801 **RISK-BENEFIT RATIO IN IMMUNOTHERAPY (IO) WITH OR WITHOUT CHEMOTHERAPY (CT) ACCORDING TO PD-L1 EXPRESSION: A MODEL-BASED APPROACH TO INFORM TREATMENT DECISIONS IN METASTATIC NON-SMALL CELL LUNG CANCER**

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Background Anti-programmed death-(ligand)1 (PD-[L]1) therapies, either as monotherapy or in combination, have demonstrated remarkable efficacy in first-line (1L) treatment for metastatic non-small cell lung cancer (mNSCLC). Treatment decisions are often influenced by multiple factors, e.g., PD-L1 expression level or adverse event (AE) profile. Model-based meta-analyses (MBMA) of safety and efficacy can evaluate clinical risk-benefit ratio among FDA-approved IO therapies and inform treatment decisions in mNSCLC patients.

Methods MBMA of median overall survival (mOS) and treatment-related AEs Grade 3–5 (TRAEs Gr3+) were conducted using a curated database containing results from both randomized controlled and single-arm studies (published from 2015 to 2022) with FDA-approved (as of January 2023) IO-based treatments in mNSCLC patients. The analysis dataset comprised mOS and TRAEs Gr3+ results from 49 and 45 studies, and represented 17,918 and 19,238 patients, respectively. The mOS dataset included 34, 28, and 11 studies containing treatment of IO monotherapy, CT, and IO+CT, respectively. In the TRAE analysis, there were 33, 23, and 12 studies containing treatment of IO monotherapy, CT, and IO+CT, respectively. Analyses of endpoints utilized linear models in appropriately transformed domains (i.e., log for mOS, logit for TRAE Gr3+) and data were weighted by standard error of the outcome. After accounting for differential outcomes from specific treatments, potential impact of baseline characteristics (e.g., PD-L1 expression, line of therapy, ECOG PS, sex, histology, and geography/race) on the risk and benefit was evaluated. Models included between-study random effects and all covariates were additive.

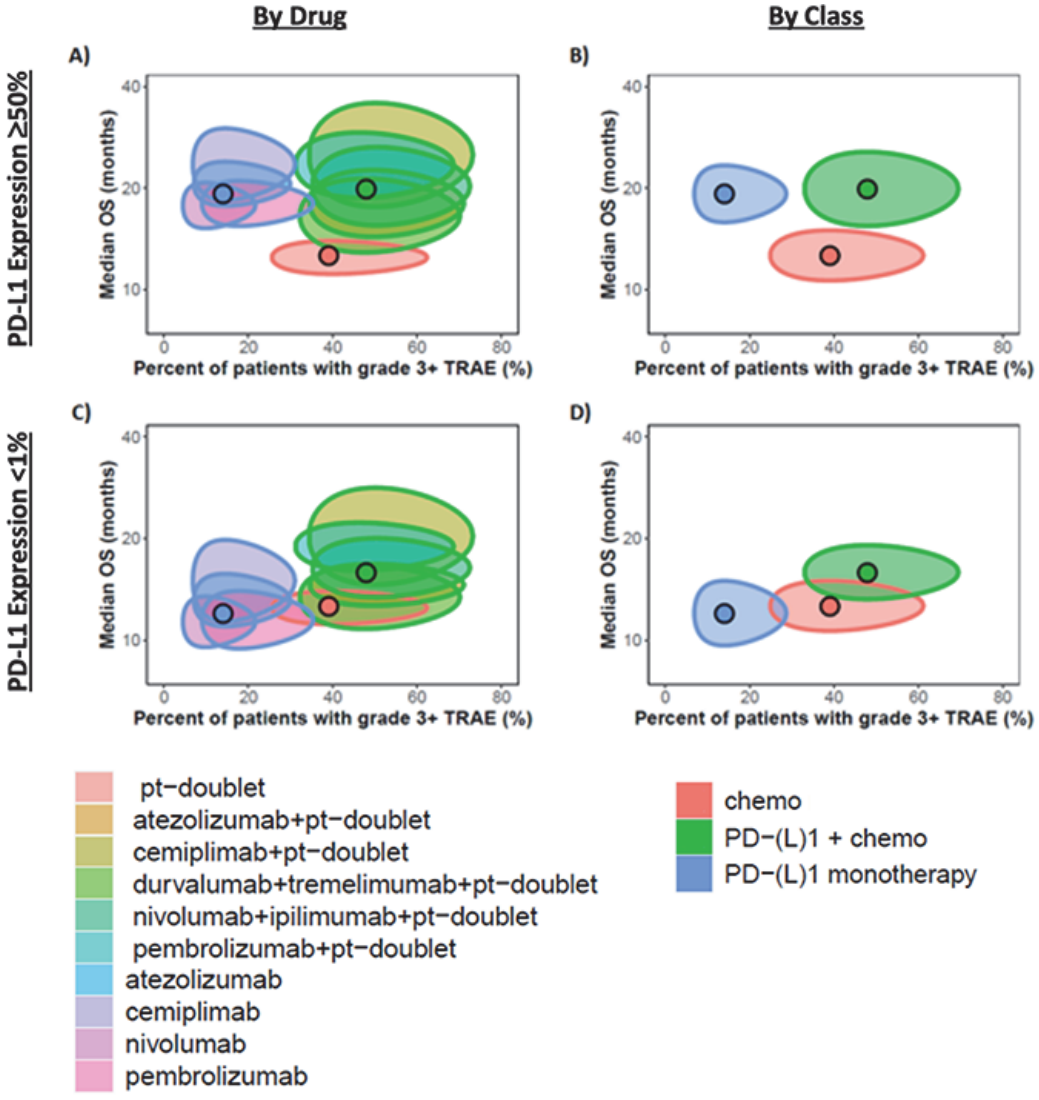
Results Regardless of specific IO agent or PD-L1 expression level, fewer patients experienced TRAEs Gr3+ with IO alone (14% [6.2–29]) compared to CT alone (39% [21–61]) or IO+CT (48% [27–70]). Among patients with PD-L1 expression ^{3}50%, mOS was comparable for IO with or without CT (figure 1A,B). In patients with PD-L1 expression <1% (figure 1C,D), therapeutic benefit was higher for IO+CT (16 months [13–19]) than IO alone (12 months [10–15]), justifying the choice of IO+CT in this patient population despite higher TRAEs than IO alone. table 1 summarizes all model parameter estimates, including influential covariates on mOS. No clinically meaningful covariates were identified for TRAEs Gr3+.

