Supplementary appendix

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Table 1: Real-world evidence data comparator mixes

Category	Treatment	Distribution
Untreated population		
Immunotherapy	Pembrolizumab	86.8%
	Atezolizumab	1.6%
	Nivolumab	3.9%
	Nivolumab/ipilimumab	7.7%
Immunotherapy plus chemotherapy	Pembrolizumab/ pemetrexed/ platinum	66.7%
	Atezolizumab/ bevacizumab/ carboplatin/ paclitaxel	10.5%
	Pembrolizumab/ carboplatin/ paclitaxel	22.8%
Previously treated		
Chemotherapy	Docetaxel/ platinum	1.6%
	Gemcitabine/ platinum	1.8%
	Paclitaxel/ platinum	11.8%
	Vinorelbine/ platinum	0.0%
	Pemetrexed/ platinum	47.8%
	Docetaxel monotherapy	15.5%
	Docetaxel/ nintedanib	0.9%
	Docetaxel/ gemcitabine	6.1%
	Gemcitabine monotherapy	3.3%
	Vinorelbine monotherapy	0.0%
	Bevacizumab/ carboplatin/ paclitaxel	11.2%

Table 2: HRQL model parameters

Parameter	Value		Source	
Progression-free utility	0.719		VISION	
Post-progression utility	0.647		VISION	
Adverse event	**Disutility**	**Duration (days)**	**Disutility source**	**Duration source**
Alanine aminotransferase increase	-0.050	50.5	Assumption based on TA347 [19]	VISION
Alopecia	-0.045	37.2	Nafees et al, 2008 [52]	Assumed based on mean duration of all AEs in VISION
Amylase increase	-0.050	372.9	Assumed same as ALT increase	VISION
Anaemia	-0.073	77.3	Assumed same as Fatigue	VISION
Asthenia	-0.073	59.0	Assumed same as fatigue	VISION
Bilirubin increased	-0.050	37.2	Assumed same as ALT increase	Assumed based on mean duration of all AEs in VISION
Cardiac failure	-0.105	62.8	McMurray et al, 2018 [53]	VISION
Cough	-0.046	22.0	Doyle et al, 2008 [54]	VISION
Diarrhoea	-0.047	5.5	Nafees et al, 2008 [52]	VISION
Dyspnoea	-0.050	31.4	Parcha et al, 2018 [55] (Doyle et al, 2008 [54])	VISION
Fatigue	-0.073	526.7	Nafees et al, 2008 [52]	VISION
Febrile neutropenia	-0.090	7.1	Nafees et al, 2008 [52]	VISION
Hyperglycaemia	-0.122	1.0	Palmer et al, 2016 [55] (Currie et al, 2006 [56])	VISION
Hypertension	-0.030	107.0	Paracha et al, 2018 [55]	VISION
Hypoalbuminemia	-0.050	486.6	Assumed same as white blood cell count decrease	VISION
Hypomagnesemia	-0.003	7.0	CADTH, 2020 [57]	VISION

Hypophosphatemia	-0.003	193.3	Assumed same as hypomagnesemia	VISION
Increased Aspartate Aminotransferase	-0.050	25.1	Assumed same as ALT increase	VISION
Infection	-0.050	19.8	Assumption based on TA347 [19]	VISION
Leukopenia	-0.090	200.0	Assumed same as Neutropenia	VISION
Lipase increase	-0.073	76.8	Assumed same as anaemia	VISION
Lymphocyte count decrease	-0.050	122.0	Assumed same as white blood cell count decrease	VISION
Nausea	-0.048	7.8	Nafees et al, 2008 [52]	VISION
Neuromotor	-0.150	37.2	Tabberer et al, 2006 [58]	Assumed based on mean duration of all AEs in VISION
Neurosensory	-0.150	37.2	Tabberer et al, 2006 [58]	Assumed based on mean duration of all AEs in VISION
Neutropenia	-0.090	87.0	Nafees et al, 2008 [52]	VISION
Neutrophil count decrease	-0.090	33.3	Assumed same as neutropenia	VISION
Oedema peripheral/other	-0.085	311.3	Hagiwara et al, 2018 [59]	VISION
Pain	-0.069	31.0	Doyle et al, 2008 [54]	VISION
Platelet count decrease	-0.050	370.0	Assumed same as white blood cell count decrease	VISION
Pleural effusion	-0.008	246.6	Assumed same as pneumonia	VISION
Pneumonitis / pneumonia	-0.008	39.7	Marti et al, 2013 [60]	VISION
Pulmonary/Resp. Tract infection	-0.186	61.9	Hunter et al, 2015 [61]	VISION
Thrombocytopenia	-0.003	165.5	Handorf et al, 2012 [62]	VISION
Vomiting	-0.048	16.3	Nafees et al, 2008 [52]	VISION
White blood cell count decrease	-0.050	15.5	Assumption based on TA347 [19]	VISION

