Comparative effectiveness of immune-checkpoint inhibitors for previously treated advanced non-small cell lung cancer – a systematic review and network meta-analysis of 3,024 participants

Pui San Tan[a], Pedro Aguiar Jr.[b], Benjamin Haaland[c], Gilberto Lopes[d]

[a]Nuffield Department of Primary Care Health Sciences, University of Oxford, United Kingdom

[b]Clinical Oncology Sector, Federal University of São Paulo, São Paulo, Brazil

[c]H. Milton Stewart School of Industrial and Systems Engineering, Georgia Institute of Technology Atlanta, USA

[d]Sylvester Comprehensive Cancer Center, University of Miami, USA

Corresponding author:

Pui San Tan

University of Oxford

Nuffield Department of Primary Care Health Sciences,

Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Rd,

Oxford OX2 6GG United Kingdom

Email: puisan.tan@gmail.com

Abstract

Introduction

Role of PD-L1 expression to guide immunotherapies in previously treated advanced NSCLC remains unclear and there is a lack of data comparing immune checkpoint inhibitors (ICIs) with each other. This network meta-analysis (NMA) aims to compare survival with ICIs to docetaxel and perform indirect comparisons between ICIs in the PD-L1 unselected population and by PD-L1 expression levels.

Methods

PubMed was searched and study screening was performed by two independent reviewers. NMA of survival outcomes in the PD-L1 unselected population and by PD-L1 expression levels <1%, >=1%, >=5%, >=10%, and >=50% was performed. Head-to-head indirect comparisons were constructed and treatment rankings were provided. Potential survival benefits by PD-L1 expression level as compared to a PD-L1 unselected population were estimated.

Results

5 trials with 3,024 total patients were included for meta-analysis. Overall, ICIs improved survival across PD-L1 expression levels compared to docetaxel, although there was only weak evidence of benefit for individual ICI nivolumab or atezolizumab in PD-L1<1%. PD-L1 subgroups suggested positive dose-response relationship between PD-L1 expression levels with survival benefits. In addition, there were also survival benefits due to selecting for PD-L1 in the PD-L1>=10% and >=50% subgroups as compared to the PD-L1 unselected population. Indirect comparisons of ICIs showed little evidence of differences between nivolumab, pembrolizumab and atezolizumab.

Discussion

ICIs improve survival in previously treated advanced NSCLC patients across PD-L1 expression levels compared to docetaxel. There is a positive dose-response relationship between PD-L1 expression and survival benefits, and little evidence of survival differences between nivolumab, pembrolizumab and atezolizumab.

Introduction

Lung cancer is the most common cause of cancer-related death worldwide with more than 1.5 million deaths in 2012,[1] more than breast, prostate, and colon cancer deaths combined.[1–3] Platinum based chemotherapy is the cornerstone of treatment for advanced non-small cell lung cancer (NSCLC).[4] In the last decade, new strategies have been studied, but still median overall survival (OS) with chemotherapy has not surpassed 15 months.[5]

The ability to avoid the immune system is one of the hallmarks of cancer.[6] Lung cancer has a high mutational burden and this may lead to a high immunogenicity.[7] There are many complex interactions between antigen presenting cells, lymphocytes, and tumor cells. The most studied is the link between the lymphocytes membrane receptor, Program Cell Death 1 (PD-1), and its ligand 1 or 2 (PD-L1 or PD-L2), which are expressed by some tumor cells.[8] This interaction inhibits lymphocytes.[8] As a consequence, in a short period of time, many PD-1 and PD-L1 inhibitors have reached late phase development in lung cancer.[9–13]

Several immunotherapies have been approved by FDA in record time due to strong clinical benefits and milder side effects.[9–14] These results have rapidly reset the management of advanced non-small cell lung cancer (NSCLC). Nevertheless, some questions regarding lung cancer immunotherapy remain unclear, especially the role of PD-L1 expression as a biomarker, even for second-line treatment. In addition, all clinical trials that included previously treated patients compared immune checkpoint inhibitors (ICI) to docetaxel, and there is a lack of data comparing agents with one another.[9–13]

Therefore, a meta-analysis assessing all relevant data published until now should endorses the benefit of immunotherapy versus docetaxel. Moreover, a meta-analysis should provide a better understanding regarding biomarkers and indirectly compare each immunotherapy agent. The current study investigates these issues, and provides evidence to improve the treatment of patients with advanced NSCLC after chemotherapy failure. A network meta-analysis will be performed to compare survival benefits of ICIs nivolumab, pembrolizumab, and atezolizumab to docetaxel in previously treated advanced NSCLC

patients by PD-L1 expression levels (i) unselected, (ii) <1%, (iii) ≥1%, (iv) ≥5%, (v) ≥10%, and (vi) ≥50%.

Methods

Systematic review

PubMed was searched for randomized controlled trials evaluating immunotherapy ICI in advanced NSCLC using the following search phrase with no time restrictions: ("non-small cell lung cancer" OR "non small-cell lung cancer" OR "non-small-cell lung cancer" OR "non small cell lung cancer" OR "NSCLC") AND ("atezolizumab" OR "pembrolizumab" OR "nivolumab") AND (randomized controlled trial[pt] OR randomized controlled trial)

Inclusion criteria was phase II/III randomized controlled trials evaluating nivolumab, pembrolizumab, or atezolizumab for the treatment of previously treated advanced NSCLC. Two independent reviewers performed study screening. Data extraction was performed using a standardized extraction sheet.

Outcomes evaluation

Treatment efficacies were evaluated in terms of overall survival (OS) for patient populations comprising of (i) PD-L1 unselected, (ii) PD-L1<1%, (iii) PD-L1>=1%, (iv) PD-L1>=5%, (v) PD-L1>=10%, and (vi) PD-L1>=50%. Additional subgroup analyses were performed comparing ICIs by histology and PD-L1 expression levels.

Statistical analysis

Meta-analysis was performed using a Bayesian hierarchical model. Individual treatment efficacies were meta-analyzed on the logarithmic scale centered at the mean with two components of variance; within and between study heterogeneities. Within study heterogeneity was modeled using individual studies' reported variances while between study heterogeneity was modeled using a partially informative prior allowing treatment efficacies to vary up to two-fold study to study.

