TUMOR MUTATION BURDEN (TMB) BY NGS ASSOCIATES WITH SURVIVAL IN LUNGMAP IMMUNOTHERAPY TRIALS: S1400I and S1400A

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DISCLOSURES

Commercial Interest	Relationship(s)
Bristol-Myers Squibb	Scientific advisory board
AstraZeneca/ Daiichi	Scientific advisory board
Genentech/Roche	Scientific advisory board
Merck	Scientific advisory board
Regeneron/ Sanofi	Scientific advisory board
Lilly/Loxo	Scientific advisory board
Novartis	Scientific advisory board
OncoCyte	Scientific advisory board

BACKGROUND and RATIONALE

- PD-L1 and TMB have each shown predictive value in studies with PD-L1/PD-1 checkpoint inhibitor (CPI) immunotherapeutics as single agents, including nivolumab

- TMB has also shown predictive value for PD-L1/PD-1 + CTLA4 combination therapies such as nivolumab + ipilimumab and durvalumab + tremelimumab (e.g., CM 227 and MYSTIC)

- Several methodologies have been employed to measure TMB
  - FoundationOne NGS is an analytically and clinically validated assay that correlates with WES and predicted neoantigen load

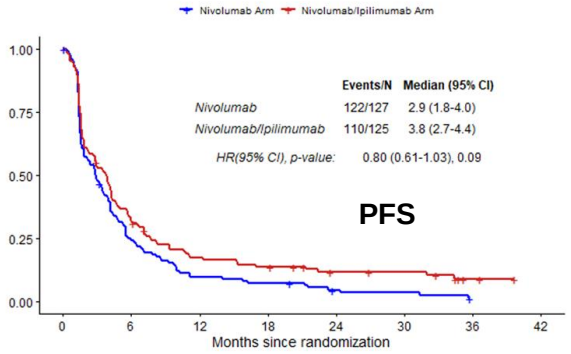
- **Hypothesis: A Combination Index of PD-L1 + TMB will enhance interpretation of trials comparing PD-L1/PD-1-based therapies.**

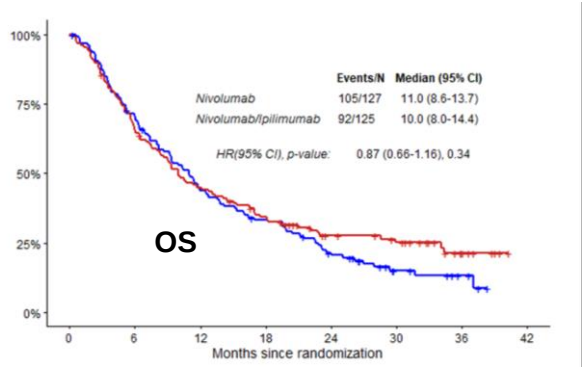
- Here we describe TMB, PD-L1 and genomic signatures within the Lung MAP S1400I and S1400A trials to investigate associations with patient outcomes in checkpoint monotherapy vs combination therapy

Lung MAP Studies: Previously treated, IO-naïve, stage IV Sq NSCLC

S1400I: Randomized Phase III study: Nivolumab + Ipilumumab vs Nivolumab

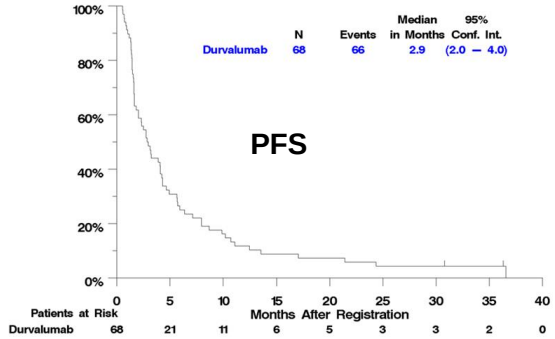
Gettinger S. et al
(ASCO 2019, WCLC 2019)