Table 3: Chosen base case curves for each comparison

Comparison	Treatment	OS curve	PFS curve
MAIC			
Tepotinib vs pembrolizumab + chemotherapy	Tepotinib	Log-logistic	Log-normal
	Pembrolizumab + chemotherapy	Log-logistic	Log-logistic
Tepotinib vs pembrolizumab monotherapy	Tepotinib	Log-normal	Log-normal
	Pembrolizumab	Log-normal	Generalised gamma
Tepotinib vs docetaxel + nintedanib	Tepotinib	Log-normal	Log-normal
	Docetaxel + nintedanib	Gamma	Log-logistic
Tepotinib vs docetaxel	Tepotinib	Exponential	Log-normal
	Docetaxel	Generalised gamma	Log-logistic
RWE ITC			
Tepotinib vs Immunotherapy ± chemotherapy	Tepotinib	Log-logistic	Log-logistic
	Immunotherapy	Exponential	Weibull
	Immunotherapy + chemotherapy	Exponential	Log-normal
	Tepotinib	Log-normal	Log-normal

Comparison	Treatment	OS curve	PFS curve
Tepotinib vs chemotherapy	Chemotherapy	Weibull	Log-logistic

Table 4: Base-case deterministic pairwise QALY results – real-world data

Health state	Tepotinib total	Comparator total	Incremental
Vs Immunotherapy			
Progression-free	1.35	0.66	0.69
Post-progression	0.69	0.68	0.01
Adverse events	-0.02180	-0.00295	-0.01885
Total	2.02	1.33	0.68
Vs Immunotherapy + chemotherapy			
Progression-free	1.35	0.74	0.61
Post-progression	0.69	0.70	-0.01
Adverse events	-0.02180	-0.01553	-0.00627
Total	2.02	1.42	0.60
Vs Chemotherapy			
Progression-free	0.90	0.50	0.40
Post-progression	0.70	0.61	0.10
Adverse events	-0.02279	-0.00920	-0.01359
Total	1.58	1.10	0.48

Table 5: Model predicted survival versus observed/weighted trial data

Untreated population															
Survival		Tepotinib vs pembrolizumab + chemotherapy				Tepotinib vs pembrolizumab				Tepotinib versus immunotherapy ± chemotherapy					
		Tepotinib		Pembrolizumab + chemotherapy		Tepotinib		Pembrolizumab		Tepotinib		Immunotherapy		Immunotherapy + chemotherapy	
		Observed [a]	Model	Observed	Model	Observed [a]	Model	Observed	Model	Observed	Model	Observed	Model	Observed	Model
Overall survival	Median (months)	32.7	37.0	22.3	21.6	29.8	34.7	26.0	25.5	21.3	20.5	19.8	17.7	19.3	19.1
	Lifetime mean (years)	-	5.9	-	3.7	-	6.3	-	5.2	-	3.6	-	2.1	-	2.3
	1 year	80.2%	81.2%	70.8%	70.0%	74.6%	75.9%	70.0%	68.7%	65.1%	67.0%	68.5%	62.7%	73.0%	64.8%
	2 years	60.8%	63.8%	46.2%	46.7%	57.0%	59.8%	52.5%	51.8%	44.4%	45.2%	25.8%	39.3%	34.6%	42.0%
	3 years	44.4%	51.1%	32.6%	33.1%	43.6%	49.3%	44.4%	41.5%	32.0%	32.7%	22.1%	24.6%	15.3%	27.2%
	4 years	44.2%	41.8%	-	24.8%	43.5%	41.8%	36.4%	34.5%	30.3%	25.1%	7.5%	15.4%	-	17.7%
Progression-free survival	Median (months)	15.8	20.7	9.2	9.7	13.5	17.7	8.3	8.5	8.7	10.8	3.6	5.3	6.7	6.9
	Lifetime mean (years)	-	4.5	-	1.7	-	4.5	-	3.0	-	2.2	-	1.0	-	1.1
	1 year	62.9%	64.1%	40.3%	42.1%	57.1%	59.1%	41.6%	42.2%	43.2%	47.1%	35.7%	30.1%	37.9%	31.6%
	2 years	47.2%	46.6%	22.4%	20.1%	43.1%	43.0%	28.3%	27.4%	31.0%	26.8%	14.9%	14.0%	15.9%	13.8%
	3 years	42.0%	36.4%	12.1%	11.9%	40.9%	34.0%	23.1%	20.6%	23.5%	17.8%	-	7.3%	4.0%	7.4%
	4 years	42.0%	29.7%	-	8.0%	40.9%	28.1%	16.6%	16.6%	23.5%	13.0%	-	4.0%	-	4.5%

