RATIONALE-307: Updated biomarker analysis of Phase 3 study of tislelizumab plus chemotherapy vs chemotherapy alone for 1L advanced sq-NSCLC

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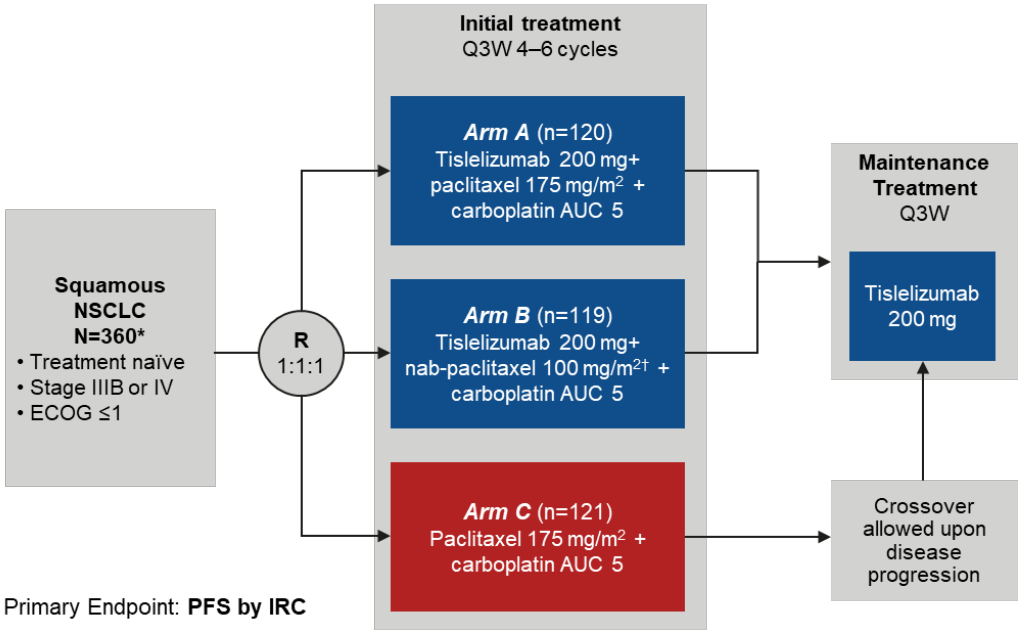
Presenter DISCLOSURES

I do not have any financial relationships to disclose

Ineligible Company (formerly: Commercial Interest)	**Relationship(s)**

Background and Aim

- RATIONALE-307 was an open-label, randomized, multicenter phase 3 study that compared the efficacy and safety of tislelizumab plus chemotherapy vs chemotherapy alone as a first-line treatment for advanced squamous non-small cell lung cancer (NSCLC)[1]
- Tislelizumab plus chemotherapy significantly improved PFS[1]:
  - Arm A vs Arm C: HR=0.524
  - Arm B vs Arm C: HR=0.478
- PD-L1, TMB, and GEP are biomarkers of interest for immune checkpoint inhibitors in NSCLC



Objective of this exploratory analysis: To evaluate associations of PD-L1, tTMB, bTMB, and TIS with PFS benefit of tislelizumab in combination with chemotherapy vs chemotherapy alone