Meta-estimates for treatment efficacies were expressed as hazard ratios (HRs) with corresponding 95% credible intervals (CrIs). Indirect comparisons were constructed in terms of HR with corresponding 95% CrI and probability for an individual ICI to be best (probability best). Treatment rankings were

estimated using surface under cumulative ranking curve (SUCRA) by taking the average cumulative ranking probabilities following the expression $SUCRA_j = \frac{\sum_{r=1}^{c-1} cum_{j,r}}{c-1}$ on a percent scale, where c denotes the number of treatments compared.[15] SUCRA was computed to provide summary estimates of ranking efficacies, with higher values representing better treatments.[15]

Results

14 studies were screened and 5 trials comprised of 3,024 patients were included for meta-analysis (Figure 1).[16] Included trials compared ICIs nivolumab, pembrolizumab, or atezolizumab to docetaxel for previously treated patients who had disease progression (Table 1, Appendix Figure 1).[9–13] Median survival was approximately 9 to 14 months for patients treated with ICIs with survival gain ranging from approximately 2 to 4 months versus docetaxel.[9–13] Details on characteristics of included studies are provided in Table 1.

Four trials, which evaluated nivolumab or atezolizumab, enrolled patients with no pre-defined PD-L1 biomarker status[9,10,12,13] while KEYNOTE-010, which evaluated pembrolizumab, enrolled patients with PD-L1 expression on at least 1% of tumor cells.[11] Trials which evaluated nivolumab and pembrolizumab measured PD-L1 expression using tumor cell cutoffs[9–11] while atezolizumab trials measured PD-L1 expression using both tumor cell and/or immune cell cut-offs.[12,13] PD-L1>=50% for atezolizumab trials included patients with tumor cell PD-L1>=50% or immune cell PD-L1>=10%.[12,13]

Overall survival by PD-L1 expression

Figure 2 shows overall survival in individual trials and pooled meta-estimates for nivolumab, pembrolizumab, and atezolizumab compared to docetaxel by PD-L1 expression. In patients with unselected PD-L1 biomarker status, meta-estimates showed evidence of survival benefits for both nivolumab and atezolizumab compared to docetaxel with HR 0.67 (95% CrI 0.54-0.83) and 0.73 (0.59-0.90) respectively. In patients with PD-L1<1%, meta-estimates showed weaker evidence of survival benefits for both nivolumab and atezolizumab compared to docetaxel with HR 0.77 (0.57-1.04) and 0.81 (0.62-1.08) respectively. In patients with PD-L1>=1%, meta-estimates showed evidence of survival benefits for nivolumab, pembrolizumab, and atezolizumab compared to docetaxel with HR 0.63 (0.47-0.84), 0.67 (0.51-0.87) and 0.69 (0.53-0.88) respectively. In patients with PD-L1>=5%, meta-estimates showed evidence of survival benefits for nivolumab and atezolizumab compared to docetaxel with HR 0.46 (0.33-0.65) and 0.63 (0.46-0.84) respectively. In patients with PD-L1>=10%, meta-estimates showed evidence of survival benefits for nivolumab compared to docetaxel with HR

0.43 (0.30-0.63). In patients with PD-L1>=50%, meta-estimates showed evidence of survival benefits for pembrolizumab and atezolizumab compared to docetaxel with HR 0.53 (0.38-0.75) and 0.43 (0.28-0.65) respectively.

Indirect comparisons by PD-L1 expression

Figure 3 shows indirect comparisons of nivolumab, pembrolizumab, and atezolizumab by PD-L1 expression for overall survival. Results showed little evidence of differences between nivolumab vs pembrolizumab, nivolumab vs atezolizumab or pembrolizumab vs atezolizumab across all compared PD-L1 expression levels. However, there was weak evidence suggesting that nivolumab could outperform atezolizumab.

SUCRA rankings and probability best by PD-L1 expression

Figure 4 shows SUCRA rankings and probability for an ICI to be best by PD-L1 expression levels. For PD-L1 unselected, <1%, >=1%, >=5%, >=10%, nivolumab ranking corresponded to the highest SUCRA and probability best. For PD-L1 >=50%, atezolizumab was ranked higher than pembrolizumab and docetaxel.

ICI in PD-L1 selected vs unselected populations

Figure 5 (top panel) shows pooled survival estimates of ICIs by PD-L1 expression. Results showed evidence of survival benefits of ICI in the unselected population with HR 0.70 (0.61-0.81). However, subgroup results suggested a dose-response relationship of PD-L1 expression levels with survival benefit, with the least benefit observed in PD-L1<1% with HR 0.79 (0.65-0.97) and greatest benefit in PD-L1>=10% and >=50% with HR 0.43 (0.30-0.63) and 0.49 (0.37-0.63) respectively. In addition, Figure 5 (bottom panel) suggested survival benefits for patient selection by PD-L1 status. Compared to the PD-L1 unselected population, patient selection by PD-L1>=10% and >=50% had improved survival with HRs 0.62 (0.42-0.92) and 0.69 (0.51-0.93) respectively.

Subgroup analyses by histology

Further subgroup analyses by histology showed no decisive evidence of survival differences between nonsquamous vs squamous histology in either PD-L1 unselected or PD-L1>= 1% patients. Detailed results are shown in Appendix Table A1.

Discussion

This meta-analysis showed that immunotherapy PD-L1 ICIs improved overall survival in previously treated advanced NSCLC patients irrespective of PD-L1 status as compared to docetaxel, although there was only weak evidence of benefit for use of individual ICI nivolumab or atezolizumab in PD-L1<1%. Results from PD-L1 subgroups further suggested a positive dose-response relationship between PD-L1 expression levels with survival benefits. In addition, there was also evidence of survival benefits by selecting PD-L1>=10% and >=50% as compared to the PD-L1 unselected population. Indirect comparisons of ICIs showed little evidence of differences between nivolumab, pembrolizumab and atezolizumab, although there was weak evidence suggesting that nivolumab could be superior.