Previously treated population													
Survival		Tepotinib vs docetaxel + nintedanib				Tepotinib vs docetaxel				Tepotinib vs chemotherapy			
		Tepotinib		Docetaxel + nintedanib		Tepotinib		Docetaxel		Tepotinib		Chemotherapy	
		Observed [a]	Model	Observed	Model	Observed [a]	Model	Observed	Model	Observed	Model	Observed	Model
Overall survival	Median (months)	18.8	18.2	12.9	13.1	23.7	21.8	9.3	9.0	19.3	18.6	11.0	14.7
	Lifetime mean (years)	-	2.9	-	1.5	-	2.6	-	1.2	-	2.7	-	1.8
	1 year	62.4%	64.4%	52.6%	54.1%	66.8%	68.4%	37.6%	39.7%	67.8%	66.4%	45.7%	57.6%
	2 years	43.9%	40.9%	25.5%	25.5%	49.6%	46.9%	17.7%	17.3%	38.4%	40.6%	28.7%	32.2%
	3 years	29.7%	28.1%	-	11.6%	31.6%	32.1%	-	8.7%	26.5%	26.7%	22.8%	17.9%
	4 years	19.0%	20.4%	-	5.2%	20.8%	22.0%	-	4.7%	18.5%	18.5%	22.8%	9.8%
Progression-free survival	Median (months)	8.3	8.5	4.1	3.5	11.0	9.7	3.1	3.2	8.3	9.2	4.8	5.1
	Lifetime mean (years)	-	1.3	-	0.5	-	1.6	-	0.5	-	1.4	-	0.7
	1 year	38.5%	38.3%	8.1%	7.8%	41.2%	43.5%	7.8%	9.1%	36.2%	40.5%	20.3%	21.9%
	2 years	18.8%	17.1%	-	2.0%	24.6%	23.2%	1.5%	2.8%	19.2%	18.3%	5.7%	7.1%
	3 years	17.9%	9.2%	-	0.9%	23.5%	14.4%	-	1.4%	14.1%	9.8%	5.7%	2.8%
	4 years	17.9%	5.5%	-	0.5%	23.5%	9.7%	-	0.8%	14.1%	5.9%	-	1.3%

[a] Observed data from VISION has been re-weighted to match the comparator population

Fig. 1: Modelled versus observed outcomes - untreated population – versus published clinical trials

A: Tepotinib versus pembrolizumab plus chemotherapy OS. **B:** Tepotinib versus pembrolizumab OS. **C:** Tepotinib versus pembrolizumab plus chemotherapy PFS. **D:** Tepotinib versus pembrolizumab PFS. **Notes:** Tepotinib numbers at risk represent the weighted sample size (WSS) after the weights from the MAIC have been applied.

