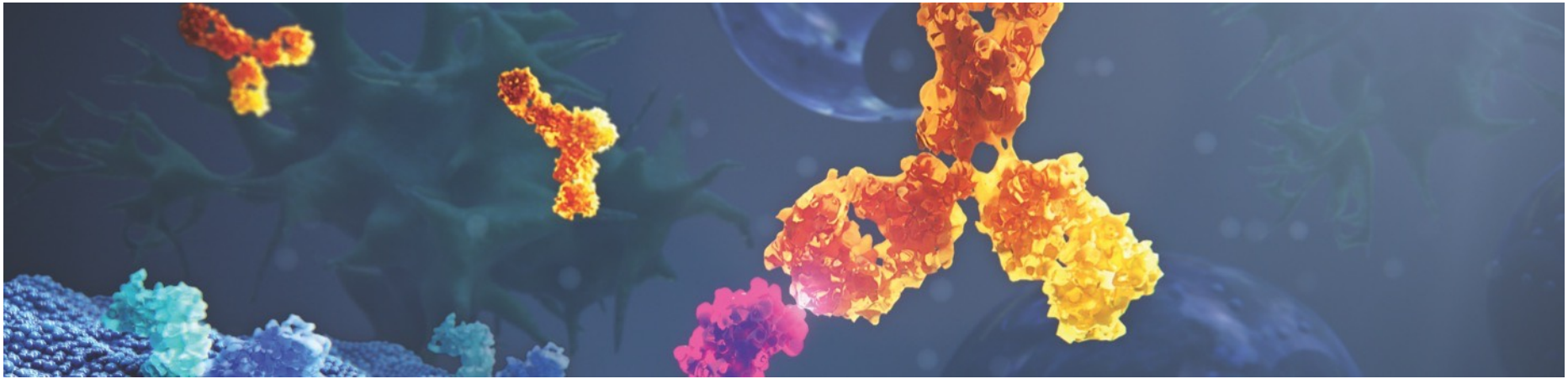
Difficulties with network meta-analysis when starting to use PD-L1 thresholds



Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to AstraZeneca.

Summary presentation

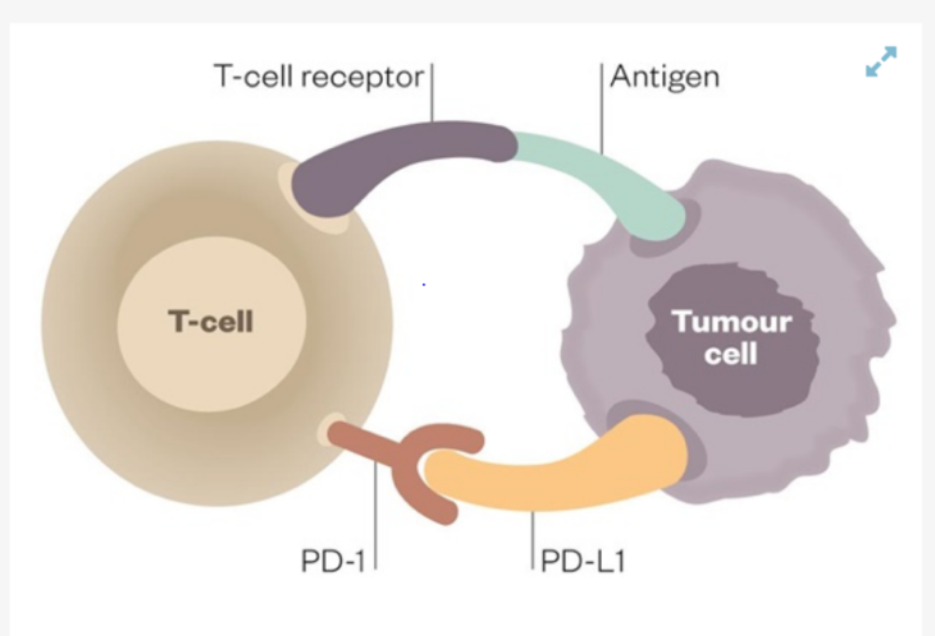
- Objective: To compare nivolumab with pembrolizumab within NSCLC 2nd line or later
- PD-L1 is an important effect modifier for immuno oncology treatments in NSCLC
- As such, the Network Meta Analysis of Kim et al (2018) compared nivolumab with pembrolizumab per PD-L1 level
- However, Kim et al (2018) used hazard ratios where the proportional hazards assumption is violated
- In this presentation, non-proportionality is accounted for by the use of splines
- Results of the spline approach will be presented and seem to contradict conclusions of Kim et al (2018)