A caveat when interpreting results from this study is the variability of assays that were used in individual trials for measuring PD-L1 expression levels.[9–13] Results from the Blueprint PD-L1 IHC Assay Comparison Project showed that the 28-8 (Dako) assay used for nivolumab and 22C3 (Dako) assay used for pembrolizumab trials were comparable for tumor cells staining while the SP142 (Ventana) assay used for atezolizumab resulted in lower tumor cells staining.[9–13,17] In addition, nivolumab and pembrolizumab trials have used tumor cell staining cut-offs for PD-L1 expression levels while the atezolizumab trials have used both tumor cell and/or immune staining cut-offs.[9–13] Hence, results should be interpreted with caution when evaluating results for atezolizumab as this serves as a limitation in our study. In addition, when interpreting results, it is worth noting that indirect comparisons make two assumptions (i) transitivity assumptions between common comparator treatment arms i.e. patient populations and effect modifiers in included trials are comparable, and (ii) consistency between indirect and direct evidence, although this could not be evaluated in current study due to the lack of direct evidence from head-to-head trials.[18]

Nonetheless, this is the first meta-analysis to pool all currently available evidence from immunotherapy trials and report summary evidence of survival benefits in a PD-L1 unselected population and by PD-L1 status. In addition, head-to-head comparative effectiveness of nivolumab, pembrolizumab, and atezolizumab serves to inform clinical decision making and as guidance for future clinical trials.

Results from this meta-analysis suggest that PD-L1 ICIs improve survival in advanced NSCLC patients who failed previous chemotherapy across PD-L1 expression levels. However, as high costs of immunotherapy remain an important issue among patients and healthcare systems,[19] cost-effectiveness might be feasible in subgroups of patients with higher PD-L1 expression levels who potentially obtain a greater clinical benefit from immunotherapy.

In addition, as early findings from trials have suggested durable responses of immunotherapy,[9–13] it is important to evaluate the long-term survival benefits of immunotherapies in future research. Due to high costs of immunotherapies,[19] future research should evaluate the optimal treatment duration of immunotherapies which would prove to be cost-effective and elicit patient preferences for treatment options in the terminal setting of advanced NSCLC.

In conclusion, this meta-analysis showed that PD-L1 immune checkpoint inhibitors improve survival in advanced NSCLC patients who failed previous chemotherapy irrespective of PD-L1 expression, although there was only weak evidence of benefit for use of individual ICI nivolumab or atezolizumab in PD-L1<1%. Further selection by PD-L1 status increased survival benefits with positive dose-response relationship between PD-L1 expression levels and survival. Indirect comparisons of ICIs showed little evidence of differences between nivolumab, pembrolizumab and atezolizumab.

Statement of Authorship

GL and PST conceived the research idea. PST and PAJ performed studies screening and PST extracted data. PST and BH participated in data analysis. All authors contributed to the manuscript preparation.

Conflicts of interest

PAJ reports being speaker for MSD and Roche and advisory board of BMS, Astra Zeneca, and Novartis. All other authors declare no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1 Ferlay J, Soerjomataram I, Dikshit R, *et al.* Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359–86.

2 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74–108.

3 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; **66**: 7–30.

4 Schiller JH, Harrington D, Belani CP, *et al.* Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002; **346**: 92–8.

5 Patel JD, Socinski MA, Garon EB, *et al.* PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB o. *J Clin Oncol* 2013; **31**: 4349–57.

6 Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646–74.

7 Lawrence MS, Stojanov P, Polak P, *et al.* Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature* 2013; **499**: 214–8.

8 Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy--inhibiting programmed death-ligand 1 and programmed death-1. *Clin Cancer Res* 2012; **18**: 6580–7.

9 Borghaei H, Paz-Ares L, Horn L, *et al.* Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med* 2015; **373**: 1627–39.

10 Brahmer J, Reckamp KL, Baas P, *et al.* Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med* 2015; **373**: 123–35.

11 Herbst RS, Baas P, Kim DW, *et al.* Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. *Lancet* 2016; **387**: 1540–50.

12 Fehrenbacher L, Spira A, Ballinger M, *et al.* Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): A multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016; **387**: 1837–46.

13 Rittmeyer A, Barlesi F, Waterkamp D, *et al.* Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017; **389**: 255–65.

14 FDA Adds Immunotherapy Approvals for Lung Cancer - National Cancer Institute. Natl. Cancer Inst. https://www.cancer.gov/news-events/cancer-currents-blog/2016/fda-atezolizumab-pembrolizumab-lung (accessed April 29, 2017).

15 Salanti G, Ades A., Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; **64**: 163–71.

16 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097.

17 Hirsch FR, McElhinny A, Stanforth D, *et al.* PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the 'Blueprint PD-L1 IHC Assay Comparison Project'. *J Thorac Oncol* 2016; **12**: 208–22.

18 Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012; **3**: 80–97.

19 Ledford H. Immunotherapy's cancer remit widens. *Nature* 2013; **497**: 544–544.

Highlights

- ICIs improve OS across PD-L1 expressions in previously treated advanced NSCLC.
- Positive dose-response relationship exists between PD-L1 expression and OS.
- There is little OS difference between nivolumab, pembrolizumab, and atezolizumab.

Figure legends

Figure 1: Search flow diagram according to PRISMA guidelines[16]

Figure 2: Overall survival meta-estimates for ICIs versus docetaxel by PD-L1 expression. Individual trial estimates are expressed in HR (95% CI).

Figure 3: Overall survival head-to-head indirect comparisons of ICIs by PD-L1 expression.