Fig. 2: Modelled versus observed outcomes – previously treated population – versus published clinical trials

A

Overall survival (100% to 0%)

Years (0 to 30)

Model - tepotinib — KM - tepotinib
Model - Docetaxel + nintedanib — KM - Docetaxel + nintedanib

| Tepotinib | 45 | 28 | 14 | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Docetaxel + nintedanib | 322 | 163 | 72 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

B

Overall survival (100% to 0%)

Years (0 to 30)

Model - tepotinib — KM - tepotinib — Model - Docetaxel — KM - Docetaxel

| Tepotinib | 54 | 33 | 19 | 3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Docetaxel | 125 | 40 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

C

Progression-free survival (100% to 0%)

Years (0 to 30)

Model - Tepotinib — KM - Tepotinib
Model - Docetaxel + nintedanib — KM - Docetaxel + nintedanib

| Tepotinib | 45 | 15 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Docetaxel + nintedanib | 277 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

D

Progression-free survival (100% to 0%)

Years (0 to 30)

Model - Tepotinib — KM - Tepotinib — Model - Docetaxel — KM - Docetaxel

| Tepotinib | 54 | 12 | 4 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Docetaxel | 124 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

A: Tepotinib versus docetaxel plus nintedanib OS. **B:** Tepotinib versus docetaxel OS. **C:** Tepotinib versus docetaxel plus nintedanib PFS. **D:** Tepotinib versus docetaxel PFS. **Notes:** Tepotinib numbers at risk represent the weighted sample size (WSS) after the weights from the MAIC have been applied.

Fig. 3: Modelled versus observed outcomes – versus real-world data

A: Tepotinib versus immunotherapy (untreated) OS. **B:** Tepotinib versus immunotherapy + chemotherapy (untreated) OS. **C:** Tepotinib versus chemotherapy (previously treated) OS.

D: Tepotinib versus immunotherapy (untreated) PFS. **E:** Tepotinib versus immunotherapy + chemotherapy (untreated) PFS. **F:** Tepotinib versus chemotherapy (previously treated) PFS

Notes: Comparator numbers at risk represent the weighted sample size (WSS) after the weights from the propensity scoring has been applied.

Table 6: Scenario analysis – incremental life-years and QALYs – versus published clinical trials