Lung cancer (NSCLC) and its treatment

- Lung cancer (NSCLC) is the leading cause of cancer death
- Docetaxel is the standard of care for second-line or third-line NSCLC treatment
- PD-1 and PD-L1 inhibitors (Immuno Oncology treatments) have become available or are under investigation offering improved efficacy

Immuno-oncology: PD-1 and PD-L1 inhibitors

PD1 and PD-L1 inhibitors:
Different mode of Action to docetaxel



Docetaxel

Docetaxel blocks the growth of the cancer by stopping the cancer cells from dividing and multiplying.

PD1 and PD-L1 inhibitors

PD1 and PD-L1 inhibitors block response of the tumour cells generated via PD-L1 or PD-1 to T cells and

prevent against inactivation of T-cells, which themselves are scanning the body for abnormalities and infections

NMA: 2018 scientific report comparing atezolizumab, nivolumab and pembrolizumab at different PD-L1 levels

Jinchul Kim, Jinhyun Cho, Moon Hee Lee, Joo Han Lim, Relative Efficacy of Checkpoint inhibitors for advanced NSCLC According to Programmed Death-Ligand-1 Expression: A Systema Review and Network Meta-Analysis. Sci Rep. 2018; 8: 11738.

Objective: Network meta-analysis aimed to assess the survival benefit and comparative efficacy of checkpoint inhibitors according to PD-L1 expression level: <1%, 1–49%, and ≥50%.

Method: A fixed-effects Bayesian network meta-analysis (NMA) was performed to estimate hazard ratios (HRs) for overall survival (OS) with 95% credible intervals (CrIs).

Conclusion: Atezolizumab, nivolumab, and nivolumab were the most effective agents for second- or later-line settings in the PD-L1 < 1%, PD-L1 1–49%, and PD-L1 ≥ 50% subgroups, respectively.

2nd line or later nivolumab and pembrolizumab trials included in Kim et al (2018)

2nd line or later nivolumab and pembrolizumab trials included in Kim et al (2018):

- Nivolumab: Checkmate 017 squamous and Checkmate 057 non squamous
- Pembrolizumab: Keynote 010 79% non-squamous
- Same docetaxel prescription and only ECOG 0/1 for all trials

PD-L1 levels

Study	N	PD-L1 inclusion	Pre-specified PD-L1 levels
CM 017 Squamous	135 nivolumab 137 docetaxel	All comers	• >=1% • >=5% • >=10%
CM 057 Non-squamous	292 nivolumab 290 docetaxel	All comers	• >=1% • >=5% • >=10%
KN 010 79% non-squamous	345 pembro 2mg 346 pembro 10mg 343 docetaxel	>=1%	• >=1% • >=50%

Only for these levels, KM data are publically available

HR second line or later nivolumab and pembrolizumab; PD-L1 dependency

HR 1-49%:

Nivolumab versus docetaxel

- Checkmate 017: 0.75 [0.49, 1.16]
- Checkmate 057: 0.77 [0.55, 1.08]

Pembrolizumab versus docetaxel

- Keynote 010: 0.76 [0.64, 0.89]

- Checkmate 017 Squamous showing much less change than Checkmate 057 Non-squamous
- Pembrolizumab in between with 79% non-squamous