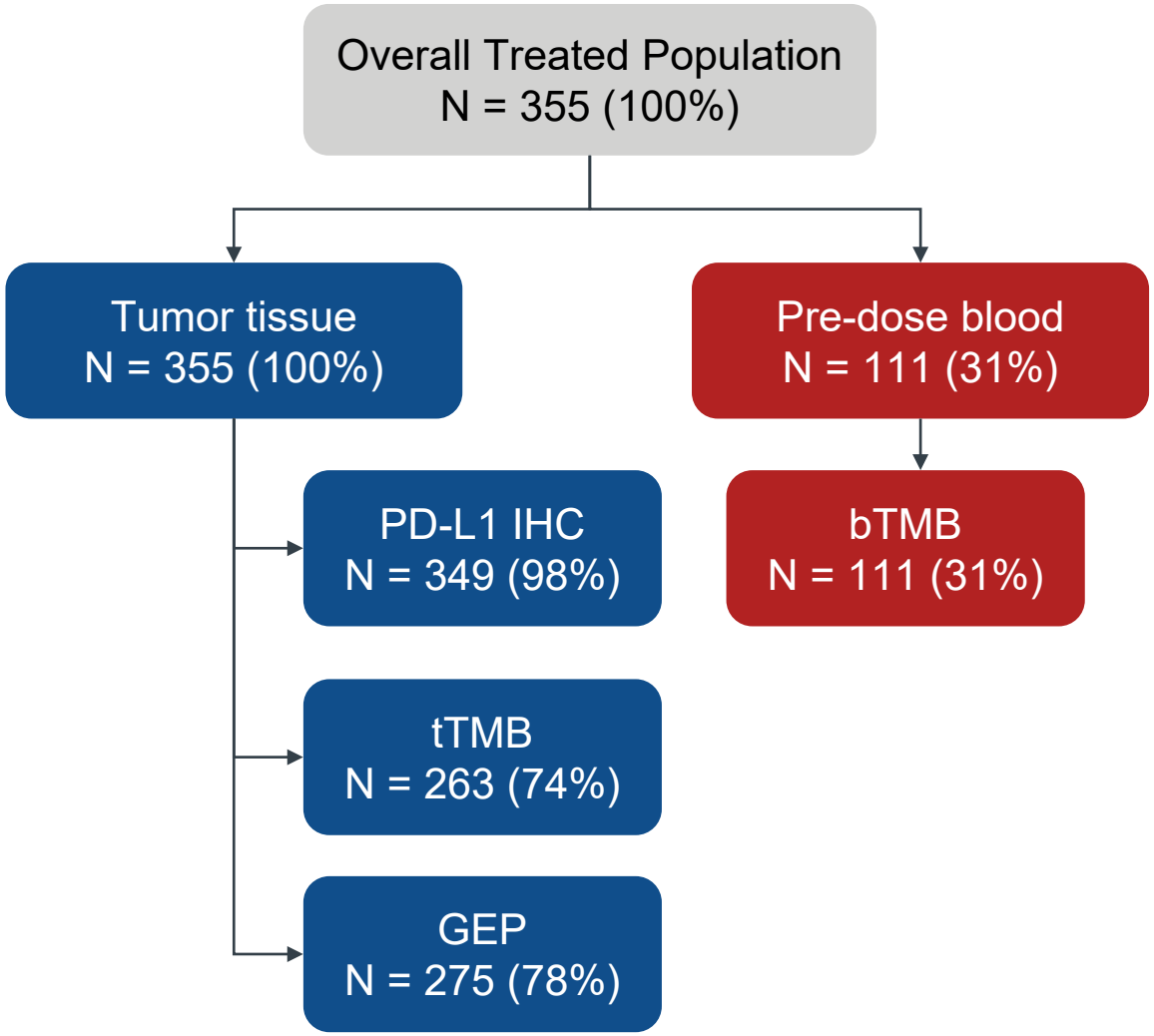
Data cutoff: December 6, 2019
*A total of 360 patients were randomized; 5 patients (n=1 [B]; n=4 [C]) did not receive study treatment; † nab-paclitaxel was dosed on Days 1, 8 and 15 of each cycle

Abbreviations: bTMB, blood tumor mutational burden; ECOG, Eastern Cooperative Oncology Group; GEP, gene expression profiling; HR, hazard ratio; nab, nanoparticle albumin-bound; IRC: independent review committee; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized; TIS: tumor inflammation signature; tTMB: tissue tumor mutational burden