Scenario		Vs pembrolizumab + chemotherapy		Vs pembrolizumab		Vs docetaxel + nintedanib		Vs docetaxel		Vs Immunotherapy		Vs Immunotherapy + chemotherapy		Vs Chemotherapy	
		Inc. LYs	Inc. QALYs	Inc. LYs	Inc. QALYs	Inc. LYs	Inc. QALYs	Inc. LYs	Inc. QALYs	Inc. LYs	Inc. QALYs	Inc. LYs	Inc. QALYs	Inc. LYs	Inc. QALYs
Tepotinib OS	Exponential	0.95	0.69	-1.08	-0.26	**0.91**	**0.54**	*1.40*	*0.85*	**0.55**	**0.33**	**0.38**	**0.24**	**0.60**	**0.35**
	Gen Gamma	**1.80**	**1.01**	**0.62**	**0.39**	2.24	1.04	2.25	1.18	**1.27**	**0.63**	**1.10**	**0.55**	**0.84**	**0.45**
	Gompertz	**2.07**	**1.10**	2.08	0.88	**0.87**	**0.52**	1.18	0.75	1.80	0.84	**1.64**	**0.75**	**0.50**	**0.31**
	Log-logistic	*2.28*	*1.17*	*0.67*	*0.38*	1.70	0.83	2.43	1.24	*1.42*	*0.68*	*1.25*	*0.60*	0.99	0.50
	Log-normal	**2.85**	**1.38**	**1.11**	**0.56**	*1.44*	*0.75*	2.17	1.15	**1.60**	**0.77**	**1.44**	**0.68**	*0.91*	*0.48*
	Weibull	0.67	0.57	-0.95	-0.20	**0.79**	**0.49**	1.26	0.79	**0.54**	**0.33**	**0.38**	**0.24**	**0.42**	**0.27**
	Gamma	0.67	0.57	-1.07	-0.25	**0.79**	**0.49**	1.28	0.80	**0.50**	**0.31**	**0.33**	**0.22**	**0.43**	**0.27**
Tepotinib PFS	Exponential	2.28	1.09	1.11	0.47	**1.44**	**0.74**	1.40	0.84	**1.42**	**0.66**	**1.25**	**0.57**	0.91	0.47
	Gen Gamma	2.28	1.20	1.11	0.61	**1.44**	**0.77**	1.40	0.87	**1.42**	**0.70**	**1.25**	**0.62**	**0.91**	**0.50**
	Gompertz	2.28	1.21	1.11	0.62	**1.44**	**0.77**	1.40	0.87	1.42	0.72	1.25	0.64	0.91	0.50
	Log-logistic	**2.28**	**1.16**	**1.11**	**0.55**	1.44	0.75	1.40	0.85	*1.42*	*0.68*	*1.25*	*0.60*	0.91	0.48
	Log-normal	*2.28*	*1.17*	*1.11*	*0.56*	*1.44*	*0.75*	*1.40*	*0.85*	1.42	0.69	1.25	0.60	*0.91*	*0.48*
	Weibull	2.28	1.11	1.11	0.51	**1.44**	**0.74**	1.40	0.84	1.42	0.66	1.25	0.58	0.91	0.47
	Gamma	2.28	1.10	1.11	0.50	**1.44**	**0.74**	1.40	0.83	1.42	0.66	1.25	0.57	0.91	0.47
Comparator OS	Exponential	**3.28**	**1.55**	**2.59**	**1.05**	1.39	0.73	1.50	0.90	*1.42*	*0.68*	*1.25*	*0.60*	0.88	0.46
	Gen Gamma	**3.44**	**1.63**	**1.57**	**0.71**	1.33	0.70	*1.40*	*0.85*	1.65	0.80	**1.30**	**0.63**	0.23	0.20
	Gompertz	3.65	1.74	**1.20**	**0.59**	1.46	0.76	1.51	0.91	1.69	0.82	1.65	0.80	-0.46	-0.07
	Log-logistic	*2.28*	*1.17*	1.10	0.55	0.92	0.53	1.12	0.73	0.82	0.43	1.42	0.70	**0.57**	**0.36**
	Log-normal	**2.13**	**1.09**	*1.11*	*0.56*	1.09	0.59	1.24	0.77	0.75	0.39	1.43	0.69	0.57	0.34
	Weibull	**3.50**	**1.66**	**2.27**	**0.94**	**1.45**	**0.75**	**1.55**	**0.93**	**1.64**	**0.79**	**1.69**	**0.82**	*0.91*	*0.48*
	Gamma	**3.44**	**1.63**	**2.40**	**0.98**	*1.44*	*0.75*	1.55	0.93	1.58	0.76	1.69	0.82	0.95	0.50
Comparator PFS	Exponential	**2.28**	**1.18**	1.11	0.60	**1.44**	**0.75**	1.40	0.86	1.42	0.69	1.25	0.60	0.91	0.48
	Gen Gamma	**2.28**	**1.17**	**1.11**	**0.56**	**1.44**	**0.75**	1.40	0.85	1.42	0.68	1.25	0.60	*0.91*	*0.48*
	Gompertz	**2.28**	**1.18**	1.11	0.53	**1.44**	**0.76**	1.40	0.86	1.42	0.67	**1.25**	**0.60**	0.91	0.47
	Log-logistic	*2.28*	*1.17*	**1.11**	**0.58**	*1.44*	*0.75*	*1.40*	*0.85*	1.42	0.67	1.25	0.59	0.91	0.48
	Log-normal	**2.28**	**1.17**	**1.11**	**0.58**	1.44	0.75	1.40	0.86	1.42	0.67	**1.25**	**0.60**	0.91	0.47
	Weibull	2.28	1.18	1.11	0.60	**1.44**	**0.75**	1.40	0.86	*1.42*	*0.68*	1.25	0.60	0.91	0.48
	Gamma	2.28	1.18	1.11	0.60	**1.44**	**0.75**	1.40	0.86	1.42	0.69	1.25	0.60	0.91	0.48
Utility source: KN024		2.28	1.34	1.11	0.63	1.44	0.92	1.40	1.03	1.42	0.81	1.25	0.71	0.91	0.58

Key: Inc, incremental; LYs, life-years; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life-years. *Italic underlined* = base case; **Bold** = plausible curves

