SE				-		
PD Pem+platin+bevacizumab on	= PD Chemotherapy on	0.578	0.676	Beta(mean, SE)		
PD Pem+platin+bevacizumab off	= PD Chemotherapy off	0.514	0.630	Beta(mean, SE)		
For partitioned survival analysis model (scenario analysis)						NICE 2021 HTA [5] (page 99/481)
PD Immunotherapy	0.65 (0.01)					
PD Chemotherapy	0.58 (0.02)					
PD Pem+platin+bevacizumab						
Survival modelling overall	Type of fitted distribution or HR					
OS Immunotherapy	Spline Normal 1 knot	95%LCL	95% UCL			Re-created KM curves, selected best fitting curve + extrapolation
OS Chemotherapy	Spline Normal 1 knot					
OS HR Chemotherapy vs Chemotherapy+ Bevacizumab	0.77 base case	0.62	0.95	0.084 (Scenario: se(ln(HR))=0.1083)		Adjusted HR [15]
PFS Immunotherapy	Spline Normal 1 knot					Re-created KM curves, selected best fitting curve + extrapolation
PFS Chemotherapy	Hazard 2 knots					
PFS HR Chemotherapy vs Chemotherapy+ Bevacizumab	0.61 base case (0.60 scenario)	0.50	0.75	0.064 (Scenario: se(ln(HR))=0.1002)	Unadjusted HR and se from model of re-created data	Adjusted HR [15]
Epithelioid subgroup						
OS Immunotherapy	Spline Normal 1 knot					
OS Chemotherapy	Spline Odds 1 knot					
PFS Immunotherapy	Generalised gamma					
PFS Chemotherapy	Spline Odds 2 knots					

Input parameter	Estimate	DA Min	DA Max	PA distribution	Description / Comment	Source
Non-Epithelioid subgroup						
OS Immunotherapy	Loglogistic					
OS Chemotherapy	Odds 1 knot					
PFS Immunotherapy	Hazard 2 knots					
PFS Chemotherapy	Loglogistic					
Budget Impact Model inputs						
Swiss population (end of 2021)	8,738,800	-	-			FSO [16]
Swiss population in 2020, 2019, 2018	8,670,000 8,606,000 8,545,000	-	-			FSO [17]
Annual population growth	0.8%	-	-			FSO [16]
MPM incidence rate (per 100,000) in 2019	2.25	-	-			NICER [18]
Yearly increase in MPM incidence number between 2022 and 2026	2.6 persons per year	-	-		Resulted in estimated 206 (2022), 211 (2023), 215 (2024), 219 (2025), 224 (2026) incident MPM patients in Switzerland	Derived from SUVA "Unfallbericht" 2020 assuming linear increase [19]
Percentage with non-epithelioid (mean 2015-2019)	58.2%	-	-			NICER [18]
Percentage of PD-L1 >=1% within epithelioid histology group	43.7%	-	-			Cedrés [20]
Market shares in Supplementary Table 8						

AL Analysis List, *CHF* Swiss Francs, *D* Day, *DA* deterministic analysis, *FSO* Swiss Federal Statistical Office, *Gem* gemcitabine, *HR* hazard ratio, *HTA* Health Technology Assessment, *i.v*. intravenous, *KM* Kaplan-Meier, *max* maximum value, *mg* milligram, *ml* millilitre, *min* minimum value, *MPM* malignant pleural mesothelioma, *NICER* Foundation National Institute for Cancer Epidemiology and Registration, *OS* overall survival, *PD* progressed disease, *PD-L1* programmed death-ligand 1, *pem* pemetrexed, *PFS* progression-free survival, *PA* probabilistic analysis, *Q3W* every 3 weeks, *sd* standard deviation, *se* standard error, *SL* (Swiss) specialty list, *SUVA* Swiss Institute for Accident Insurance, *vino* vinorelbine, *1L* first-line, *2L* second-line, *3L* third-line. All costs are in Swiss Francs

