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.
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

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

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):

• 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

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>PD-L1 inclusion</th>
<th>Pre-specified PD-L1 levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM 017 Squamous</td>
<td>135 nivolumab 137 docetaxel</td>
<td>All comers</td>
<td>• &gt;=1%</td>
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<td></td>
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<td>• &gt;=5%</td>
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<td></td>
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<td>• &gt;=10%</td>
</tr>
<tr>
<td>CM 057 Non-squamous</td>
<td>292 nivolumab 290 docetaxel</td>
<td>All comers</td>
<td>• &gt;=1%</td>
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<td>• &gt;=10%</td>
</tr>
<tr>
<td>KN 010 79% non-squamous</td>
<td>345 pembro 2mg 346 pembro 10mg 343 docetaxel</td>
<td>&gt;=1%</td>
<td>• &gt;=1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• &gt;=50%</td>
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</tbody>
</table>

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%

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
  
  - 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)
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%)
Simple NMA: Combining vectors ignoring covariance

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:
\[-3.23 + 0.37 = -2.86\]

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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)
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