Fig. 4: External validation of OS and PFS – versus published clinical trials
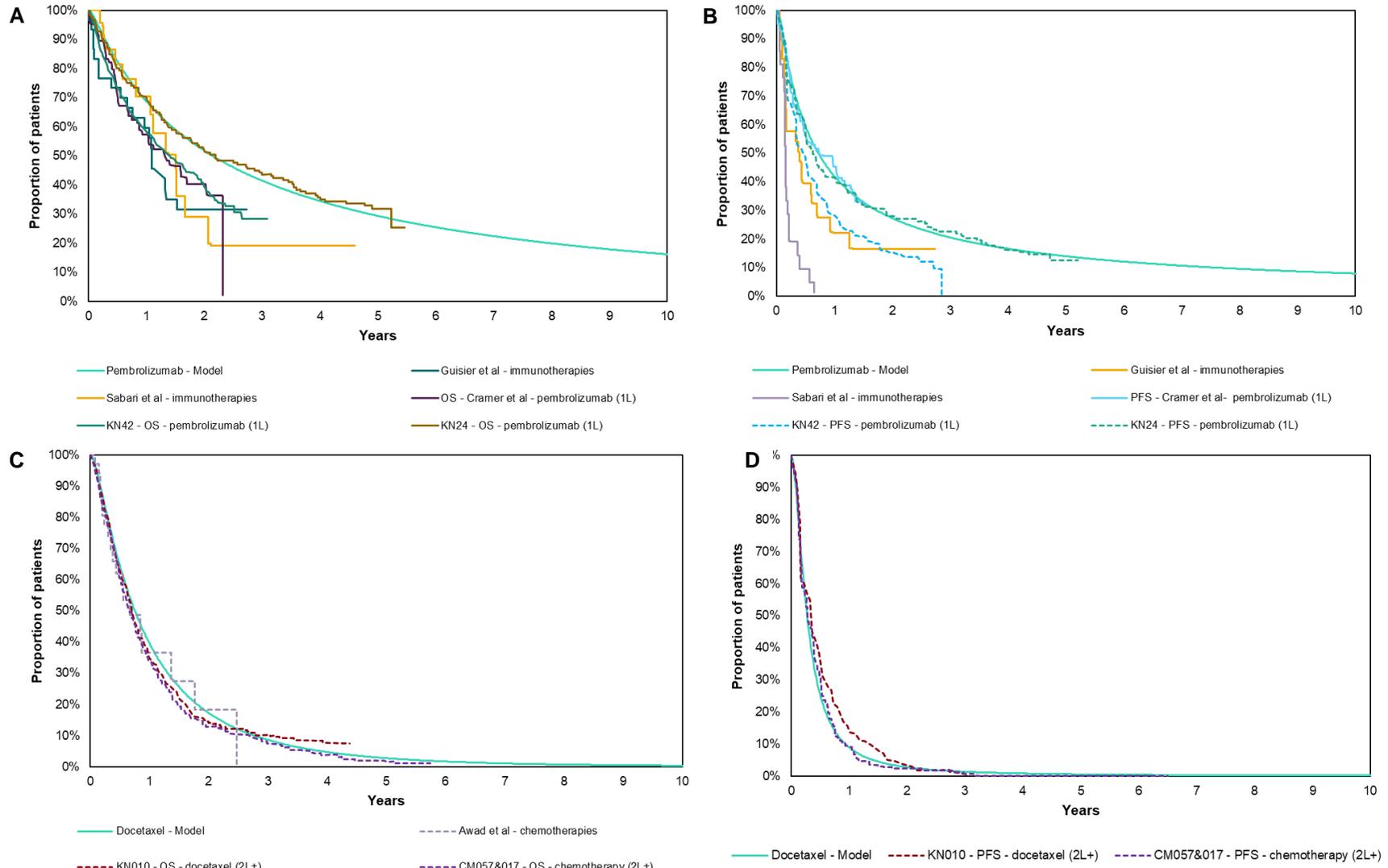
A: Pembrolizumab OS. **B:** Pembrolizumab PFS. **C:** Docetaxel OS. **D:** Docetaxel PFS