9 Adverse events

Supplementary Table 9. Adverse event occurrences and costs

Adverse event types	Percentages of treatment-related AEs				Further AE information		Inpatient costs before weighting (in CHF)[2]	Outpatient costs before weighting (in CHF)	Total costs (in CHF)	AE costs per treatment arm			
	CM-743		MAPS							CM-743		MAPS	
	Ipi + Nivo	Mainly Carbo+ Pem	Cis+ Pem	Cis+Pem +Beva	% inpatient (%outpatient)	Inpatient DRG [12] codes[1] or outpatient sources				Ipi + Nivo	Mainly Carbo+ Pem	Cis+Pem	Cis+Pem+ Beva
Anaemia	0.3%	11.3%	13.40%	7.20%	0% (100%)	AL [14], SL [11], TARMED [13], Erythrocyte concentrate [21], Jetscan [22]	-	989	989	3	112	132	71
Thrombocytopenia	0.7%	3.5%	9.4%	9.9%	0% (100%)	AL [14], SL [11], TARMED [13], Thrombocyte concentrate [21], Jetscan [22]	-	1,863	1,863	13	65	175	184
Febrile Neutropenia	0%	1.1%	3.1%	1.8%	100% (0%)	Q60A (10% weight), Q60B (90% weight)	10,353 7,478	-	7,766	0	85	241	140
Colitis / diarrhoea	5.6%	1.1%	0.9%	0.5%	100% (0%)	G87B Infliximab supplementary charges	15,419 1,124	-	16,543	926	182	149	83
Vomiting or nausea	0.3%	4.6%	8.0%	0.081	100% (0%)	G72A (10%), G72B (90%)	6,684 4,563	-	4,775	14	220	382	387
Cardiovascular AEs			0.9%	28.8%	100% (0%)	F62D (45%), F66B (45%), F75D (10%)	8,051 5,227 19,088	-	7,884	0	0	71	2,271
Hypertension			0%	23.0%	20% (80%)	Inpatient DRG: F67A (90%), F67B (10%) Outpatient:	4,664 7,227		1,005	0	0	0	231
Arterial and venous thromboembolic events			0.9%	5.8%	0% (100%)	Cost items: drugs (rivaroxaban, dalteparin), physician visit, ultrasound & angio CT;	-	3,236	3,236	0	0	29	188

Adverse event types	Percentages of treatment-related AEs				Further AE information		Inpatient costs before weighting (in CHF)[2]	Outpatient costs before weighting (in CHF)	Total costs (in CHF)	AE costs per treatment arm			
	CM-743		MAPS							CM-743		MAPS	
	Ipi + Nivo	Mainly Carbo+ Pem	Cis+ Pem	Cis+Pem +Beva	% inpatient (%outpatient)	Inpatient DRG [12] codes[1] or outpatient sources				Ipi + Nivo	Mainly Carbo+ Pem	Cis+Pem	Cis+Pem+ Beva
						Cost sources: AL [14], SL [11], TARMED [13], Real-world angio CT costs from Cantonal Hospital of Lucerne							
Leukopenia	0	2.8%			0% (100%)		-	0	0				
Dermatitis (rash, pruritus)	2%	0			20% (80%)	Inpatient DRG: J61D Outpatient: SL [11], TARMED [13]	7,428 489		1,877	38	0	0	0
Increased lipase	4.3%	0.4%			0% (100%)	TARMED [13]	-	704	704	30	3	0	0
Increased amylase	2.3%	0.0%			0% (100%)	TARMED [13]	-	704	704	16	0	0	0
Creatinine concentration increase			1.8%	3.6%	0% (100%)	TARMED [13]	-	704	704	0	0	13	25
Asthenia or fatigue	1.0%	6.0%	12.5%	13.50%	0% (100%)	Real-world costs from Cantonal Hospital of Lucerne for 2 consultations for nutritional counselling	-	176	176	2	11	22	24
Anorexia			4.0%	2.3%	0% (100%)		-	176	176	0	0	7	4
Neutropenia	0.6%	15.1%	44.6%	44.1%	0% (100%)	Assumption of clinical expert group	-	0	0				
									Summed costs per treatment arm (in CHF):	1,042	677	1,221	3,608

AE adverse event, *AL* analysis list, *beva* bevacizumab, *carbo* carboplatin, *CHF* Swiss Francs, *cis* cisplatin, *CT* computed tomography, *DRG* Diagnosis Related Group, *ipi* ipilimumab, *nivo* nivolumab, *pem* pemetrexed, *SL* specialty list, TARMED Swiss outpatient tariff system

[1] In case several DRGs were relevant for a particular AE (inpatient hospital treatment), we applied the weights indicated in brackets after the DRG code in order to calculate averaged AE costs.

[2] Hospital inpatient costs were estimated in multiplying the cost weights of relevant diagnosis related group (DRG) codes of the SwissDRG 11.0 system with the latest available (2021/2022) averaged Swiss Cantonal DRG base weights (10,051).

10 Resource use

Supplementary Table 10. Resource use

Resource type	Description of resource use
Physician visits	
On treatment	According to dosage administration
	For the chemotherapy arm only: After 2 weeks short intermediate oncologist visit + small lab
Off treatment	Every 3 months oncologist visit including report
Imaging	
Biopsy	Once at screening
CT scan	PFD state: Every 6 weeks during the first year, every 3 months afterwards
	PD: Every 3 months
	During cisplatin treatment, CT scan counted separately and not included in inpatient DRG
Late-stage palliative care	3-monthly oncologist visit + laboratory tests

CT computed tomography, *DRG* diagnosis related group, *PD* progressed disease, *PFD* progressed-free disease