1. Wang J, et al. JAMA Oncol 2021; doi:10.1001/jamaoncol.2021.0366

Methods

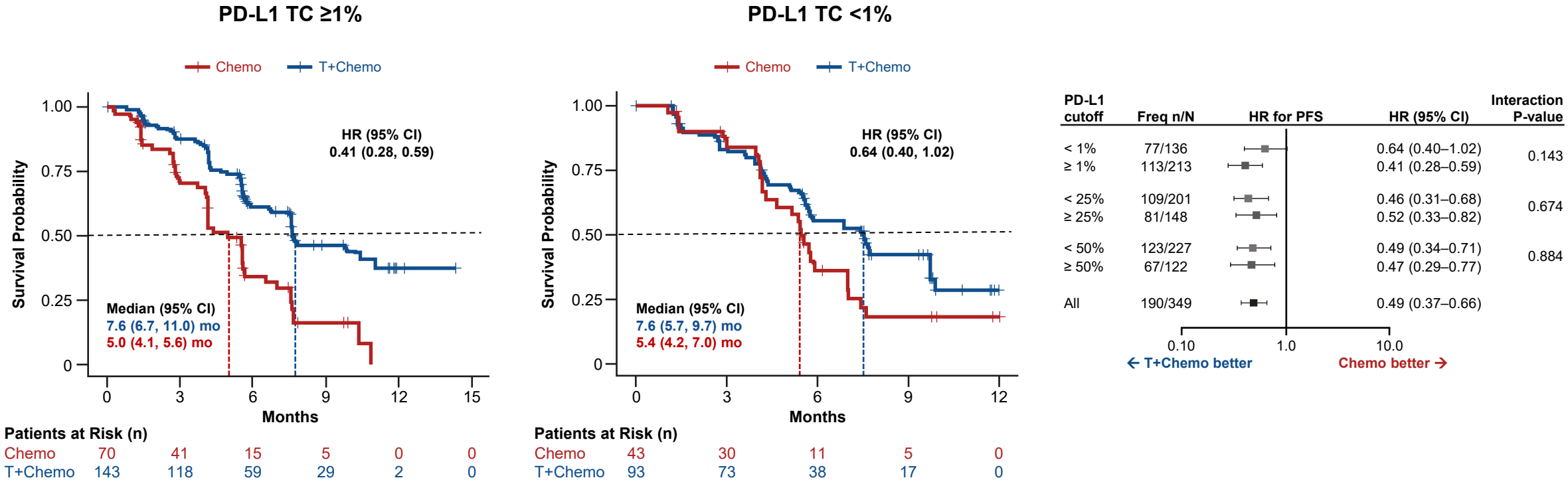
- Two tislelizumab-containing regimens were combined as a single tislelizumab plus chemotherapy arm (T + Chemo) for comparison with the chemotherapy arm (Chemo)
- Biomarker assessments on tumor tissue or blood samples were collected at baseline:
  - PD-L1 IHC by Ventana SP263
  - tTMB and bTMB by OncoScreen Plus
  - GEP by HTG EdgeSeq Precision Immuno-Oncology Panel
    - 1392 genes were included
    - TIS score was calculated by GSVA
- The biomarker evaluable populations and overall treated population had similar baseline characteristics and efficacy outcomes



Data cutoff: December 6, 2019

Abbreviations: bTMB, blood tumor mutation burden; GEP, gene expression profiling; IHC, immunohistochemistry; PD-L1, programmed death-ligand 1; tTMB, tissue tumor mutation burden; TIS: tumor inflammation signature; GSVA: gene set variation analysis

PFS benefit of tislelizumab plus chemotherapy was observed regardless of PD-L1 expression