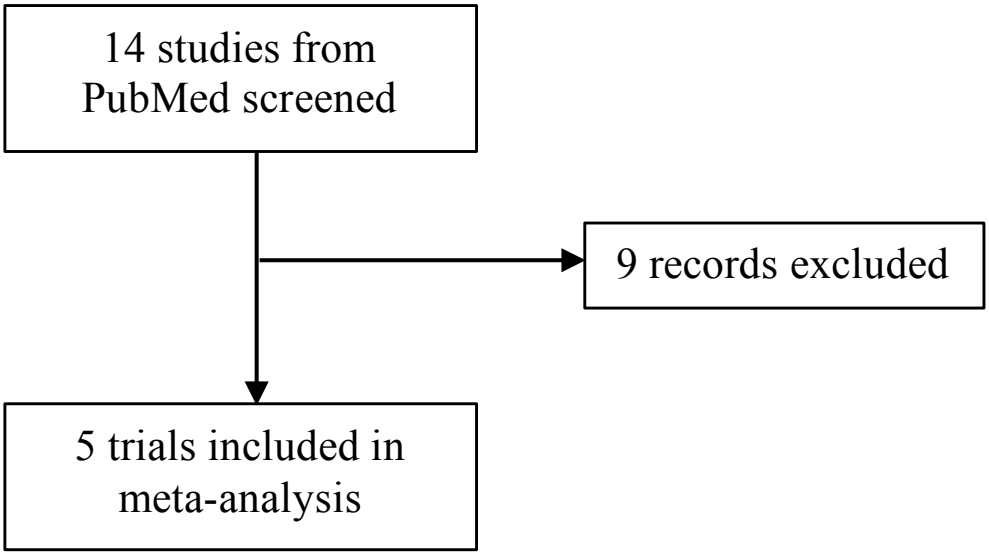
Figure 4: Overall survival SUCRA rankings and probability for a ICI to be best by PD-L1 expression.

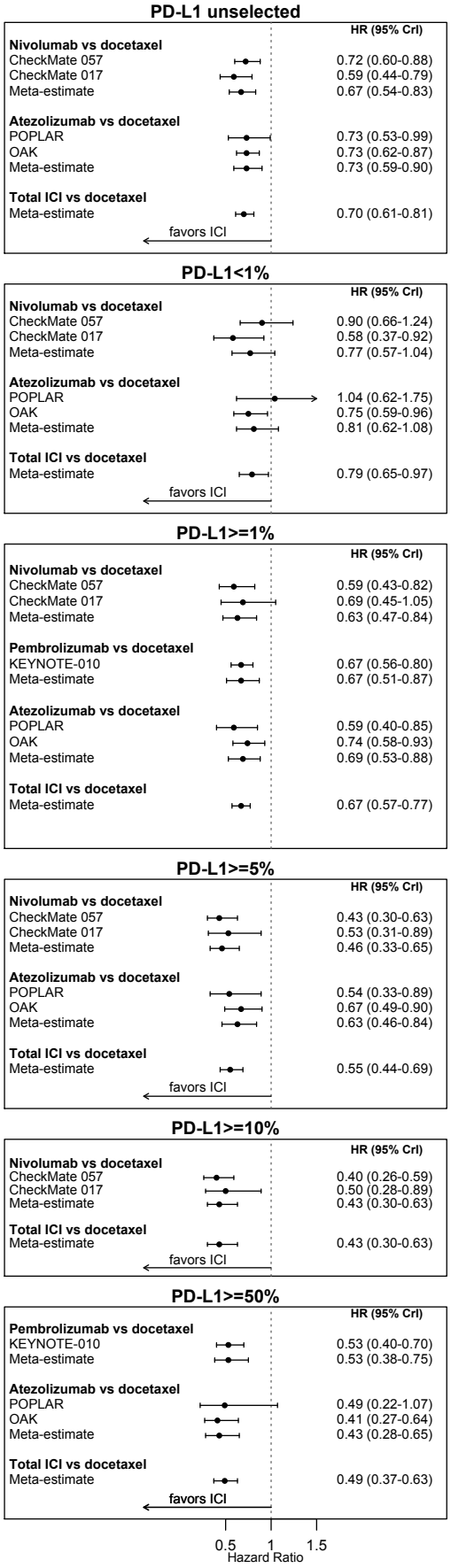
Figure 5: Overall survival of ICIs by PD-L1 expression (top) and by PD-L1 selection compared to PD-L1 unselected population (bottom).

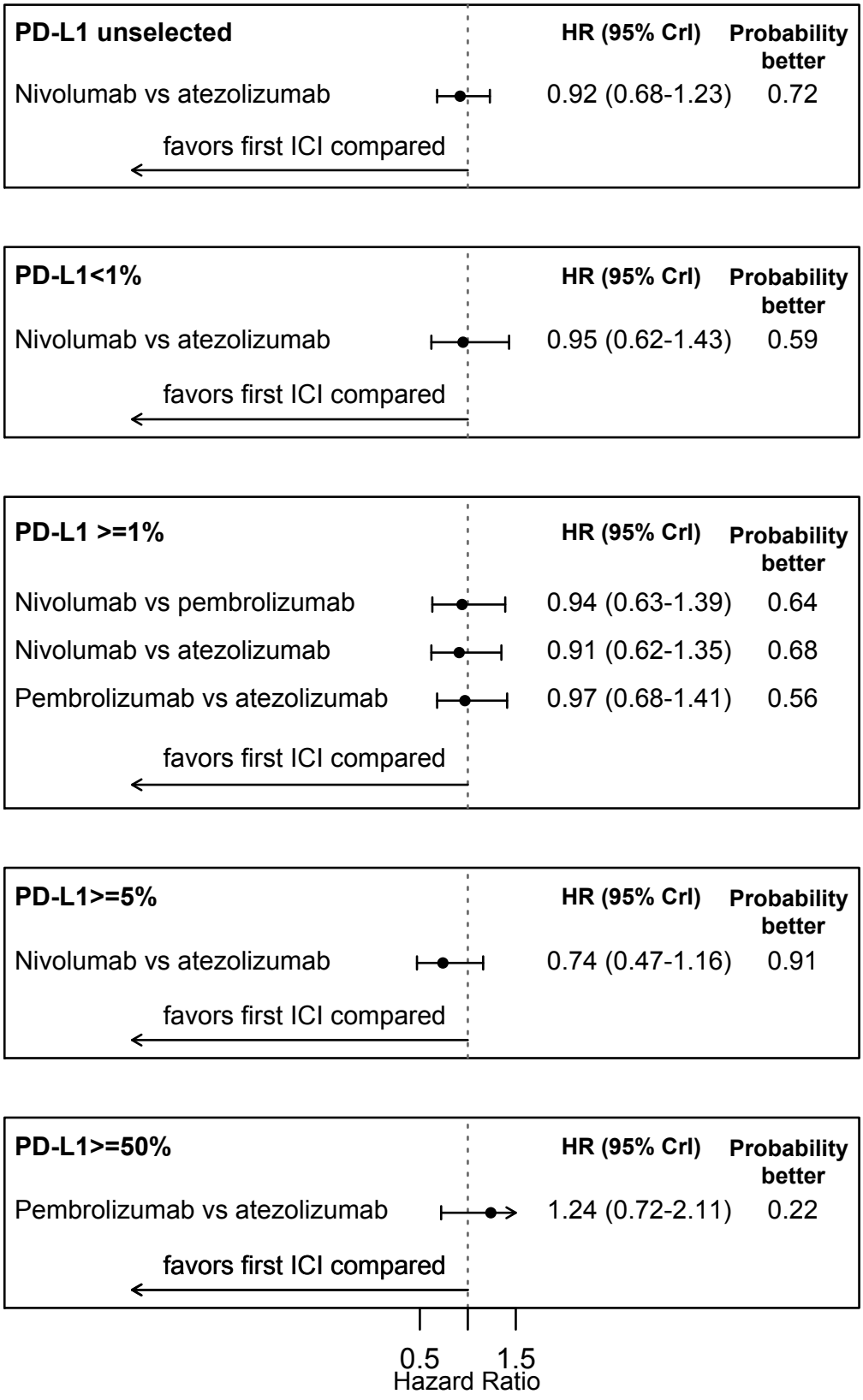
Table 1: Characteristics of included studies