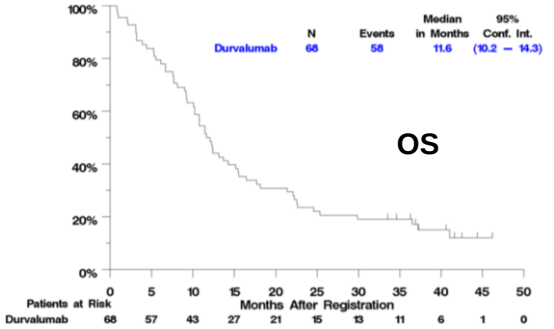




S1400A: Single-arm phase II study: Durvalumab

Borghaei H et al. Clin Lung Cancer, in press





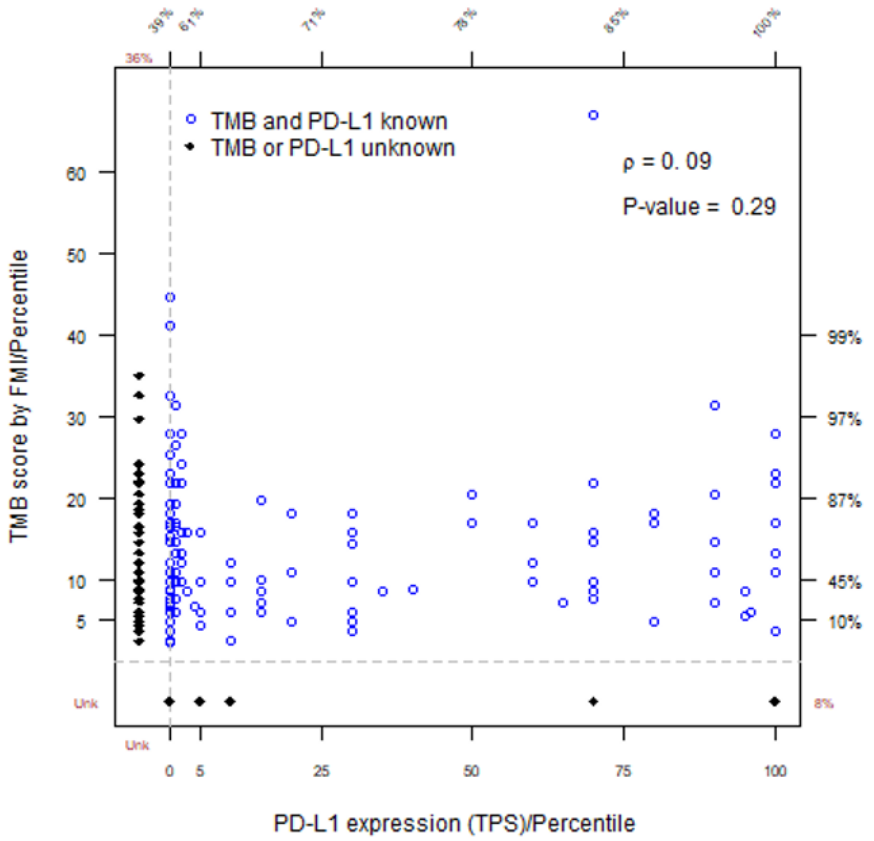
METHODOLOGIES AND STATISTICAL APPROACH

- **METHODS:**
  - **TMB: NGS employing FoundationOne T5 platform**
    Specimens: DNA; archived FFPE tumor specimens and/or fresh biopsies
    Assessment: Continuous and dichotomized at 10 mt/Mb

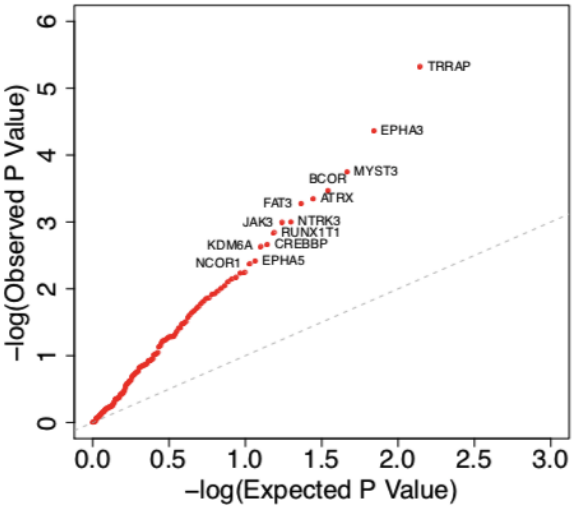
  - **PD-L1: using DAKO 28-8 ab (nivolumab)**
    Assessment: Continuous and dichotomized at 0% vs >0%