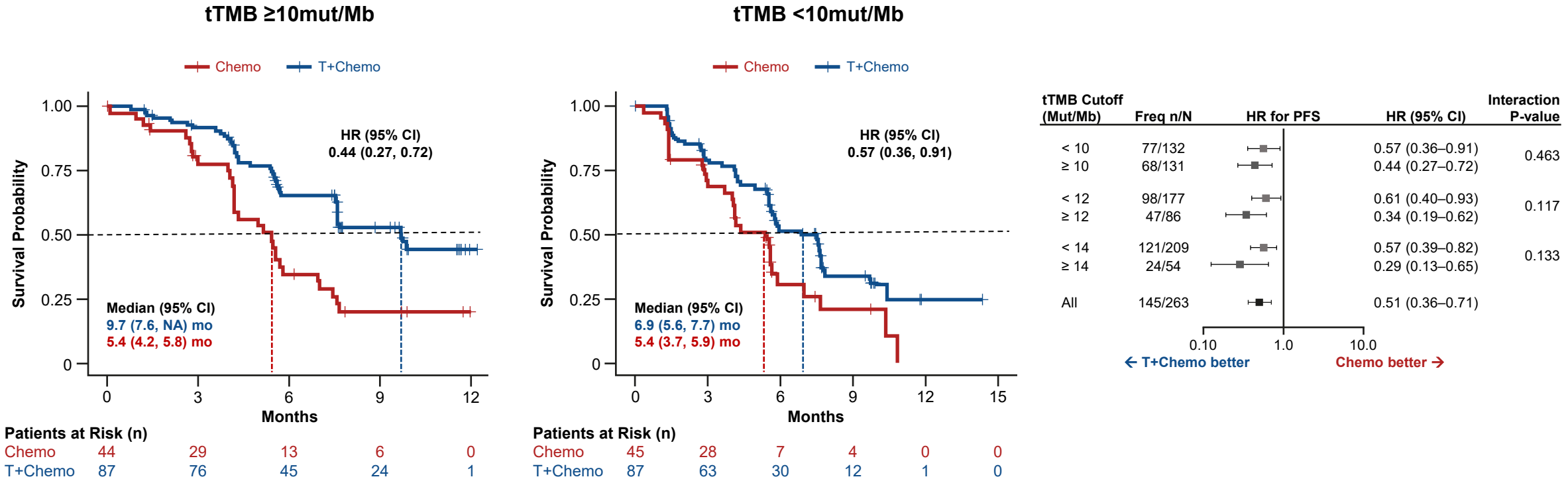


Data cutoff: December 6, 2019

Abbreviations: Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; mo, months; PD-L1, programmed death-ligand 1; PFS, progression-free survival; T, tislelizumab

The PD-L1 cutoff of 1% was recommended by receiver operating characteristic (ROC) analysis in the T + Chemo arm.

PFS benefit of tislelizumab plus chemotherapy was observed in both tTMB high and tTMB low subgroups

