RATIONALE-309: Updated PFS, PFS2, and OS from a Phase 3 double-blind trial of tislelizumab versus placebo, plus chemotherapy, as first-line treatment for recurrent/metastatic nasopharyngeal cancer

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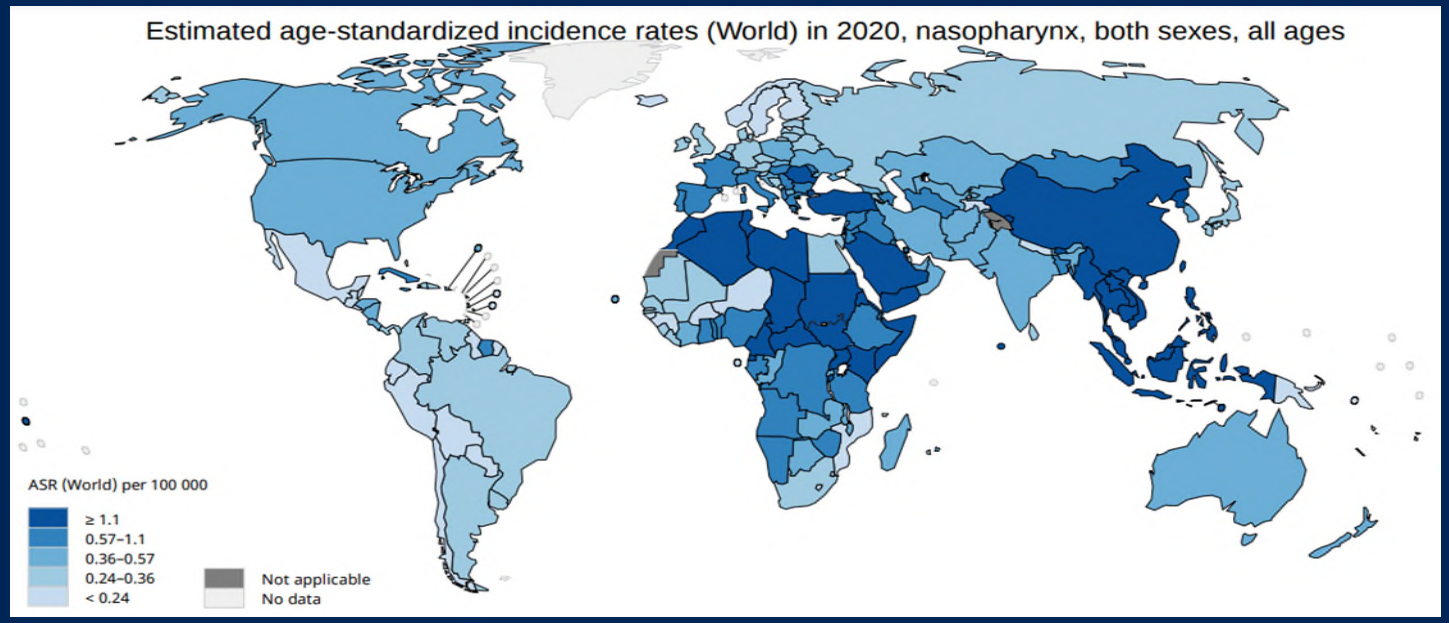
Background

- NPC accounts for ~133,000 new cancer cases and 80,000 deaths per year worldwide[1]



- The prognosis for patients with R/M NPC treated with 1L chemotherapy remains poor, highlighting the unmet medical need in this setting
  - Median PFS=7.0 months; median OS=22.1 months[2,3]

1L, first-line; NPC, nasopharyngeal cancer; OS, overall survival; PFS, progression-free survival; R/M, recurrent or metastatic

1. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/4-Nasopharynx-fact-sheet.pdf. Accessed February 22, 2022;
2. Zhang L, et al. Lancet 2016;388:1883–92; 3. Hong S, et al. J Clin Oncol 2021;39:3273–82

Background

- Tislelizumab, a humanized anti-PD-1 IgG4 monoclonal antibody, was engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent cellular phagocytosis, a mechanism of T-cell clearance and potential anti-PD-1 resistance[1,2]

- Tislelizumab efficacy has been demonstrated in Phase 2 and 3 trials across multiple tumor types, including NPC, EC, GC, HCC, NSCLC, UC, and MSI-high/dMMR solid tumors[3–9]