HR 50%+

Nivolumab versus docetaxel

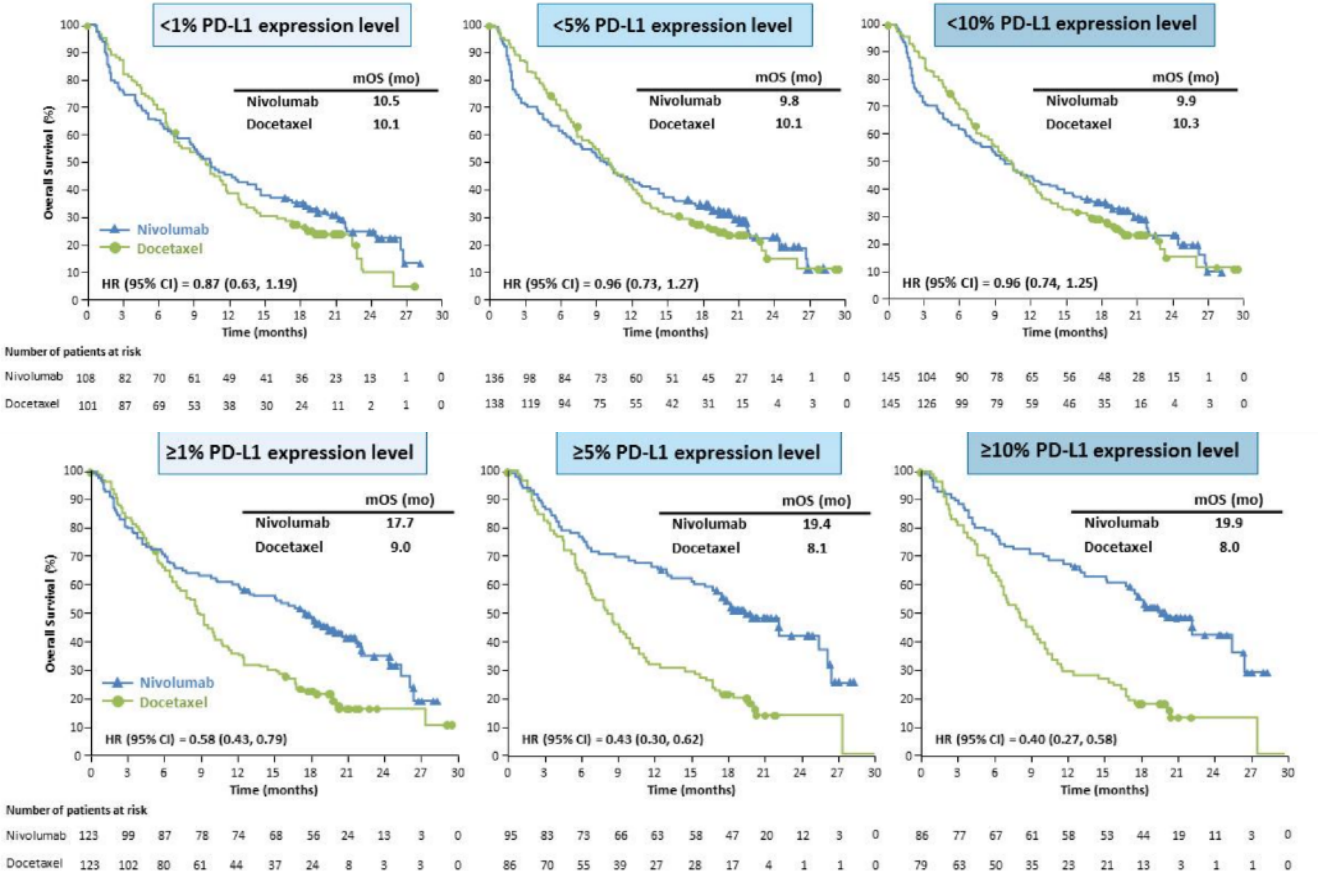
Checkmate 017: 0.68 [0.27, 1.66]

Checkmate 057: 0.35 [0.22, 0.55]