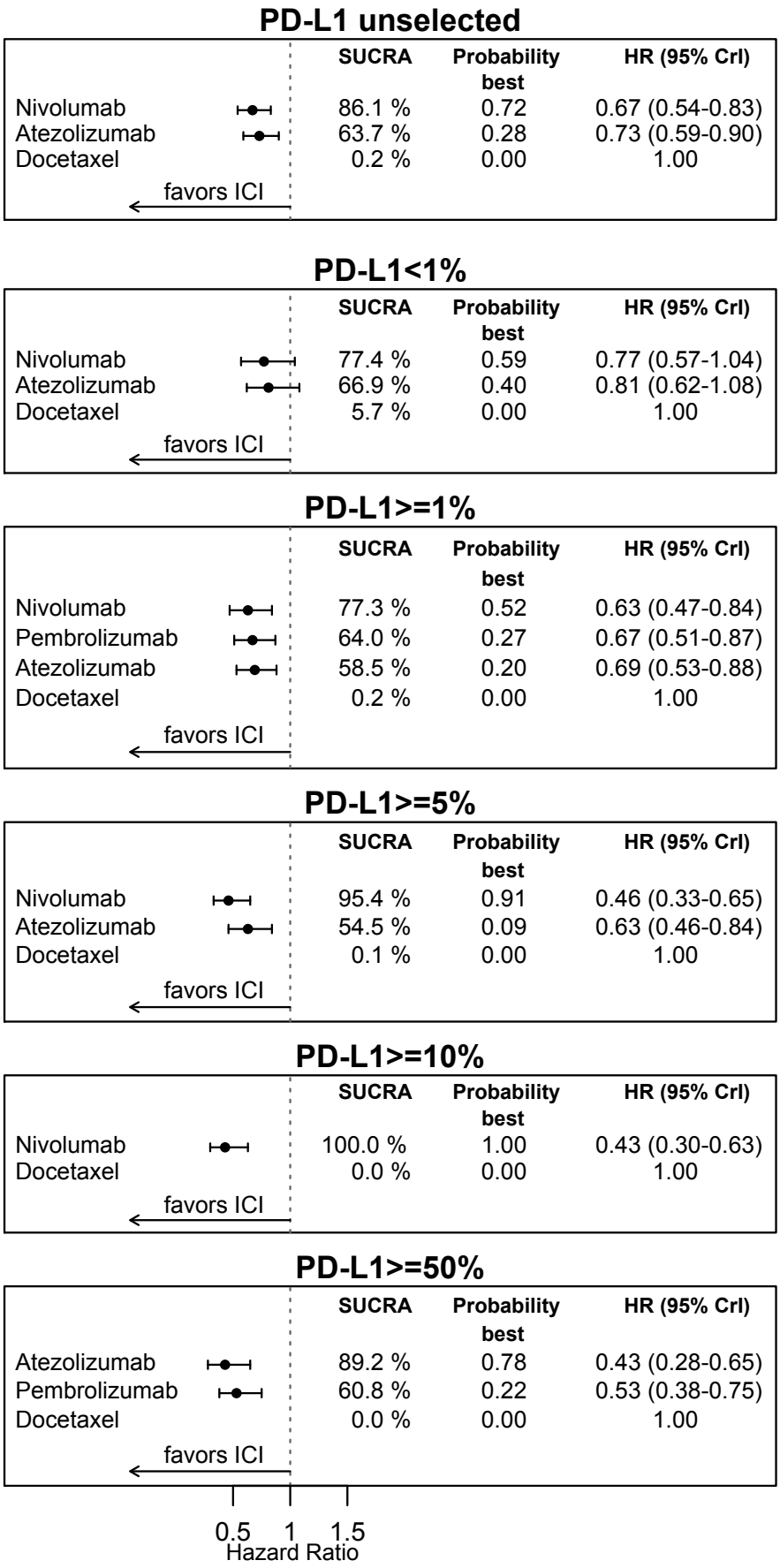
Study	Population	Treatment comparisons	N	Median OS (months)	OS HR (95% CI)
CheckMate 057[9]	Stage IIIb/IV or recurrent nonsquamous NSCLC patients who had disease recurrence/progression during/after one prior platinum-based chemotherapy doublet (not selected by PD-L1 status)	Nivolumab 3 mg/kg every 2 weeks vs docetaxel 75 mg/m^2 every 3 weeks	582	12.2 vs 9.4	0.72 (0.60-0.88)
CheckMate 017[10]	Stage IIIb/IV squamous NSCLC patients who had disease recurrence after one prior platinum-based chemotherapy (not selected by PD-L1 status)	Nivolumab 3 mg/kg every 2 weeks vs docetaxel 75 mg/m^2 every 3 weeks	272	9.2 vs 6.0	0.59 (0.44-0.79)
KEYNOTE-010[11]	Advanced NSCLC patients who had progressed after two or more cycles of platinum-based chemotherapy/TKI with PD-L1 expression on at least 1% of tumour cells (TPS>=1%)	Pembrolizumab 2mg/kg vs docetaxel 75 mg/m^2 every 3 weeks	687	10.4 vs 8.5	0.71 (0.58–0.88)
		Pembrolizumab 10mg/kg vs docetaxel 75 mg/m^2 every 3 weeks	689	12.7 vs 8.5	0.61 (0.49–0.75)
POPLAR[12]	Advanced or metastatic NSCLC who had progressed after 1-2 previous platinum-based chemotherapy (not selected by PD-L1 status)	Atezolizumab 1200 mg vs docetaxel 75 mg/m^2 every 3 weeks	287	12.6 vs 9.7	0.73 (0.53-0.99)
OAK[13]	Advanced or metastatic stage IIIb/IV NSCLC patients who had progressed after 1-2 previous platinum-based chemotherapy/TKI (not selected by PD-L1 status)	Atezolizumab 1200 mg vs docetaxel 75 mg/m^2 every 3 weeks	850	13.8 vs 9.6	0.73 (0.62-0.87)