11 Budget impact

Supplementary Table 11. Market Shares

Strategy and treatments		Market Shares									
	2018-2021[a]	2022	2023	2024	2025	2026	2022	2023	2024	2025	2026
Applying strictly the Swissmedic approval		**Non-epithelioid OR epithelioid combined with PD-L1>=1% patients**					**Epithelioid AND PD-L1<1% patients**				
Nivolumab+ipilimumab	0%	60%	70%	80%	90%	90%	0%	0%	0%	0%	0%
Pemetrexed + carboplatin	50%	20%	15%	10%	5%	5%	50%	50%	50%	50%	50%
Pemetrexed + platinum + bevacizumab	50%	20%	15%	10%	5%	5%	50%	50%	50%	50%	50%
Targeting all patients		**Non-epithelioid patients**					**Epithelioid patients**				
Nivolumab+ipilimumab	0%	60%	70%	80%	90%	90%	60%	70%	80%	90%	90%
Pemetrexed + carboplatin	50%	20%	15%	10%	5%	5%	20%	15%	10%	5%	5%
Pemetrexed + platinum + bevacizumab	50%	20%	15%	10%	5%	5%	20%	15%	10%	5%	5%
No nivolumab+ ipilimumab		**Non-epithelioid patients**					**Epithelioid patients**				
Nivolumab+ipilimumab	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Pemetrexed + carboplatin	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Pemetrexed + platinum + bevacizumab	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%

[a] Only the follow-up treatment costs of these patients during the years 2022-2026 were included while continuing their original treatment.

PD-L1 programmed death-ligand 1

At the end of 2021, there were 8,738,800 residents permanently living in Switzerland [16]. There was a growth in the Swiss permanent resident population of 0.8% between 2020 and 2021 [16] leading to an expected population of 8,808,710 at the end of 2022 (Supplementary Table 12).

To estimate the malignant pleural meosthelioma (MPM) incidence of the years 2020 to 2026, we added a yearly increase of 2.6 persons per year to the 2019 MPM incidence rate as derived from the Suva accident statistic (UVG 2020 report [19]), based on 180 MPM patients at the end of 2026, 162 MPM patients at the beginning 2020, and assuming a linear increase.

Supplementary Table 12. Number of MPM incident patients in Switzerland

	2018	*2019*	*2020*	*2021*	**2022**	**2023**	**2024**	**2025**	**2026**	Total since 2022
Number of patients overall in CH	*8,545,000*	*8,606,000*	*8,670,000*	*8,738,800*	8,808,710	8,879,180	8,950,214	9,021,815	9,093,990	
MPM incident patients in CH	*190*	*194*	*198*	*202*	206	211	215	219	224	1'075
Non-epithelioid MPM incident patients	*79*	*81*	*83*	*84*	86	88	90	92	94	449
Epithelioid MPM incident patients	*110*	*113*	*115*	*118*	120	123	125	128	130	626
Epithelioid and PD-L1>=1%	48	49	50	51	52	54	55	56	57	273
Epithelioid and PD-L1<1%	62	63	65	66	68	69	70	72	73	352
Non-epithelioid, or epithelioid plus PD-L1>=1%	*128*	*130*	*133*	*136*	139	142	145	148	151	723

CH Switzerland, *MPM* malignant pleural mesothelioma, *PD-L1* programmed death-ligand 1

12 ICER results

Supplementary Table 13. ICER result table

Treatment	Cost (CHF)	QALY overall (in PFD state)	LY[1]	ΔCost (CHF)	ΔQALY	**ICER[2] (CHF/ QALY gained)**	LY[3]	Mean duration (in months)[3]			Costs (in CHF)								
								1L treat-ment	PFD state	PD state	Drug 1L[4]	Drug 2L	Admin	Visit	Lab	Image	AE	Late-stage pallia-tive	EOL costs
Base case: Patients progress before they die, deterministic analysis																			
Pem+Platin	76'138	1.20 (0.62)	1.71				1.78	2.9	10.5	10.9	5'930	13'305	1'894	3'457	867	22'360	677	1'238	26'409
Pem+Platin +Beva	170'108	1.56 (1.01)	2.18	93'970	0.36	Ext. dominated	2.33	17.2	17.2	10.7	86'548	13'056	6'696	6'765	2'082	24'163	3'608	1'171	26'019
Nivo+Ipi	184'639	1.76 (1.07)	2.43	108'501	0.56	**192'797**	2.61	8.2	19.0	12.3	114'462	3'752	5'058	5'937	1'940	25'113	1'042	1'516	25'818
Scenario 1: Equal death probability from PFD and PD																			
Pem+Platin	71,777	1.21 (0.63)	1.72				1.79	2.92	10.6	10.9	5'967	9'264	1'735	3'224	781	22'392	677	1'337	26'399
Pem+Platin +Beva	164,268	1.59 (1.02)	2.20	92'491	0.37	Ext. dominated	2.35	17.37	17.4	10.9	87'520	6'729	6'477	6'403	1'952	24'237	3'608	1'342	26'000
Nivo+Ipi	175,693	1.69 (0.93)	2.32	103,916	0.48	**216,905**	2.49	7.84	16.2	13.8	109'196	2'008	4'437	4'952	1'707	24'628	1'042	1'827	25'896
Scenario 2: Partitioned Survival Analysis (2L/3L treatment as one-off costs, no treatment on/off specific utilities in PD state)																			
Pem+Platin	76'520	1.08 (0.59)							10.1	10.9	5'953	13'722	1'922	3'531	871	22'507	677	1'255	26'082
Nivo+Ipi	165'727	1.58 (0.98)		89'207	0.50	**178'094**			17.5	11.9	99'194	2'798	4'264	4'941	1'677	24'708	1'042	1'517	25'586
Pem+Platin +Beva	167'191	1.45 (0.98)		1'464	-0.13	Abs. dominated			16.9	10.8	84'381	13'506	6'872	5'573	2'056	24'322	3'608	1'189	25'685
Scenario 3: Cisplatin 1L																			
Pem+Platin	95'208	1.20 (0.62)	1.71				1.78	2.9	10.5	10.9	27'983	13'305	654	1'526	512	22'360	1'221	1'238	26'409
Nivo+Ipi	184'639	1.76 (1.07)	2.43	89'431	0.56	**158'911**	2.61	8.2	19.0	12.3	114'462	3'752	5'058	5'937	1'940	25'113	1'042	1'516	25'818
Pem+Platin +Beva	186'543	1.56 (1.01)	2.18	1'904	-0.20	Abs. dominated	2.33	17.2	17.2	10.7	107'650	13'056	4'333	4'819	1'725	24'163	3'608	1'171	26'019