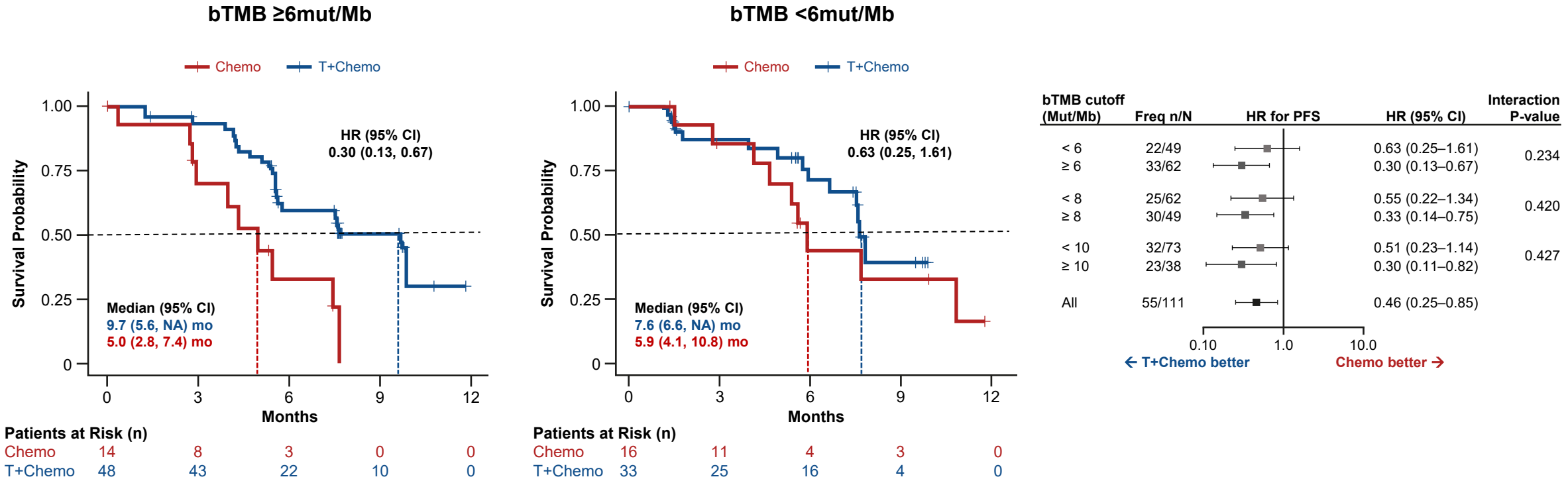


Data cutoff: December 6, 2019

Abbreviations: Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival; T, tislelizumab; tTMB, tissue tumor mutation burden

The tTMB cutoff of 10 Mut/Mb was recommended by receiver operating characteristic (ROC) analysis in the T + Chemo arm.

PFS benefit of tislelizumab plus chemotherapy was observed in both bTMB high and bTMB low subgroups