Pembrolizumab versus docetaxel

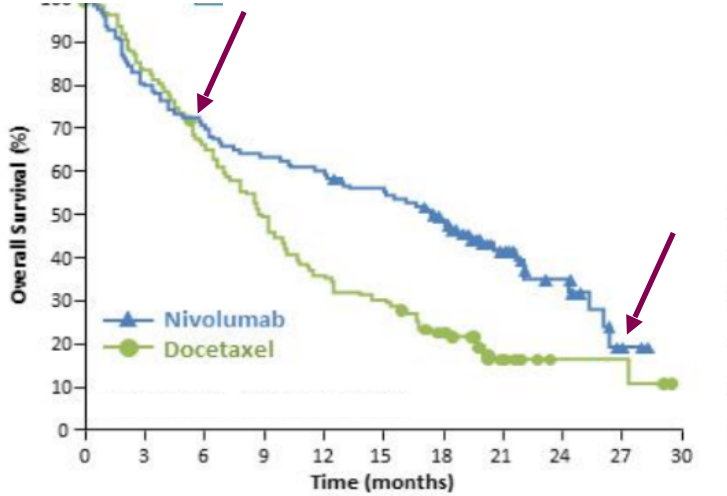
Keynote 010: 0.51 [0.41, 0.64]

PD-L1 dependent treatment effect in Checkmate 057



Included Kaplan Meiers Nivolumab for PD-L1 >= 1%

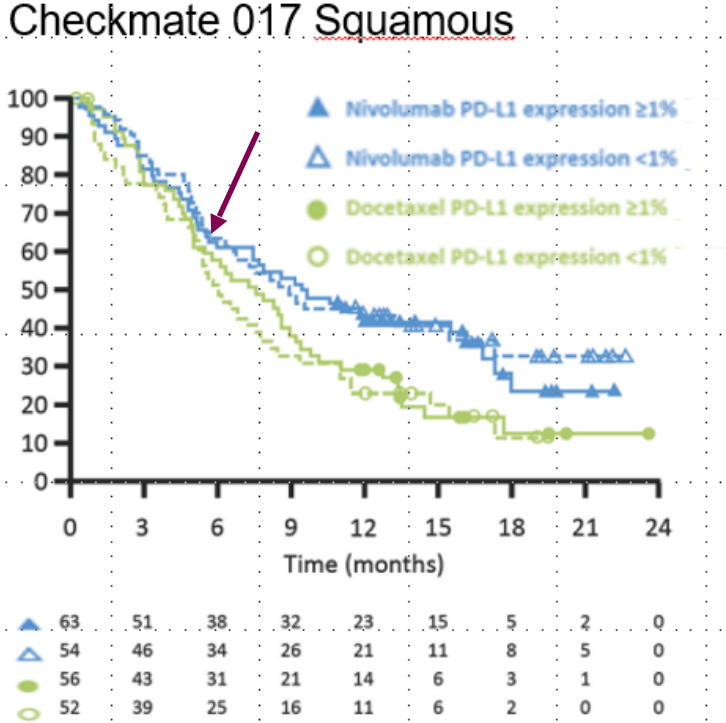
Checkmate 057 Non-squamous



HR >=1% 0.58 [0.43, 0.79]

Median: nivo 17.7, docetaxel 9.0

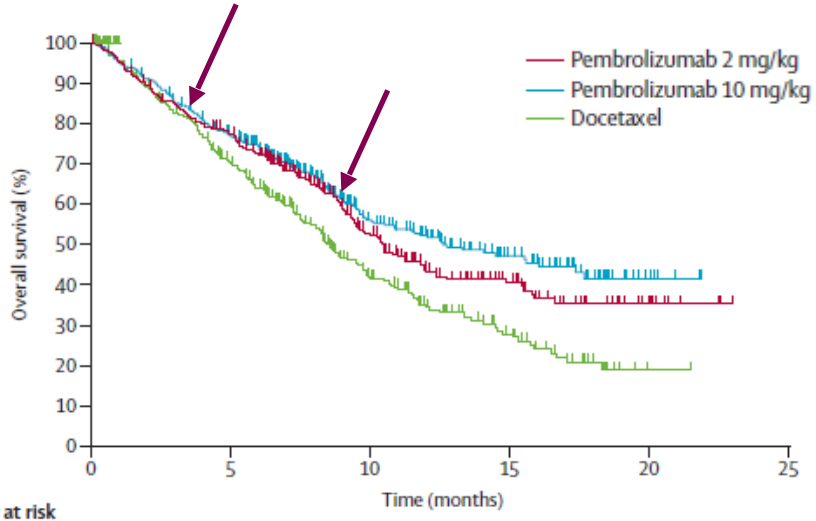
Checkmate 017 Squamous



HR >=1% 0.69 [0.45, 1.10]