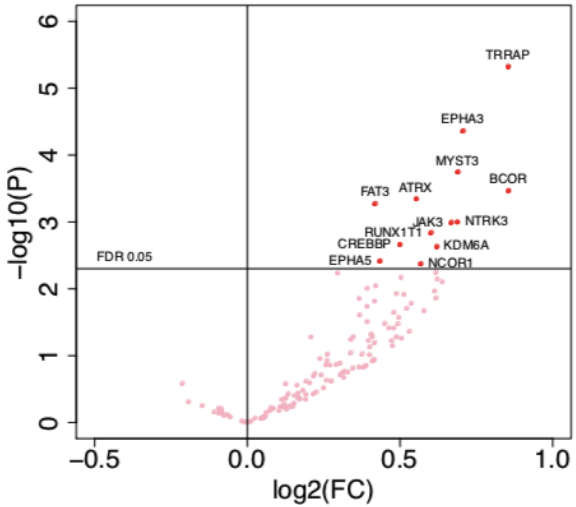
- **STATISTICAL APPROACH: Genomic alterations association with TMB: Wald test with FDR ≤ 5%**
  Combined data S1400I + S1400A: Unsupervised hierarchical clustering

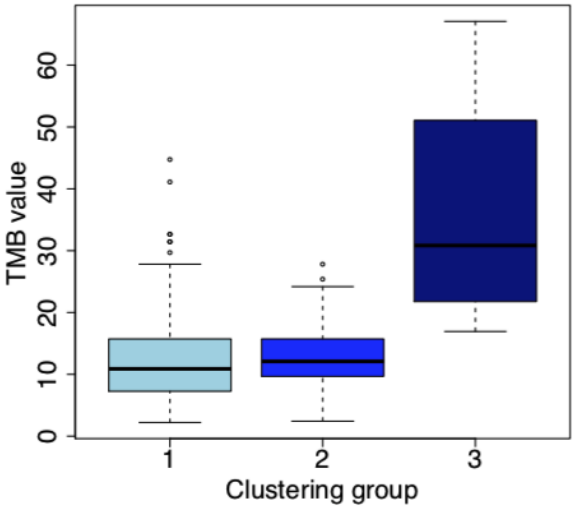
No correlation between TMB and PD-L1 expression in the S1400I study



Association between TMB and gene alterations in S1400I







Left: Q-Q plot of the observed P values and expected P values. Points higher than diagonal line suggest that there are statistical significances.

Middle: Volcano plot (log2(FC) vs -log10(P)). It suggests that all significant gene alterations are associated with higher TMB values (not surprise by the definition of TMB).