Treatment	Cost (CHF)	QALY overall (in PFD state)	LY[1]	ΔCost (CHF)	ΔQALY	**ICER[2] (CHF/ QALY gained)**	LY[3]	Mean duration (in months)[3]			Costs (in CHF)								
								1L treat-ment	PFD state	PD state	Drug 1L[4]	Drug 2L	Admin	Visit	Lab	Image	AE	Late-stage pallia-tive	EOL costs
Scenarion 4: Maximum 1L treatment duration																			
Pem+Platin	79'068	1.20 (0.63)	1.71				1.78	3.8	10.5	10.9	7'949	13'305	2'316	3'869	945	22'360	677	1'238	26'409
Pem+Platin +Beva	172'975	1.56 (1.01)	2.18	93'906	0.36	Ext. dominated	2.33	17.2	17.2	10.7	88'666	13'056	7'133	7'069	2'091	24'163	3'608	1'171	26'019
Nivo+Ipi	220'602	1.76 (1.07)	2.43	141'534	0.56	**251'714**	2.61	10.7	19.0	12.3	148'037	3'752	6'259	6'767	2'297	25'113	1'042	1'516	25'818
Scenario 5: Epithelioid subtype																			
Pem+Platin	78'693	1.44 (0.77)	2.05				2.19	2.9	13.4	12.9	5'985	14'131	1'959	3'725	951	23'680	677	1'472	26'113
Nivo+Ipi	180'101	1.75 (1.01)	2.42	101'408	0.32	**Ext. dominated**	2.60	7.9	17.9	13.3	110'293	3'720	4'901	5'746	1'869	25'042	1'042	1'668	25'820
Pem+Platin +Beva	215'397	1.95 (1.50)	2.72	136'704	0.51	**266'267**	3.03	27.7	27.7	8.6	125'278	13'136	8'866	9'034	2'899	26'162	3'608	922	25'492
Scenario 6: Non-epithelioid subtype																			
Pem+Platin	70'409	0.73 (0.47)	1.05				1.07	2.9	7.8	5.0	5'885	11'186	1'738	3'032	733	19'721	677	477	26'959
Pem+Platin +Beva	138'911	0.94 (0.74)	1.32	68'502	0.21	Ext. dominated	1.37	12.6	12.6	3.8	64'987	10'363	5'305	5'235	1'543	20'819	3'608	322	26'728
Nivo+Ipi	186'934	1.92 (1.38)	2.64	116'526	1.19	**97'894**	2.99	8.4	24.8	11.0	116'419	3'605	5'077	6'288	2'063	25'781	1'042	1'136	25'523
Scenario 7: 10-year time horizon																			
Pem+Platin	75'926	1.19 (0.62)	1.69				1.76	2.9	10.5	10.6	5'930	13'302	1'894	3'457	867	22'305	677	1'209	26'286
Pem+Platin +Beva	168'560	1.51 (1.00)	2.12	92'634	0.33	Ext. dominated	2.23	17.0	17.0	9.8	85'864	12'979	6'654	6'718	2'066	23'942	3'608	1'077	25'652
Nivo+Ipi	183'668	1.69 (1.01)	2.34	107'742	0.51	**212'460**	2.47	8.2	17.3	12.3	114'462	3'726	5'052	5'847	1'914	24'790	1'042	1'514	25'322
Scenario 8: Discount rate 0%																			
Pem+Platin	77'850	1.25 (0.63)	1.78				1.78	2.9	10.5	10.9	5'930	13'581	1'910	3'491	879	22'614	677	1'342	27'425
Pem+Platin +Beva	176'217	1.66 (1.05)	2.33	98'367	0.41	Ext. dominated	2.33	17.2	17.2	10.7	89'577	13'595	6'894	6'985	2'161	24'664	3'608	1'324	27'410
Nivo+Ipi	187'756	1.89 (1.16)	2.61	109'906	0.64	**170'908**	2.61	8.2	19.0	12.3	114'887	3'869	5'103	6'103	1'988	25'749	1'042	1'615	27'399