- RATIONALE-309 is a randomized, double-blind, Phase 3 clinical trial designed to evaluate the efficacy and safety of tislelizumab + chemotherapy vs placebo + chemotherapy as 1L treatment for R/M NPC[10]
  - RATIONALE-309 met its primary endpoint at the interim analysis (median follow-up: 10.0 months) as 1L tislelizumab + chemotherapy significantly improved IRC-assessed PFS vs placebo + chemotherapy[10]

1L, first-line; dMMR, deficient mismatch repair; EC, esophageal cancer; FcγR, Fc-gamma receptor; GC, gastric cancer; HCC, hepatocellular carcinoma; IgG, immunoglobulin; IRC, independent review committee; MSI, microsatellite instability; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PFS, progression-free survival; R/M NPC, recurrent or metastatic nasopharyngeal cancer; UC, urothelial cancer

1. Zhang T, et al. Cancer Immunol Immunother 2018;67:1079–90; 2. Dahan R, et al. Cancer Cell 2015;28:285–95; ; 3. Shen L, et al. J Immunother Cancer 2020;8:e000437; 4. Cheng A, et al. Ann Oncol 2018;29:V27–8; 5. Ye D, et al. Cancer Sci 2021;112:305–13; 6. Lu S, et al. J Thorac Oncol 2021;16:1512–22; 7. Wang J, et al. JAMA Oncol 2021;7:709–17; 8. Li J, et al. J Clin Oncol 2021;39:2569; 9. Huang D, et al. J Clin Oncol 2018;36:TPS3112; 10. Yang Y, et al. Ann Oncol 2021;32 (Abs 121O) [presented at ESMO IO 2021]

Study design
Randomized, double-blind, Phase 3 trial

Key eligibility criteria:
- Histologically or cytologically confirmed R/M NPC
- Treatment-naïve*
- Age 18–75 years
- ≥ 1 measurable lesion (RECIST v1.1)
- ECOG PS ≤ 1

N=263

R 1:1

Arm A
- Tislelizumab 200 mg IV D1 (Q3W)
- Gemcitabine 1 g/m^2 IV D1, D8 + cisplatin 80 mg/m^2 IV D1 (Q3W, 4–6 cycles)

Arm B
- Placebo 200 mg IV D1 (Q3W)
- Gemcitabine 1 g/m^2 IV D1, D8 + cisplatin 80 mg/m^2 IV D1 (Q3W, 4–6 cycles)

Until disease progression, intolerable toxicity, death, or withdrawal of consent

Tislelizumab monotherapy (200 mg IV Q3W) if investigator considers clinically beneficial

Crossover to tislelizumab monotherapy (200 mg IV Q3W) if investigator considers clinically beneficial

Stratification factors:
- Gender (male vs female)
- Liver metastases (yes vs no)

Primary endpoint: IRC-assessed PFS in the ITT population

Secondary endpoints include OS, investigator-assessed PFS2, and safety

Exploratory endpoints include biomarker analyses such as PD-L1 expression and gene expression profiling

NCT03924986. Patients were recruited from China/Thailand only
*Including immunotherapy for R/M NPC
D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; ITT, intent-to-treat; IV, intravenous; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PFS2, progression-free survival after next line of treatment;
Q3W, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria In Solid Tumors; R/M NPC, recurrent or metastatic nasopharyngeal cancer