Right: Boxplot of TMB values by the 3 clustering groups

Tumor Mutational Burden as a Continuous Variable

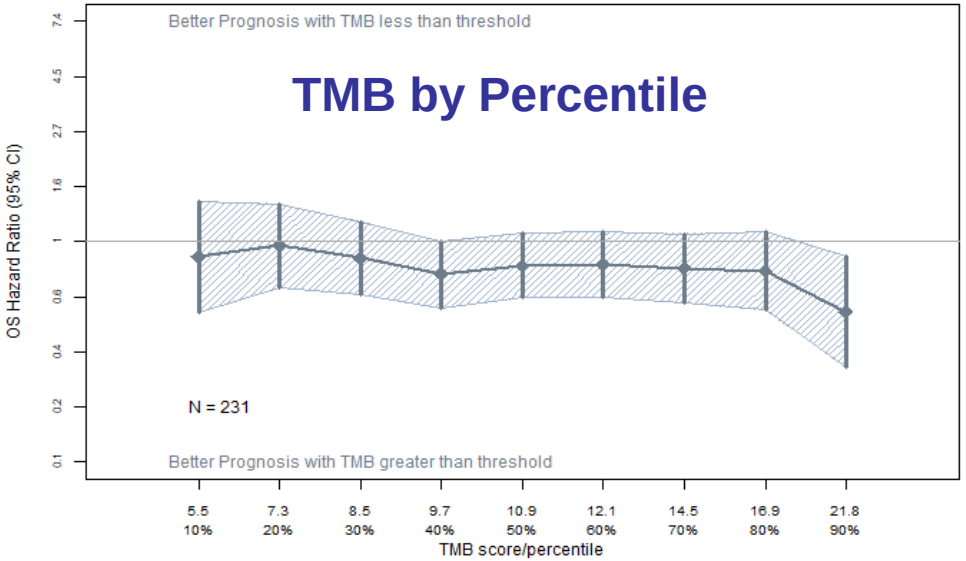
TMB by Value (per 10-unit difference)

Total pts: 252 on S1400I
68 on S1400A

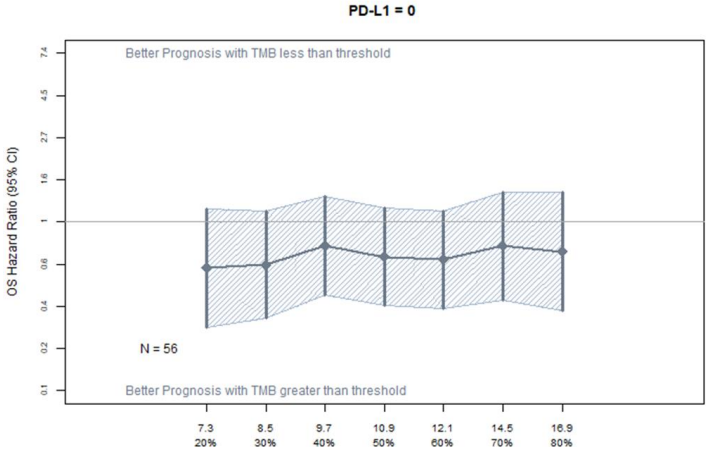
Overall Survival: higher TMB; HR; 0.80 (95% CI: 0.67;0.94), p=0.008

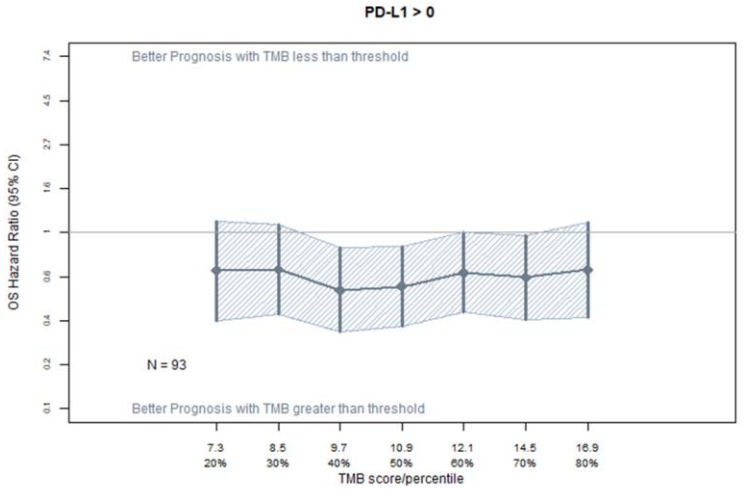
Progression Free Survival: HR: 0.80 (95% CI; 0.69;0.93), p=0.004