Median: nivo 9.3, docetaxel 7.2

Included Kaplan Meiers Pembrolizumab for PD-L1 >= 1%



Number at risk						
Pembrolizumab 2 mg/kg	344	259	115	49	12	0
Pembrolizumab 10 mg/kg	346	255	124	56	6	0
Docetaxel	343	212	79	33	1	0

Pembrolizumab 10mg
HR >=1% 0.61 [0.49, 0.75]
Median: pembro 12.7, docetaxel 8.5

Pembrolizumab 2mg
HR >=1% 0.71 [0.58, 0.88]
Median: pembro 10.4, docetaxel 8.5

Kaplan Meier extraction

- We extracted the KM of the previous slides based on

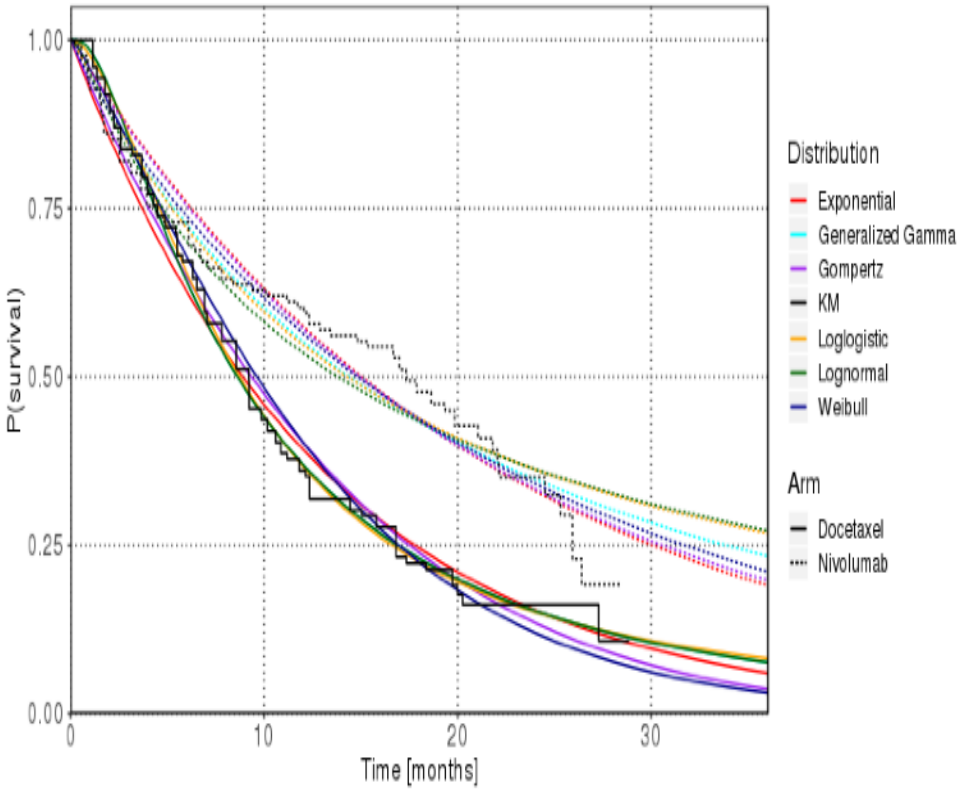
  Guyot, Ades, **Ouwens** and Welton (2012) Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves; BMC Medical Research Methodology 2012 12:9

- And wanted to apply the approach discussed in Ouwens et al based on standard extrapolation distributions:

  – Network meta−analysis of parametric survival curves
  Ouwens, Philips, Jansen accepted by NICE and referred in TSD 14
  Res Synth Methods. 2010 Jul;1(3-4):258-71. doi: 10.1002/jrsm.25. Epub 2011 Mar 11.

  – Network meta-analysis of survival data with fractional polynomials Jansen not selected as 4 out of 7 rejected by NICE (found in systematic review of NICE submissions)
  Stat Med. 2015 Jul 10;34(15):2294-311. doi: 10.1002/sim.6492. Epub 2015 Apr 15.