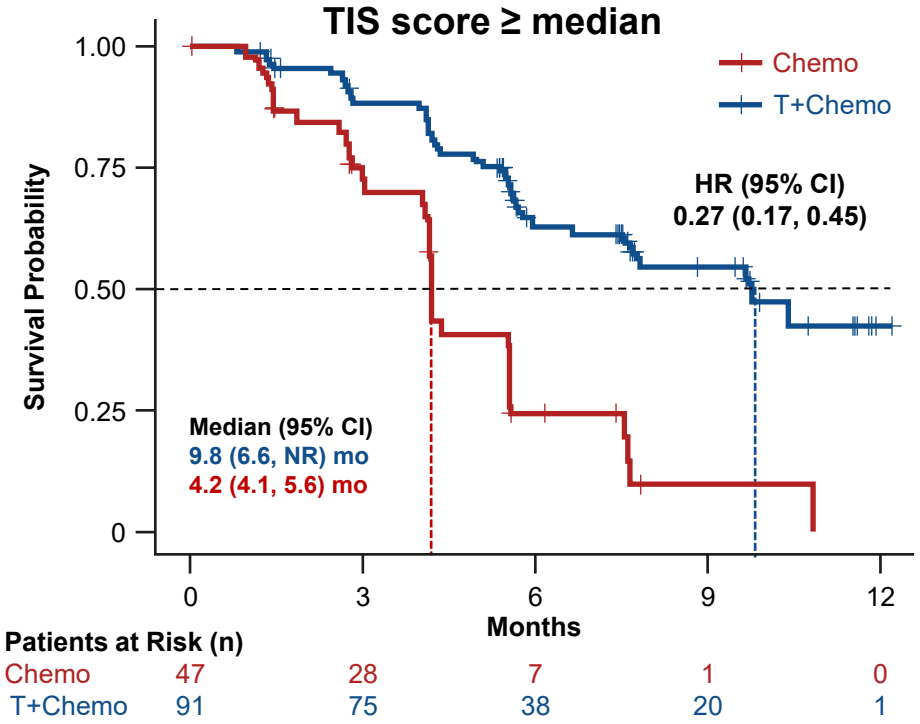


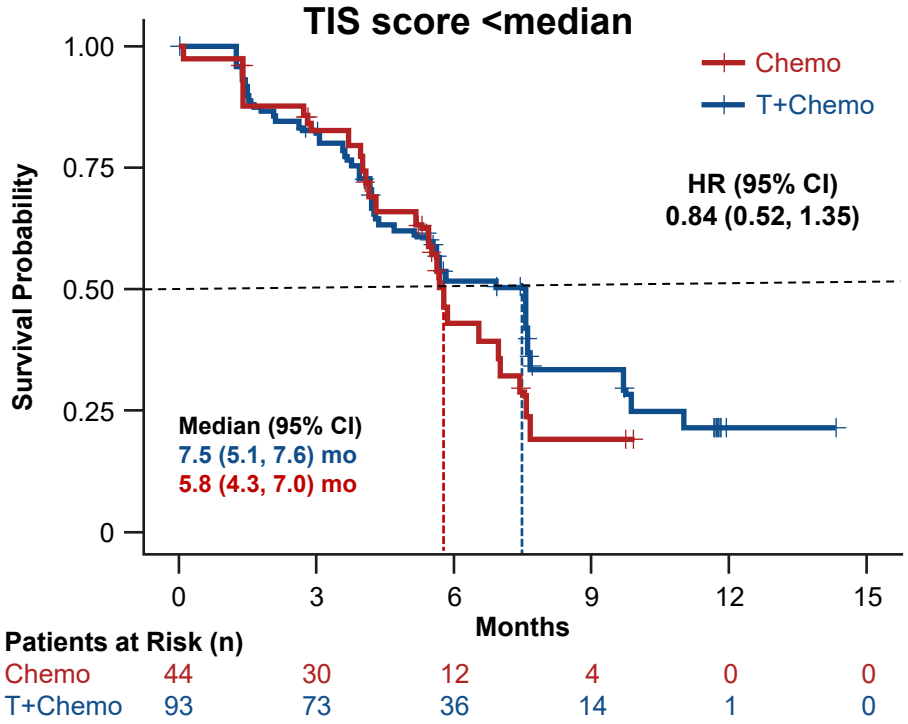
Data cutoff: December 6, 2019

Abbreviations: Chemo, chemotherapy; bTMB, blood tumor mutation burden; CI, confidence interval; HR, hazard ratio; mo; months; PFS, progression-free survival ; T, tislelizumab

The bTMB cutoff of 6 Mut/Mb was recommended by receiver operating characteristic (ROC) analysis in the T + Chemo arm.

Significant association was found between TIS score and PFS benefit of tislelizumab plus chemotherapy





- IFN related genes (e.g. PSMB9, HERC6, OAS2, etc.) were significantly associated with PFS benefit between treatment arms
- TIS was predictive to the PFS benefit of tislelizumab plus chemotherapy by median cutoff (interaction P=0.001)
- The predictive effect of TIS score was independent of PD-L1 and TMB (interaction P>0.5)

Data cutoff: December 6, 2019

Abbreviations: CI, confidence interval; HR, hazard ratio; IFN, interferon; mo, months; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TIS, tumor inflammation signature

TIS Gene: CCL5, CD27, CD274, CD276, CD8A, CMKLR1, CXCL9, CXCR6, HLA-DQA1, HLA-DRB1, HLA-E, IDO1, LAG3, NKG7, PDCD1LG2, PSMB10, STAT1, TIGIT
The TIS median cutoff was recommended by receiver operating characteristic (ROC) analysis in the T + Chemo arm.

Conclusions

- Tislelizumab plus chemotherapy had PFS benefit versus chemotherapy regardless of PD-L1 expression, blood TMB and tissue TMB
- TIS score was significantly associated with PFS benefit of tislelizumab plus chemotherapy versus chemotherapy, indicating the importance of tumor microenvironment in the clinical benefit of combination treatment

Data cutoff: December 6, 2019
Abbreviations: NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TIS, tumor inflammation signature; TMB, tumor mutation burden

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