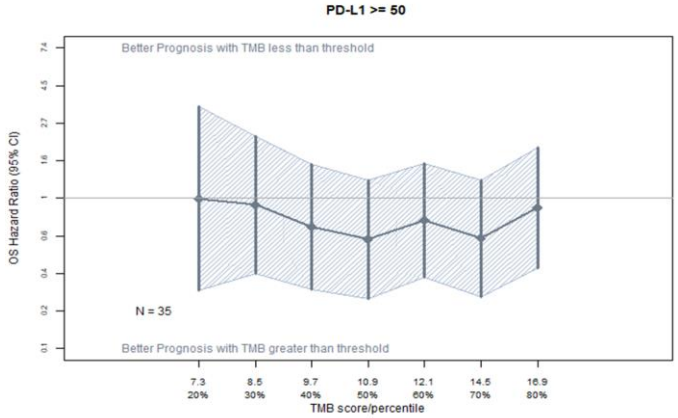
HIGHER TMB WAS SIGNIFICANTLY ASSOCIATED WITH IMPROVED OS AND PFS.



The relative risk of death comparing OS between patients with TMB levels above versus below the thresholds





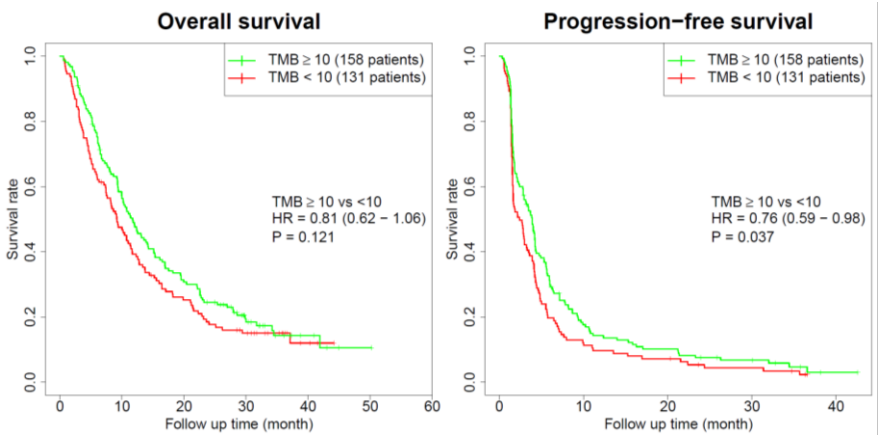


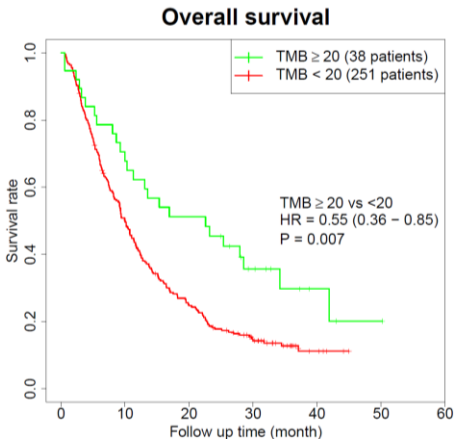
Association between TMB (continuous) and different PD-L1 expression groups : S1400I

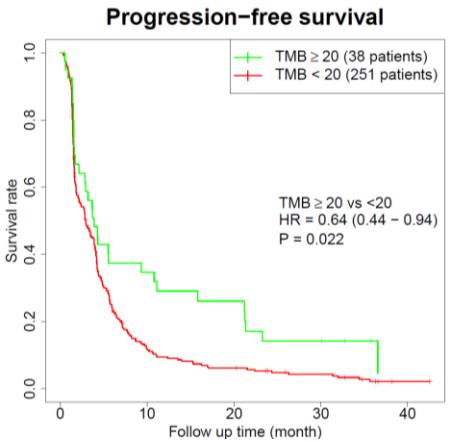
HRs ≤ 1.0 in all subgroups of PD-L1 expression.

Survival analysis in both S1400A and S 1400 I OS & PFS related to TMB by categories.