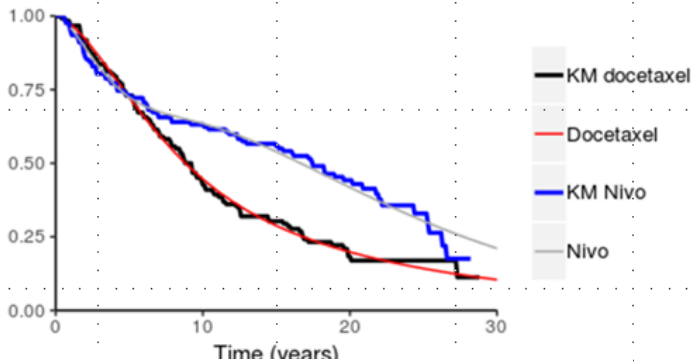
Fit of parametric distributions to Checkmate 057



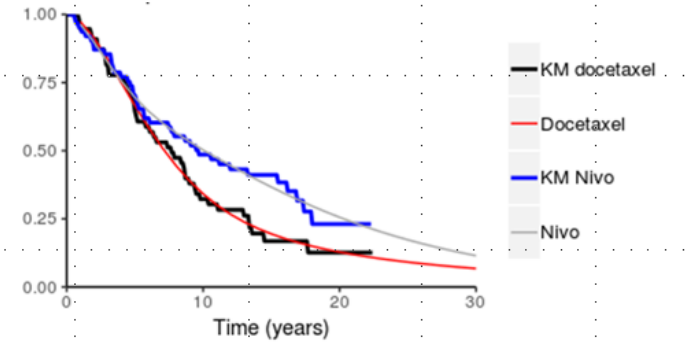
- Standard distributions provided a poor fit to the nivolumab data
- Alternative: Splines
- For the analysis:
  - Arbitrarily chosen knots: half a year and a whole year
  - Simple NMA based on inverse variance weighting of each of the coefficients
  - Log(-log(S)) as survival percentage transformation

Fit of splines (PD-L1 >=1%)

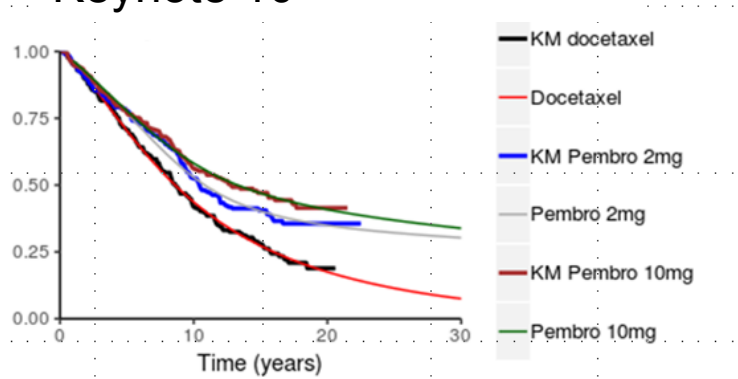
Checkmate 17



Checkmate 57



Keynote 10



Simple NMA: Combining vectors ignoring covariance

Checkmate 17

	Docetaxel		Nivolumab		Difference		
	EST	SE	EST	SE	Diff	SE	VAR
gamma0	-3.6	0.7	-3.3	0.6	0.3	0.9	0.75
gamma1	1.8	0.5	1.6	0.4	-0.2	0.7	0.47
gamma2	-0.1	0.4	0.4	0.4	0.5	0.6	0.33
gamma3	0.3	0.6	-0.4	0.5	-0.7	0.8	0.59

Simple version used
(for illustrational purposes):
inverse variance per coefficient