Statistical analyses

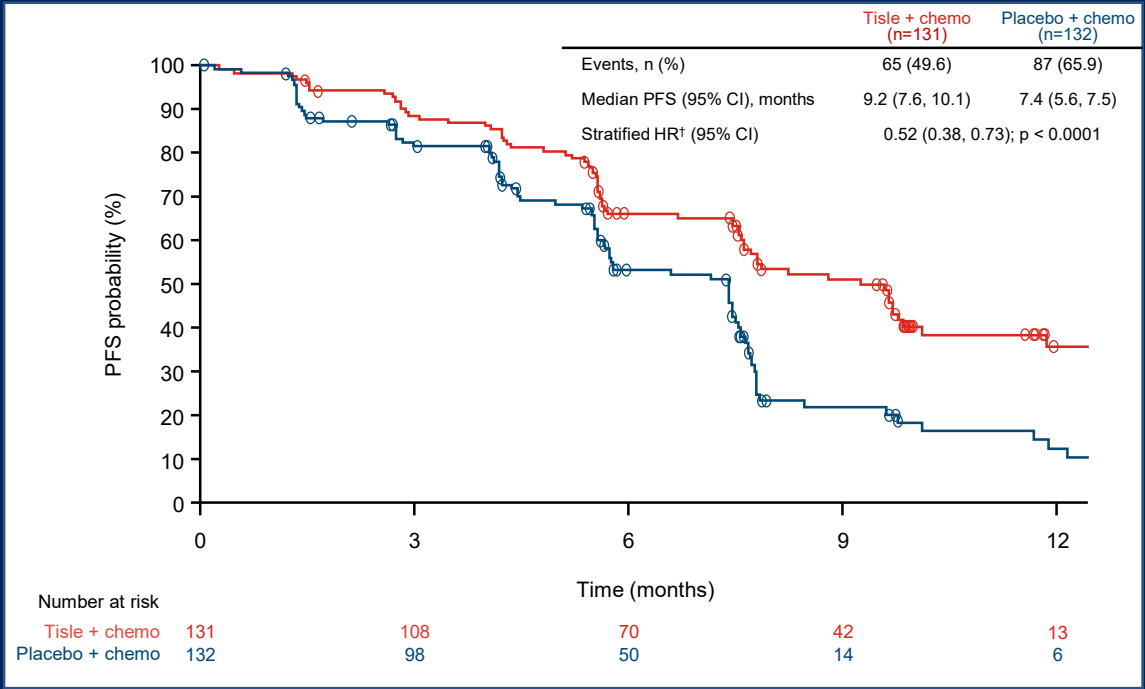
- **Sample size consideration:** 181 PFS events were required to provide 82% power to detect a HR of 0.65 for PFS between the two treatment arms, with a one-sided significance level of 0.025
- **Interim analysis** occurred when approximately 127 (70% information rate) events were observed in the ITT population[1]
  - The one-sided efficacy boundary was based on O'Brien-Fleming approximation spending function
- **Analysis methods:**
  - A stratified log-rank test was used to compare PFS between treatment groups
  - PFS was estimated using the Kaplan-Meier method and HR was through a stratified Cox regression model
- An **updated analysis** of PFS, PFS2, and OS was performed based on the latest data cutoff (September 30, 2021) for descriptive purposes

HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival after next line of treatment

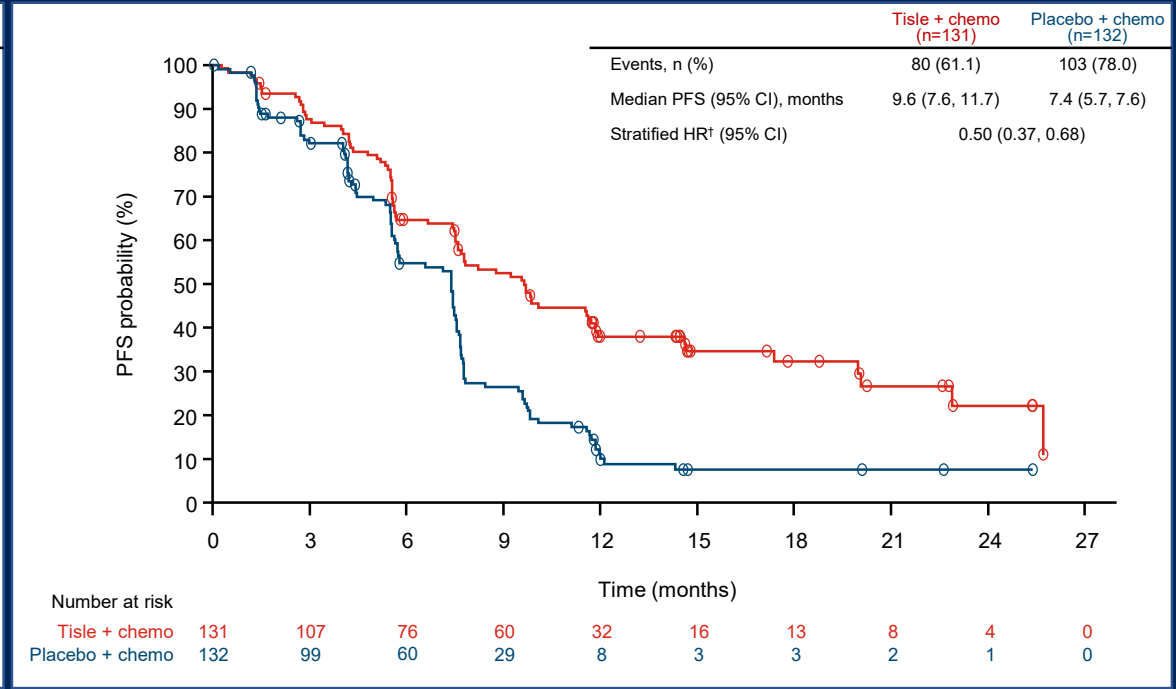
1. Yang Y, et al. Ann Oncol 2021;32 (Abs 121O) [presented at ESMO IO 2021]