Treatment	Cost (CHF)	QALY overall (in PFD state)	LY[1]	ΔCost (CHF)	ΔQALY	**ICER[2] (CHF/ QALY gained)**	LY[3]	Mean duration (in months)[3]			Costs (in CHF)								
								1L treat-ment	PFD state	PD state	Drug 1L[4]	Drug 2L	Admin	Visit	Lab	Image	AE	Late-stage pallia-tive	EOL costs
Scenario 9: Discount rate 5%																			
Pem+Platin	75'115	1.17 (0.62)	1.67				1.78	2.9	10.5	10.9	5'930	13'133	1'884	3'436	861	22'212	677	1'178	25'803
Pem+Platin +Beva	166'568	1.50 (0.99)	2.11	91'454	0.33	Ext. dominated	2.33	17.2	17.2	10.7	84'785	12'734	6'580	6'636	2'037	23'883	3'608	1'090	25'215
Nivo+Ipi	182'846	1.69 (1.02)	2.33	107'731	0.52	**206'962**	2.61	8.2	19.0	12.3	114'192	3'685	5'030	5'846	1'914	24'764	1'042	1'457	24'916

[1] discounted

[2] of non-dominated strategies

[3] undiscounted

[4] the scenario with cisplatin contains also inpatient DRG costs (including drug, admin, visit, lab). Imaging always assumed as a separate visit.

Abs absolutely, *AE* adverse event, *CHF* Swiss Francs, *EOL* end of life, *ext* extendedly, *ICER* incremental cost-effectiveness ratio, *ipi* ipilimumab, *LCL* lower confidence limit, *LYs* life years, *nivo* nivolumab, *PD* progressed disease, *PFS* progression-free survival, pem pemetrexed, *QALY* quality-adjusted life-year, *UCL* upper confidence limit, *WTP* willingness-to-pay

Supplementary Table 14. 5-year budget impact with FU costs of patients from previous years

Budget impact (costs in CHF)	**2022**	**2023**	**2024**	**2025**	**2026**	**Total**
Applying strictly the Swissmedic label	**Non-epithelioid OR epithelioid combined with PD-L1>=1%**					
Nivolumab+ ipilimumab	12'265'150	16'400'105	19'725'062	23'039'836	24'186'595	95'616'747
Pemetrexed +carboplatin	3'104'043	2'174'955	1'503'138	894'872	676'444	8'353'452
Pemetrexed +carboplatin + beva	7'159'894	5'194'532	3'655'992	2'243'715	1'599'943	19'854'077
					Subtotal 1 Costs	123'824'276
	Epithelioid AND PD-L1<1%					
Nivolumab+ ipilimumab	0	0	0	0	0	0
Pemetrexed+carboplatin	2'527'822	2'581'167	2'635'275	2'690'111	2'745'660	13'180'035
Pemetrexed +carboplatin + beva	5'461'297	5'576'572	5'693'585	5'812'228	5'932'417	28'476'099
					Subtotal 2 Costs	41'656'135
					Total costs	**165'480'411**
MS targeting all patients	**Non-epithelioid and epithelioid (since MS are the same)**					
Nivolumab+ ipilimumab	18'242'645	24'392'794	29'338'189	34'268'437	35'974'076	142'216'141
Pemetrexed +carboplatin	4'616'816	3'234'932	2'235'702	1'330'994	1'006'113	12'424'557
Pemetrexed +carboplatin + beva	10'649'312	7'726'119	5'437'761	3'337'204	2'379'685	29'530'081
					Total costs	**184'170'779**
No nivolumab+ ipilimumab	**Non-epithelioid and epithelioid (since MS are the same)**					
Nivolumab+Ipilimumab	0	0	0	0	0	0
Pemetrexed + carboplatin	7'714'630	7'877'434	8'042'563	8'209'919	8'379'448	40'223'994
Pemetrexed + platinum + bevacizumab	16'667'267	17'019'075	17'376'185	17'738'270	18'105'075	86'905'872
					Total costs	**127'129'866**