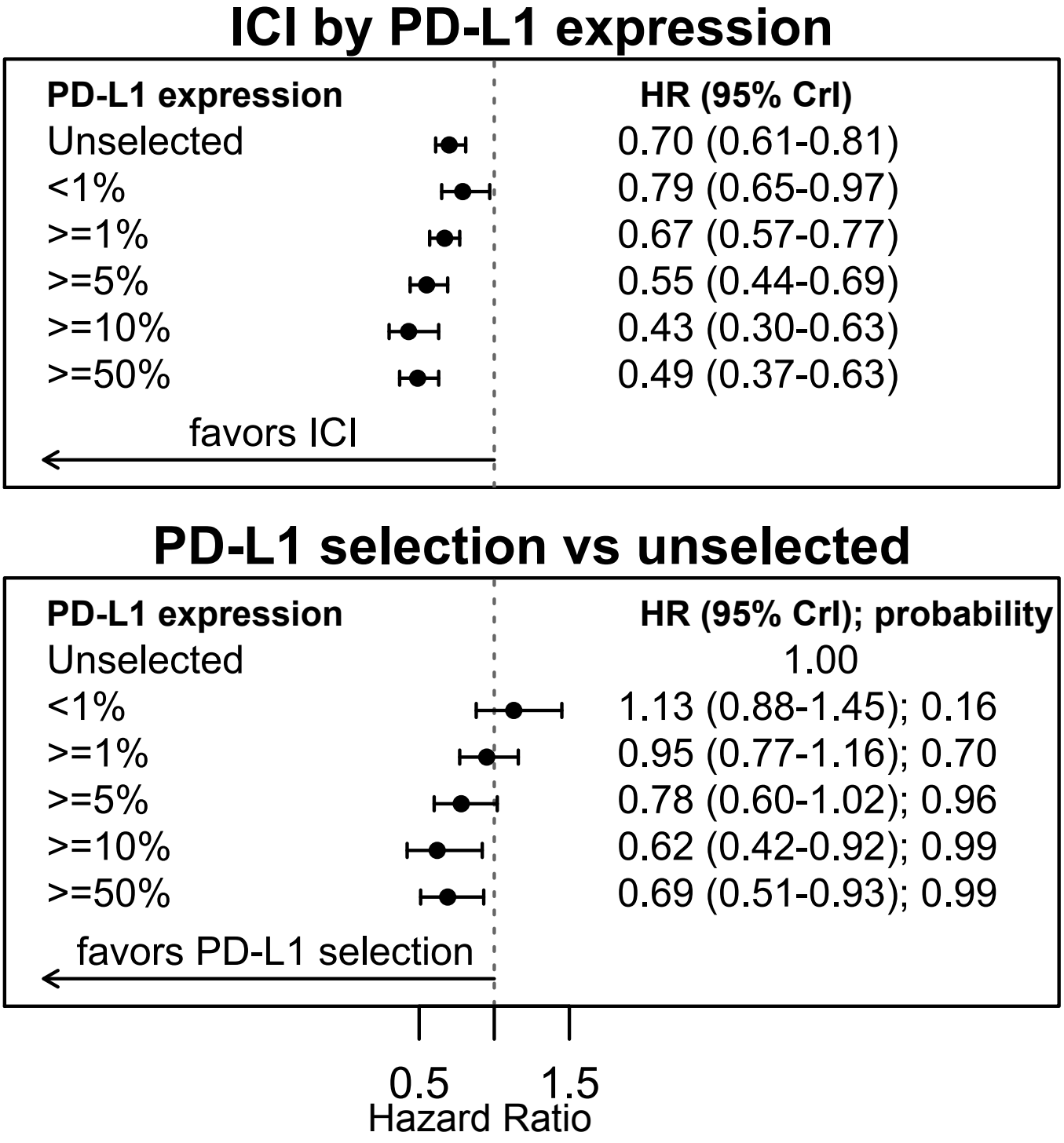
TKI-tyrosine kinase inhibitor; TPS-tumor proportion score


14 studies from PubMed screened
9 records excluded
5 trials included in meta-analysis