(0.3/0.75 + 0.4/0.35)/(1/0.75 + 1/0.35) = 0.37

Adding to Keynote 10 docetaxel:
-3.23 + 0.37 = -2.86

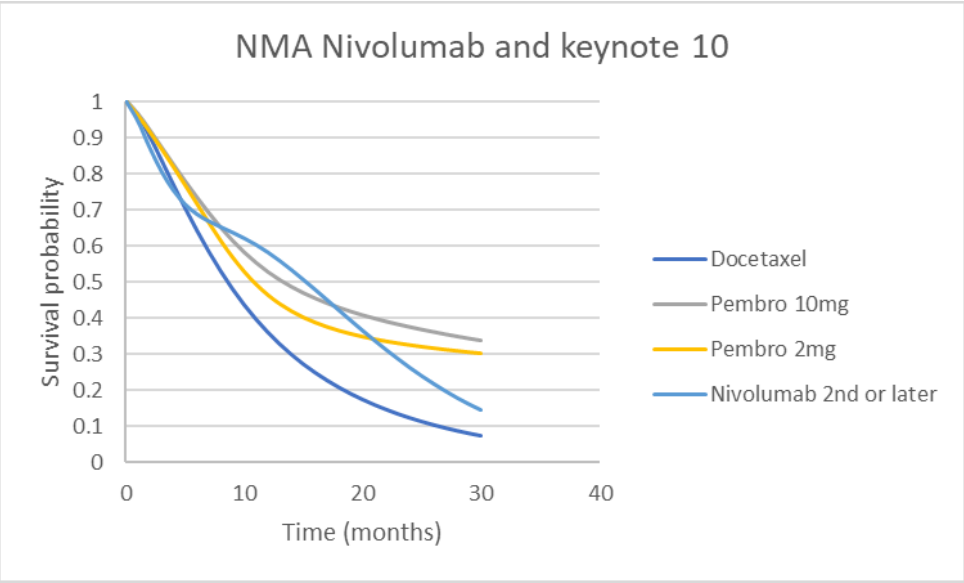
Checkmate 57

	Docetaxel		Nivolumab		Difference		
	EST	SE	EST	SE	Diff	SE	VAR
gamma0	-3.6	0.5	-3.2	0.4	0.4	0.6	0.35
gamma1	1.6	0.3	1.6	0.3	0.0	0.4	0.20
gamma2	0.0	0.2	0.8	0.2	0.8	0.3	0.10
gamma3	0.2	0.3	-1.0	0.2	-1.2	0.4	0.15

Keynote 10	Docetaxel	Diff Nivo Doce	Nivo
	EST	EST	EST
gamma0	-3.23	0.37	-2.86
gamma1	1.39	-0.08	1.31
gamma2	-0.03	0.75	0.72
gamma3	0.10	-1.06	-0.96

Better version: Suzanne Freeman, James R. Carpenter: Bayesian one-step IPD network meta-analysis of time-to-event data using Royston-Parmar models 2016

Results for PD-L1 >= 1% for 2nd line and later



- Conclusion:
  - Crossing curves
  - In the long term, rather than nivolumab, pembrolizumab may be preferred

Take home message

- Comparing efficacy across PD-L1 levels is important, but use of HR is questionable
- Spline approaches, among others, can be used when Kaplan Meiers are presented for different PD-L1 levels
- Data may not be available at a sufficient granularity to model impact of the characteristic
- Sample sizes are decreased when evaluating subgroups

Personal opinion

- In areas where biomarkers are influencing end results, we need to have consistent definitions of biomarkers and present Kaplan Meiers for all relevant categories in a consistent way across trials.

- Spline approaches may be valid per category, even while the choice of number and place of knots is subjective (may require clinical validation)

- However, insufficient information may be present to pool data across trials at all

Background slides

Accounting for PD-L1 level when Individual Patient Data are available from the own trial

- A few possible approaches would exist when individual patient data would be available
  - PD-L1 subgroup analysis
  - Estimating a PD-L1 enhancement factor from our data and applying to comparator trial in cases where equivalent PD-L1 subgroup data for the comparator are not available
  - Weighting our data using the percentages in each of the categories of the comparator trial; Estimating a beta-distribution based on the percentages in the comparator trial to get a more refined impression of the distribution of PD-L1 in the comparator trial and using this beta-distribution to reweight our data
  - Using PD-L1 as a covariate in our models for our own trial and validating the assumed relationship. Then using Simulated Treatment Comparison approaches to link our trial with the comparator trial (NICE TSD 18)

Confidentiality Notice