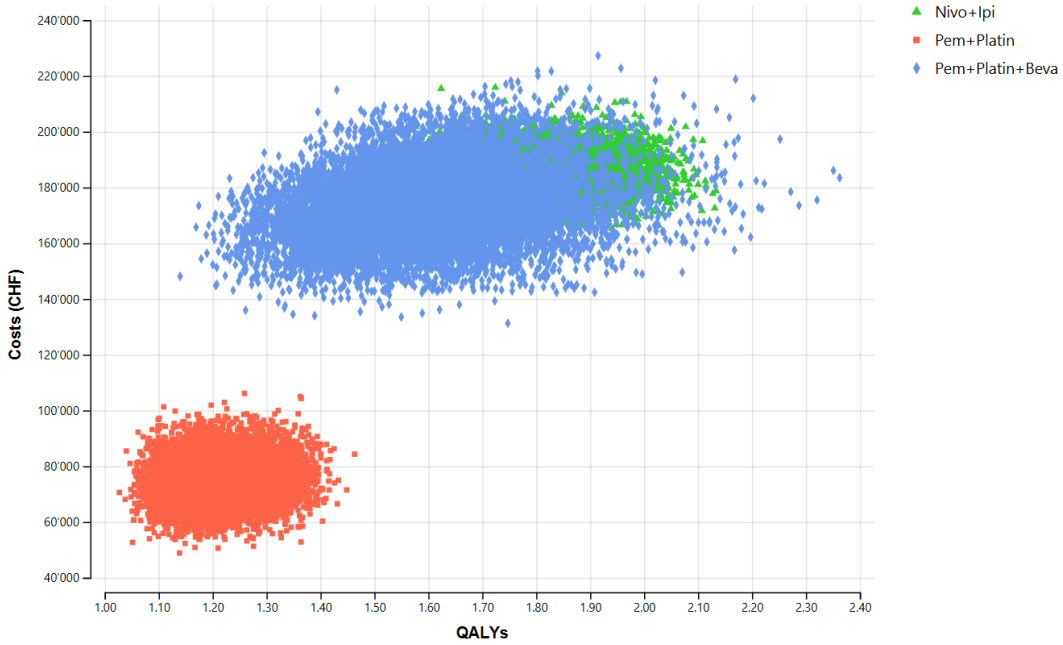
CHF Swiss Francs, *FU* follow-up, *ipi* ipilimumab, *MS* market shares, *nivo* nivolumab, *PD-L1* programmed death-ligand 1

Supplementary Table 15. 5-year budget impact without FU costs of patients from previous years

Budget impact (costs in CHF)	2022	2023	2024	2025	2026	Total
Applying strictly the Swissmedic label	**Non-epithelioid OR epithelioid combined with PD-L1**					
Nivolumab+ ipilimumab	12'265'150	16'400'105	19'725'062	23'039'836	24'186'595	95'616'747
Pemetrexed +carboplatin	1'388'510	1'490'149	1'215'046	795'851	676'444	5'566'001
Pemetrexed +carboplatin + beva	2'697'384	3'017'743	2'602'931	1'841'298	1'599'943	11'759'299
					Subtotal 1 Costs	112'942'047
	Epithelioid AND PD-L1<1%					
Nivolumab+ ipilimumab	0	0	0	0	0	0
Pemetrexed+carboplatin	1'691'747	2'247'423	2'494'871	2'641'853	2'745'660	11'821'554
Pemetrexed +carboplatin + beva	3'286'465	4'515'701	5'180'370	5'616'107	5'932'417	24'531'061
					Subtotal 2 Costs	36'352'615
					Total costs	**149'294'663**
MS targeting all patients	**Non-epithelioid and epithelioid (since MS are the same)**					
Nivolumab+ ipilimumab	18'242'645	24'392'794	29'338'189	34'268'437	35'974'076	142'216'141
Pemetrexed +carboplatin	2'065'209	2'216'382	1'807'206	1'183'714	1'006'113	8'278'625
Pemetrexed +carboplatin + beva	4'011'970	4'488'459	3'871'485	2'738'666	2'379'685	17'490'264
					Total costs	**167'985'030**
No nivolumab+ ipilimumab	**Non-epithelioid and epithelioid (since MS are the same)**					
Nivolumab+Ipilimumab	0	0	0	0	0	0
Pemetrexed + carboplatin	5'163'023	6'858'884	7'614'068	8'062'640	8'379'448	36'078'062
Pemetrexed + platinum + bevacizumab	10'029'925	13'781'415	15'809'909	17'139'732	18'105'075	74'866'055
					Total costs	**110'944'118**

CHF Swiss Francs, *FU* follow-up, *ipi* ipilimumab, *MS* market shares, *nivo* nivolumab, *PD-L1* programmed death-ligand 1