PD-L1 unselected
HR (95% CrI)
Nivolumab vs docetaxel
CheckMate 057
0.72 (0.60-0.88)
CheckMate 017
0.59 (0.44-0.79)
Meta-estimate
0.67 (0.54-0.83)
Atezolizumab vs docetaxel
POPLAR
0.73 (0.53-0.99)
OAK
0.73 (0.62-0.87)
Meta-estimate
0.73 (0.59-0.90)
Total ICI vs docetaxel
Meta-estimate
0.70 (0.61-0.81)
favors ICI
PD-L1<1%
HR (95% CrI)
Nivolumab vs docetaxel
CheckMate 057
0.90 (0.66-1.24)
CheckMate 017
0.58 (0.37-0.92)
Meta-estimate
0.77 (0.57-1.04)
Atezolizumab vs docetaxel
POPLAR
1.04 (0.62-1.75)
OAK
0.75 (0.59-0.96)
Meta-estimate
0.81 (0.62-1.08)
Total ICI vs docetaxel
Meta-estimate
0.79 (0.65-0.97)
favors ICI
PD-L1>=1%
HR (95% CrI)
Nivolumab vs docetaxel
CheckMate 057
0.59 (0.43-0.82)
CheckMate 017
0.69 (0.45-1.05)
Meta-estimate
0.63 (0.47-0.84)
Pembrolizumab vs docetaxel
KEYNOTE-010
0.67 (0.56-0.80)
Meta-estimate
0.67 (0.51-0.87)
Atezolizumab vs docetaxel
POPLAR
0.59 (0.40-0.85)
OAK
0.74 (0.58-0.93)
Meta-estimate
0.69 (0.53-0.88)
Total ICI vs docetaxel
Meta-estimate
0.67 (0.57-0.77)
PD-L1>=5%
HR (95% CrI)
Nivolumab vs docetaxel
CheckMate 057
0.43 (0.30-0.63)
CheckMate 017
0.53 (0.31-0.89)
Meta-estimate
0.46 (0.33-0.65)
Atezolizumab vs docetaxel
POPLAR
0.54 (0.33-0.89)
OAK
0.67 (0.49-0.90)
Meta-estimate
0.63 (0.46-0.84)
Total ICI vs docetaxel
Meta-estimate
0.55 (0.44-0.69)
favors ICI
PD-L1>=10%
HR (95% CrI)
Nivolumab vs docetaxel
CheckMate 057
0.40 (0.26-0.59)
CheckMate 017
0.50 (0.28-0.89)
Meta-estimate
0.43 (0.30-0.63)
Total ICI vs docetaxel
Meta-estimate
0.43 (0.30-0.63)
favors ICI
PD-L1>=50%
HR (95% CrI)
Pembrolizumab vs docetaxel
KEYNOTE-010
0.53 (0.40-0.70)
Meta-estimate
0.53 (0.38-0.75)
Atezolizumab vs docetaxel
POPLAR
0.49 (0.22-1.07)
OAK
0.41 (0.27-0.64)
Meta-estimate
0.43 (0.28-0.65)
Total ICI vs docetaxel
Meta-estimate
0.49 (0.37-0.63)
favors ICI
0.5
1
1.5
Hazard Ratio


PD-L1 unselected
HR (95% CrI)
Probability better
Nivolumab vs atezolizumab
0.92 (0.68-1.23)
0.72
favors first ICI compared
PD-L1<1%
HR (95% CrI)
Probability better
Nivolumab vs atezolizumab
0.95 (0.62-1.43)
0.59
favors first ICI compared
PD-L1 >=1%
HR (95% CrI)
Probability better
Nivolumab vs pembrolizumab
0.94 (0.63-1.39)
0.64
Nivolumab vs atezolizumab
0.91 (0.62-1.35)
0.68
Pembrolizumab vs atezolizumab
0.97 (0.68-1.41)
0.56
favors first ICI compared
PD-L1>=5%
HR (95% CrI)
Probability better
Nivolumab vs atezolizumab
0.74 (0.47-1.16)
0.91
favors first ICI compared
PD-L1>=50%
HR (95% CrI)
Probability better
Pembrolizumab vs atezolizumab
1.24 (0.72-2.11)
0.22
favors first ICI compared
0.5
1.5
Hazard Ratio


PD-L1 unselected
SUCRA
Probability best
HR (95% CrI)
Nivolumab 86.1 % 0.72 0.67 (0.54-0.83)
Atezolizumab 63.7 % 0.28 0.73 (0.59-0.90)
Docetaxel 0.2 % 0.00 1.00
favors ICI
PD-L1<1%
SUCRA
Probability best
HR (95% CrI)
Nivolumab 77.4 % 0.59 0.77 (0.57-1.04)
Atezolizumab 66.9 % 0.40 0.81 (0.62-1.08)
Docetaxel 5.7 % 0.00 1.00
favors ICI
PD-L1>=1%
SUCRA
Probability best
HR (95% CrI)
Nivolumab 77.3 % 0.52 0.63 (0.47-0.84)
Pembrolizumab 64.0 % 0.27 0.67 (0.51-0.87)
Atezolizumab 58.5 % 0.20 0.69 (0.53-0.88)
Docetaxel 0.2 % 0.00 1.00
favors ICI
PD-L1>=5%
SUCRA
Probability best
HR (95% CrI)
Nivolumab 95.4 % 0.91 0.46 (0.33-0.65)
Atezolizumab 54.5 % 0.09 0.63 (0.46-0.84)
Docetaxel 0.1 % 0.00 1.00
favors ICI
PD-L1>=10%
SUCRA
Probability best
HR (95% CrI)
Nivolumab 100.0 % 1.00 0.43 (0.30-0.63)
Docetaxel 0.0 % 0.00 1.00
favors ICI
PD-L1>=50%
SUCRA
Probability best
HR (95% CrI)
Atezolizumab 89.2 % 0.78 0.43 (0.28-0.65)
Pembrolizumab 60.8 % 0.22 0.53 (0.38-0.75)
Docetaxel 0.0 % 0.00 1.00
favors ICI
0.5
1
1.5
Hazard Ratio