Conclusions This MBMA evaluates the risk-benefit ratio and provides quantitative insight into the therapeutic utility of IO agents. Our findings are consistent with treatment guidelines for 1L patients with mNSCLC, highlighting the potential utility of a quantitative model-based approach to strengthen clinical recommendations and to facilitate decision making.

Abstract 801 Table 1 Model Parameter Estimates with 95% Confidence Intervals

	mOS*		TRAE Gr3+	
Parameter	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Treatment Effects	***months***		***%***	
atezolizumab	20.6	[17.7, 24.0]	14.5	[6.3, 29.8]
atezolizumab+pt-doublet	18.0	[14.4, 22.6]	49.5	[28.2, 71.1]
cemiplimab	23.5	[18.4, 30.1]	14.5	[6.0, 30.9]
cemiplimab+pt-doublet	25.1	[17.7, 35.8]	50.1	[27, 73.2]
durvalumab+tremelimumab+pt-doublet	16.6	[12.9, 21.3]	47.5	[25.8, 70.2]
nivolumab	17.8	[15.2, 20.8]	9.8	[4.2, 21.6]
nivolumab+ipilimumab	20.7	[16.9, 25.4]	36.0	[18.2, 58.8]
nivolumab+ipilimumab+pt-doublet	20.3	[15.5, 26.4]	50.4	[28.2, 72.6]
pembrolizumab	18.0	[15.5, 21.0]	17.8	[8.0, 35.3]
pembrolizumab+pt-doublet	23.4	[18.7, 29.3]	46.2	[25.4, 68.7]
pt-doublet	12.5	[11.1, 14.0]	39.9	[21.2, 62.3]
Covariates	***mOS ratio***			
2nd line+ vs. 1st line	0.77	[0.70, 0.85]		
squamous vs. non-squamous	0.76	[0.71, 0.82]		
Asian vs. non-Asian	1.25	[1.15, 1.37]		
PD-L1 expression <50% vs ≥50% [PD-(L)1 mono]	0.73	[0.62, 0.86]		
PD-L1 expression <50% vs ≥50% [PD-(L)1 + chemo]	0.81	[0.65, 1.01]		
PD-L1 expression <1% vs 1-49% [PD-(L)1 mono]	0.87	[0.75, 1.00]		

* Reference population in mOS model is first line, non-Asian, 39% squamous histology, PD-L1 expression ≥50%



Gr3+, grade three or higher; mNSCLC, metastatic non-small cell lung cancer; mOS, median overall survival; PD-L1, programmed death-ligand 1; pt, platinum; TRAE, treatment-related adverse events

Note: In patients with PD-L1 expression 1-49% (not shown), mOS was higher for IO+CT (16 months [13-19]) than IO alone (14 months [11-17]). Bubble size represents the 95% prediction interval for each treatment (mOS is vertical, TRAE Gr3+ is horizontal); Dots represent the predictions for the general treatment class as a whole

Abstract 801 Figure 1 Model predicated mOS and TRAE Gr3+ for first-line, non-Asian, mNSCLC patient population

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