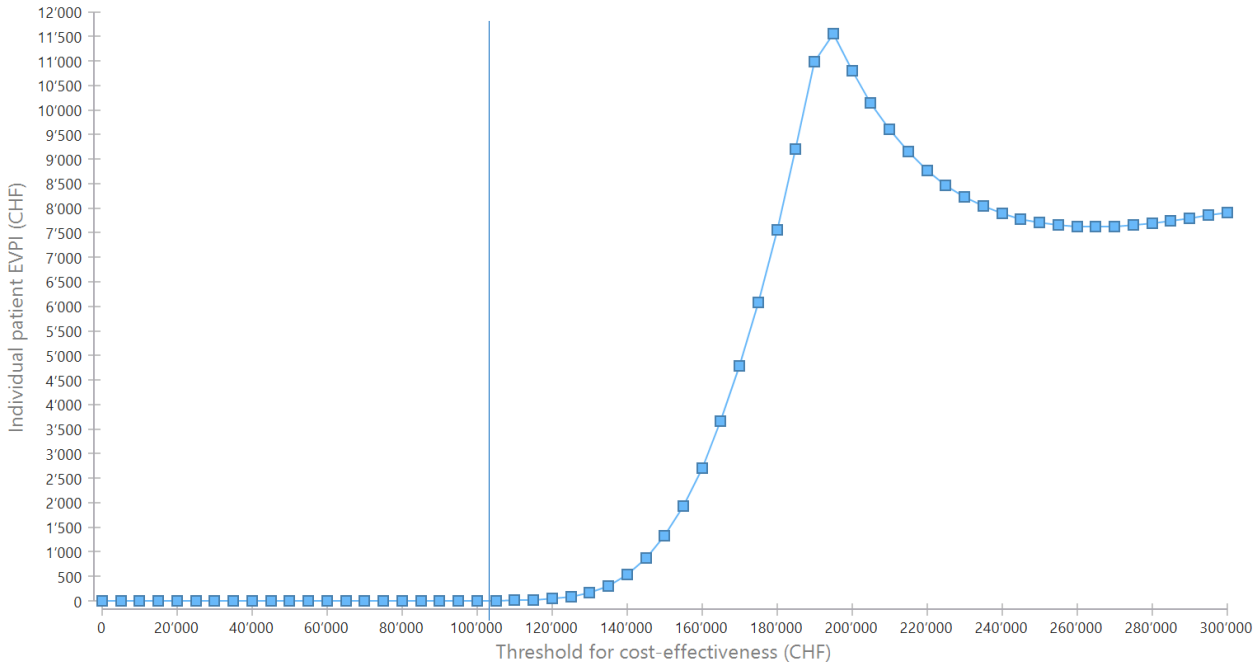
13 Scatterplot results



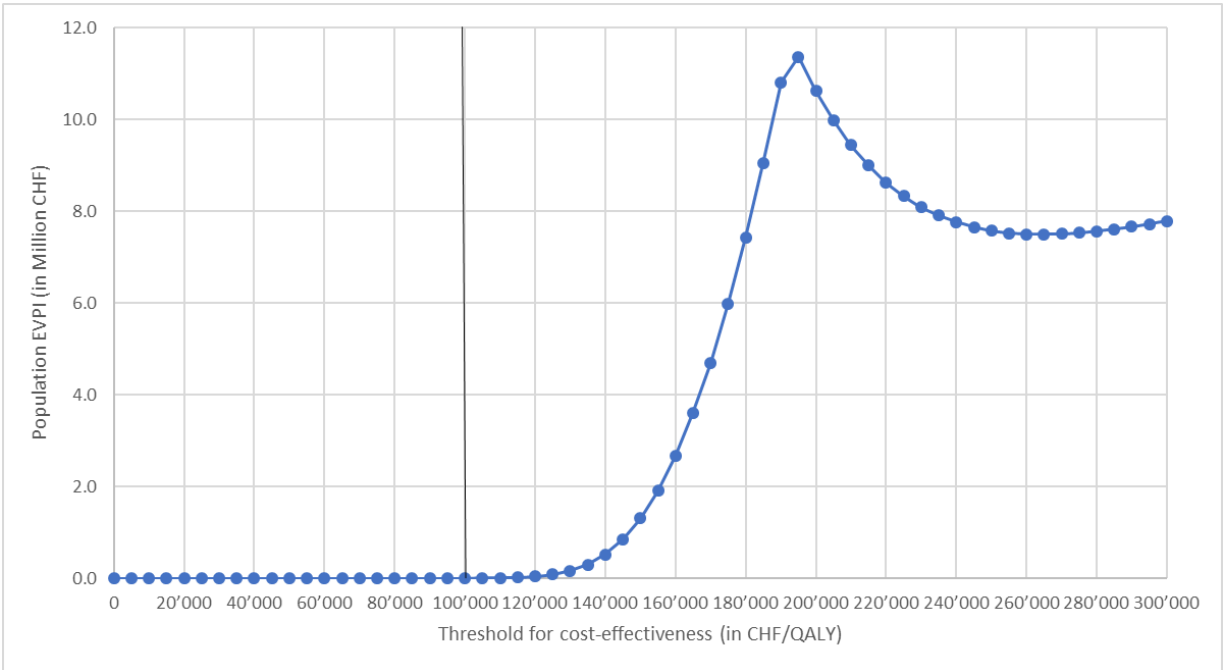
Supplementary Fig. 34 Cost-effectiveness plane (TreeAge output)