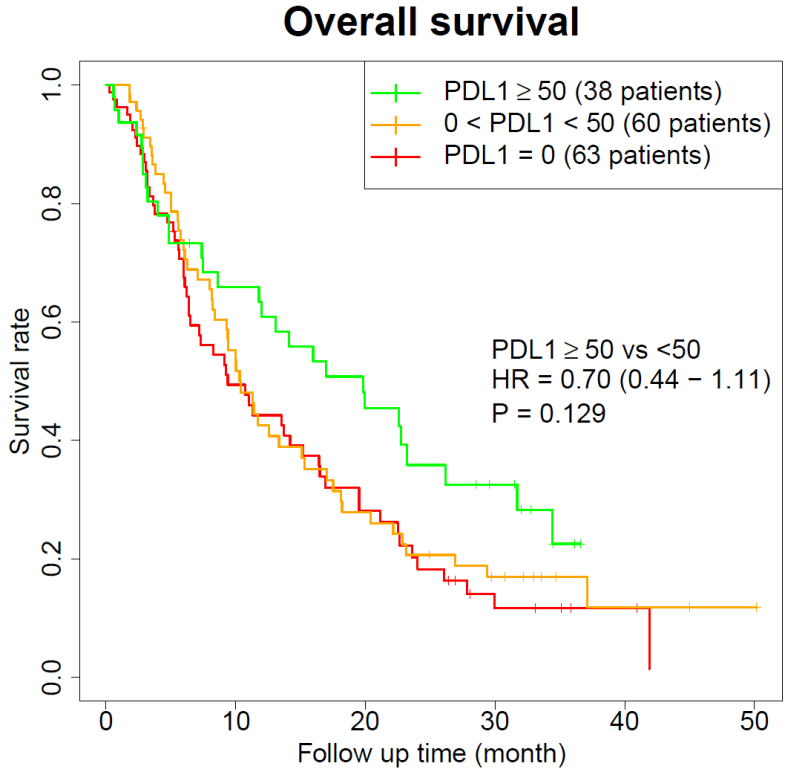
(pre-determined by cut-off of 10 mt/Mb)