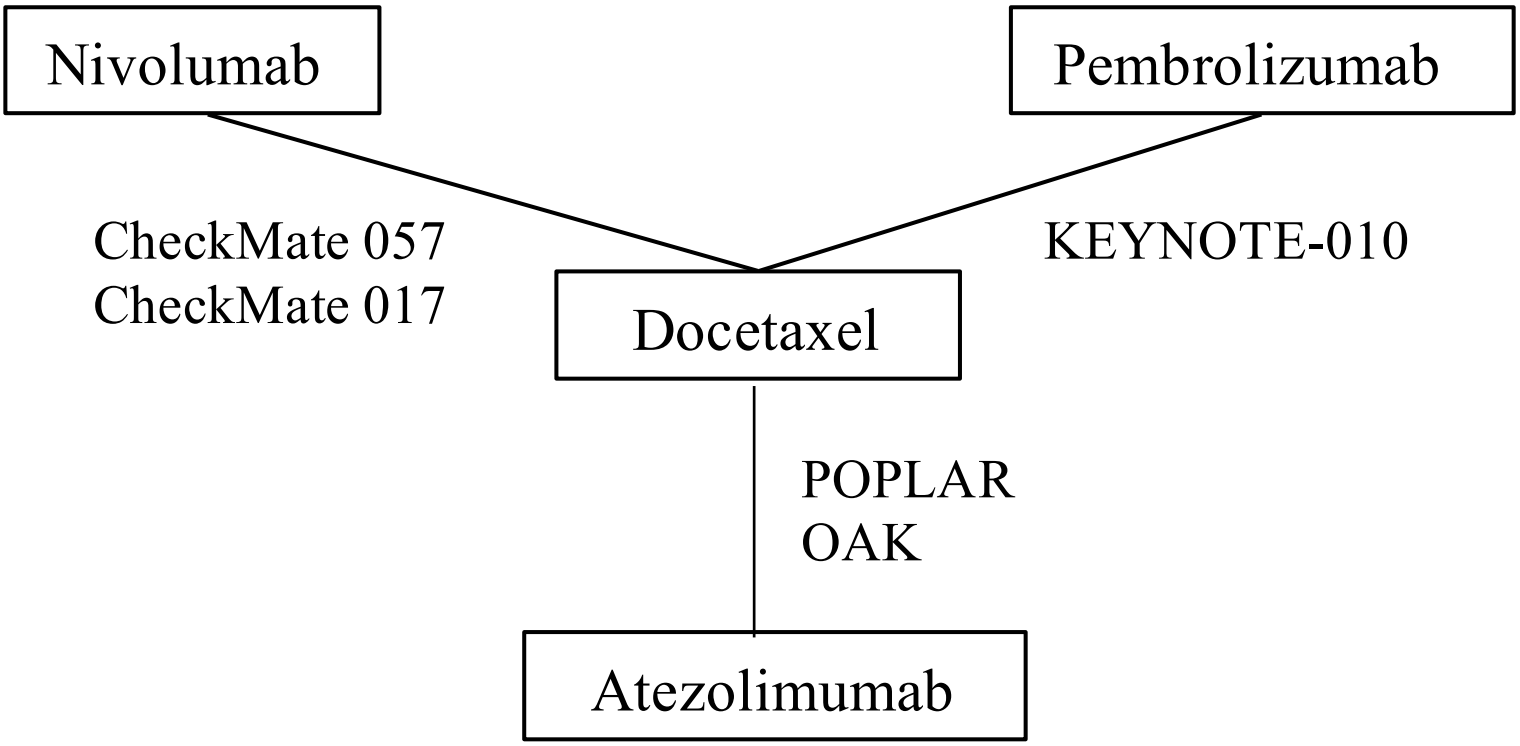

ICI by PD-L1 expression
PD-L1 expression
HR (95% CrI)
Unselected
0.70 (0.61-0.81)
<1%
0.79 (0.65-0.97)
>=1%
0.67 (0.57-0.77)
>=5%
0.55 (0.44-0.69)
>=10%
0.43 (0.30-0.63)
>=50%
0.49 (0.37-0.63)
favors ICI
PD-L1 selection vs unselected
PD-L1 expression
HR (95% CrI); probability
Unselected
1.00
<1%
1.13 (0.88-1.45); 0.16
>=1%
0.95 (0.77-1.16); 0.70
>=5%
0.78 (0.60-1.02); 0.96
>=10%
0.62 (0.42-0.92); 0.99
>=50%
0.69 (0.51-0.93); 0.99
favors PD-L1 selection
0.5
1.5
Hazard Ratio

Appendix

Table A1: Subgroup analysis of survival outcomes with ICIs by PD-L1 status and histology.

	HR (95% CrI)		
	Nonsquamous[a]	**Squamous**	**Nonsquamous[a] vs squamous**
PD-L1 unselected			
Nivolumab vs docetaxel	0.72 (0.55-0.95)	0.59 (0.41-0.84)	1.22 (0.78-1.90)
Atezolizumab vs docetaxel	0.72 (0.57-0.90)	0.75 (0.56-1.01)	0.96 (0.66-1.39)
ICI vs docetaxel (pooled estimate)	0.72 (0.61-0.85)	0.68 (0.54-0.85)	1.06 (0.80-1.40)
Nivolumab vs atezolizumab (indirect comparison)	1.00 (0.70-1.44)	0.79 (0.50-1.25)	1.27 (0.71-2.28)
PD-L1 >=1%			
Nivolumab vs docetaxel	0.59 (0.40-0.87)	0.69 (0.43-1.11)	0.86 (0.47-1.57)
Pembrolizumab vs docetaxel	0.63 (0.46-0.86)	0.74 (0.48-1.15)	0.85 (0.50-1.45)
ICI vs docetaxel (pooled estimate)	0.61 (0.49-0.78)	0.72 (0.52-0.99)	0.86 (0.58-1.27)
Nivolumab vs pembrolizumab (indirect comparison)	0.94 (0.57-1.53)	0.93 (0.49-1.78)	1.00 (0.45-2.26)

[a]Nonsquamous or adenocarcinoma histology. ICI-immune-checkpoint inhibitor.


Nivolumab
Pembrolizumab
CheckMate 057
CheckMate 017
KEYNOTE-010
Docetaxel
POPLAR
OAK
Atezolimumab