Beva bevacizumab, *CHF* Swiss Francs, *ipi* ipilimumab, *nivo* nivolumab, *pem* pemetrexed, *QALY* quality-adjusted life-year

14 EVPI



Supplementary Fig. 35 EVPI for an individual patient. *EVPI* expected value of perfect information, *WTP* willingness-to-pay



Supplementary Fig. 36 EVPI for the Swiss population. *CHF* Swiss Francs, *EVPI* expected value of perfect information, *QALY* Quality-adjusted life-year

Note: Population EVPI = Individual EVPI * $\sum_{t=1}^{T} \frac{Incidence_t}{(1+discount\ rate)^t}$, with T=effective lifetime (5 years assumed)

15 References

1. Briggs AC, Kark; Sculpher, Mark. Decision modelling for health economic evaluation2006.
2. Pahuta MA, Werier J, Wai EK, Patchell RA, Coyle D. A technique for approximating transition rates from published survival analyses. Cost Effectiveness and Resource Allocation. 2019 2019/07/01;17(1):12.
3. Zalcman G, Oulkhouir Y, Cornelissen R, Greillier L, Cid JR, Mazieres J, et al. LBA71 First-line nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) in patients (pts) with unresectable malignant pleural mesothelioma (uMPM): 4-year update from CheckMate 743. Annals of Oncology. 2022;33:S1438-S9.
4. NICE. Committee Papers 2022. Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]. 2022.
5. NICE. Committee papers 2021. Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]. 2021.
6. Peters S, Scherpereel A, Cornelissen R, Oulkhouir Y, Greillier L, Kaplan MA, et al. First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year outcomes from CheckMate 743. Ann Oncol. 2022 May;33(5):488-99.
7. NICE. Final appraisal document (FAD). Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma. 2022.
8. Baas P, Scherpereel A, Nowak AK, Fujimoto N, Peters S, Tsao AS, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. The Lancet. 2021 2021/01/30/;397(10272):375-86.
9. Popat S, Curioni-Fontecedro A, Dafni U, Shah R, O'Brien M, Pope A, et al. A multicentre randomised phase III trial comparing pembrolizumab versus single-agent chemotherapy for advanced pre-treated malignant pleural mesothelioma: the European Thoracic Oncology Platform (ETOP 9-15) PROMISE-meso trial. Annals of Oncology. 2020;31(12):1734-45.
10. Scherpereel A, Mazieres J, Greillier L, Lantuejoul S, Dô P, Bylicki O, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. Lancet Oncol. 2019 Feb;20(2):239-53.
11. Federal Office of Public Health. Swiss Specialty List ("Schweizer Spezialitätenliste"). Available from: http://www.spezialitaetenliste.ch/ShowPreparations.aspx?searchType=SUBSTANCE
12. Online Definitionshandbuch SwissDRG 9.0. 16.11.2022]; Available from: https://manual.swissdrg.org/de/11.3/supplements
13. TARMED Online Browser Tarifversion 1.09. 1.2.2021]; Available from: https://www.tarmed-browser.ch/de
14. Analysenliste (Version 1.August 2022). Swiss Federal Office of Public Health. 2022; Available from: https://www.bag.admin.ch/bag/de/home/versicherungen/krankenversicherung/krankenversicherung-leistungen-tarife/Analysenliste.html
15. Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. The Lancet. 2016;387(10026):1405-14.
16. Swiss Federal Statistical Office. Population size and change in Switzerland in 2021: definitive figures. Available from: https://www.bfs.admin.ch/bfs/en/home/statistics/population.gnpdetail.2022-0467.html
17. Swiss Federal Statistical Office. Key population figures, 1950-2021. Available from: https://www.bfs.admin.ch/bfs/en/home/statistics/population.assetdetail.23328853.html
18. National Institute for Cancer Epidemiology and Registration (NICER). Available from: https://www.nicer.org/en/home
19. Suva. Unfallstatistik UVG 2020. 2020; Available from: https://www.unfallstatistik.ch/d/publik/unfstat/unfstat_d.htm

20. Cedrés S, Ponce-Aix S, Zugazagoitia J, Sansano I, Enguita A, Navarro-Mendivil A, et al. Analysis of expression of programmed cell death 1 ligand 1 (PD-L1) in malignant pleural mesothelioma (MPM). PLoS One. 2015;10(3):e0121071.
21. Blutspende SRK Zürich. 31.8.2022]; Available from: https://www.blutspendezurich.ch/fileadmin/pdf/Preislisten/Preisliste_2022_1.2.2022_fv_WEB.pdf
22. 2021 UNlimited world trade union GmbH. 31.8.2022]; Available from: https://shop-unlimited.com/b-braun-surecan-safety-ii-caresite-g20-25-mm.html