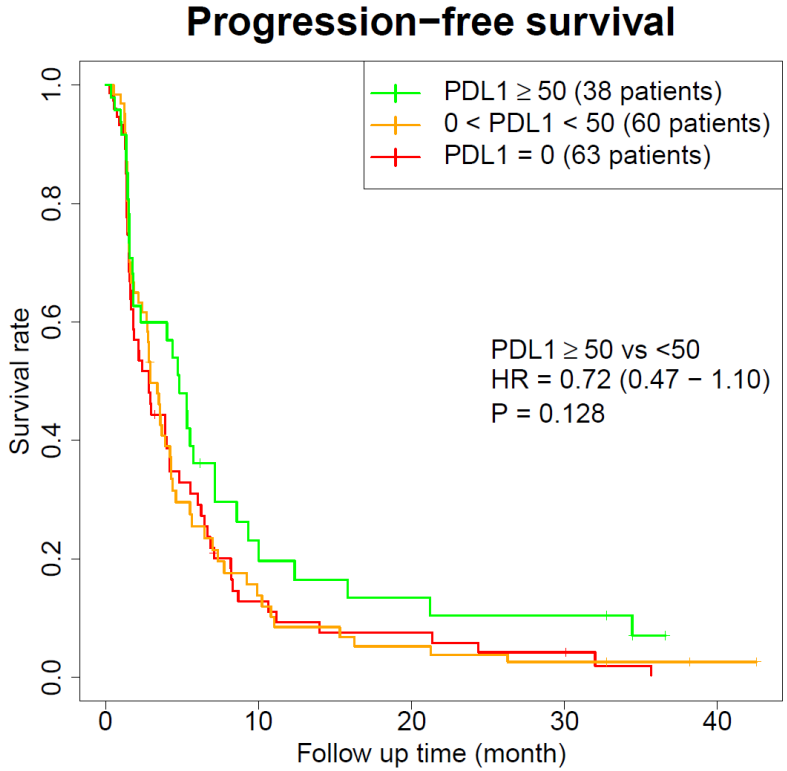






Survival analysis in S1400I OS & PFS related to PD-L1 status

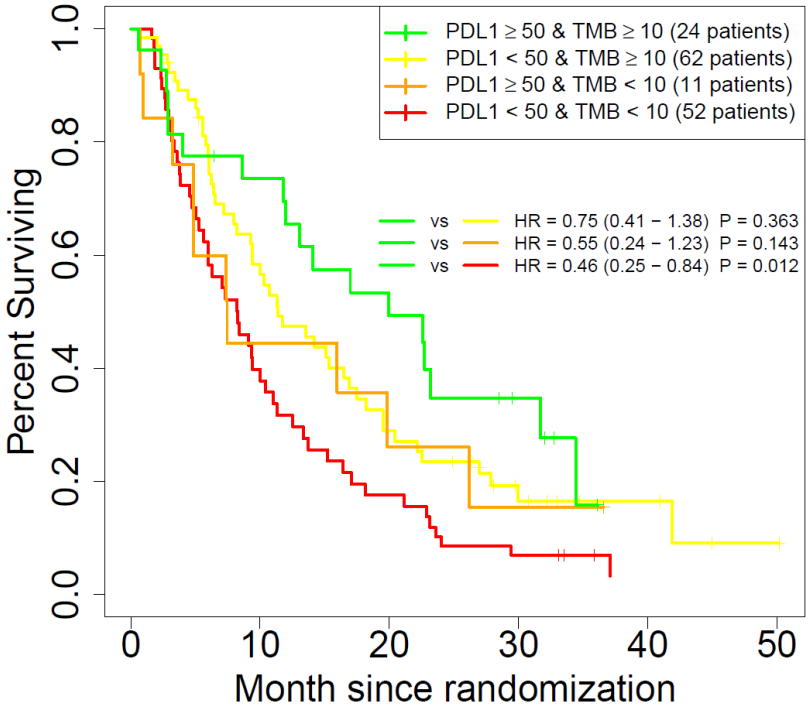




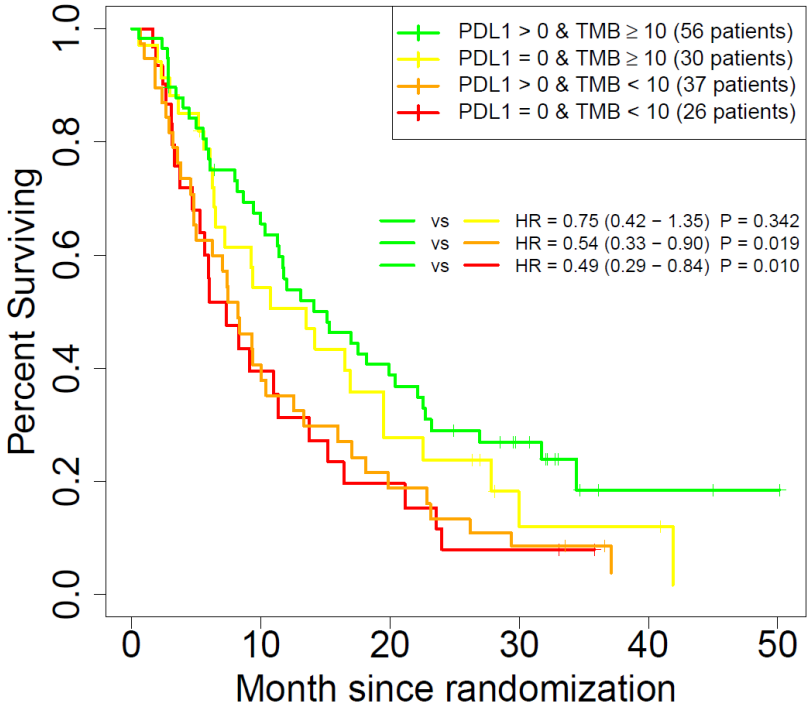
Combining PDL-1 and TMB Analysis:

- Patients high in both outperformed all other groups

OS KM by TMB at 10 and PDL1 at 50%



OS KM by TMB at 10 and PDL1 pos/neg



TAKE HOME MESSAGE

Continuous TMB variable analyses was more informative than categories

Higher TMB associated significantly with OS and PFS across two IO studies and was independent of PD-L1 status

Combination of TMB and PD- L1 expression impacted outcome in S1400I

How genetic alterations associated with high TMB contribute to clinical outcomes warrants further considerations

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