At the updated analysis, tislelizumab + chemotherapy continued to demonstrate greater PFS benefit vs placebo + chemotherapy

Interim analysis (median follow-up: 10.0 months)[1]



Updated analysis (median follow-up: 15.5 months)*

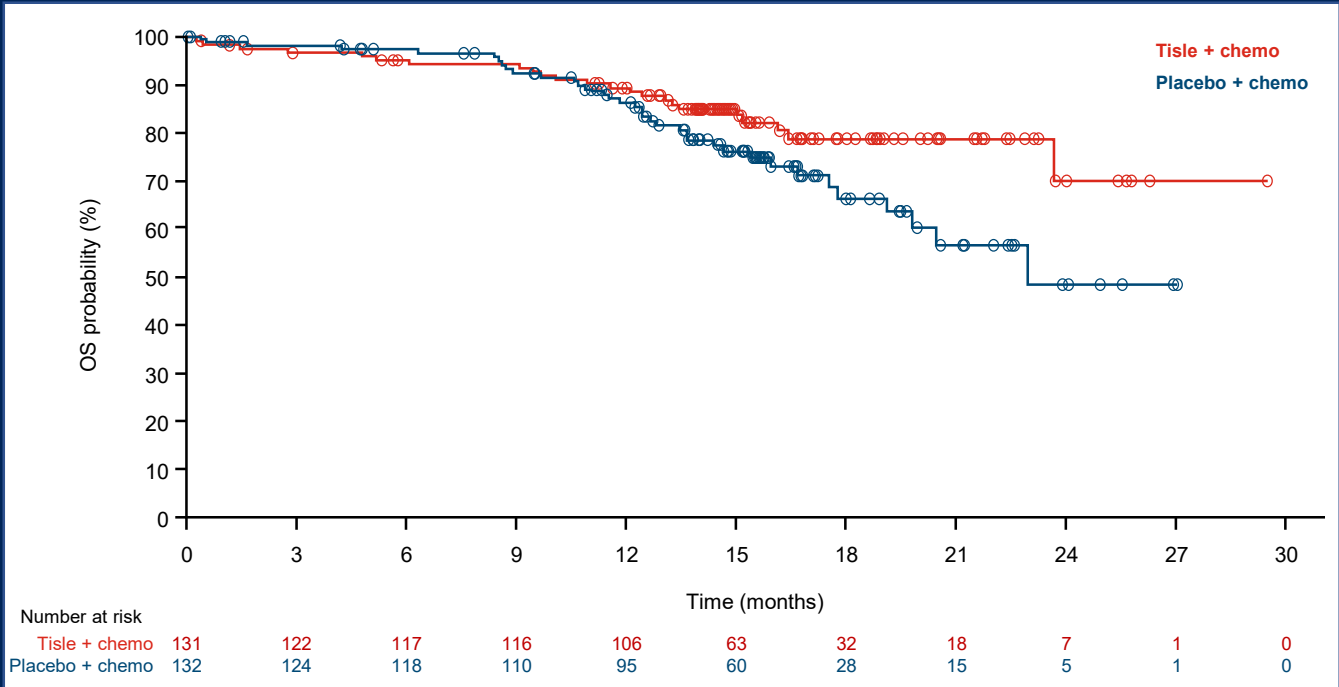


At the updated data cutoff, PFS was consistent with the interim data analysis, where a clinically meaningful improvement was observed with tislelizumab + chemotherapy vs placebo + chemotherapy

IRC-assessed PFS in the ITT population
*Data cutoff: September 30, 2021; †Stratified by gender and liver metastases
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; PFS, progression-free survival; tisle, tislelizumab
1. Yang Y, et al. Ann Oncol 2021;32 (Abs 121O) [presented at ESMO IO 2021]

Tislelizumab + chemotherapy demonstrated favorable OS benefit vs placebo + chemotherapy

Median follow-up: 15.5 months*



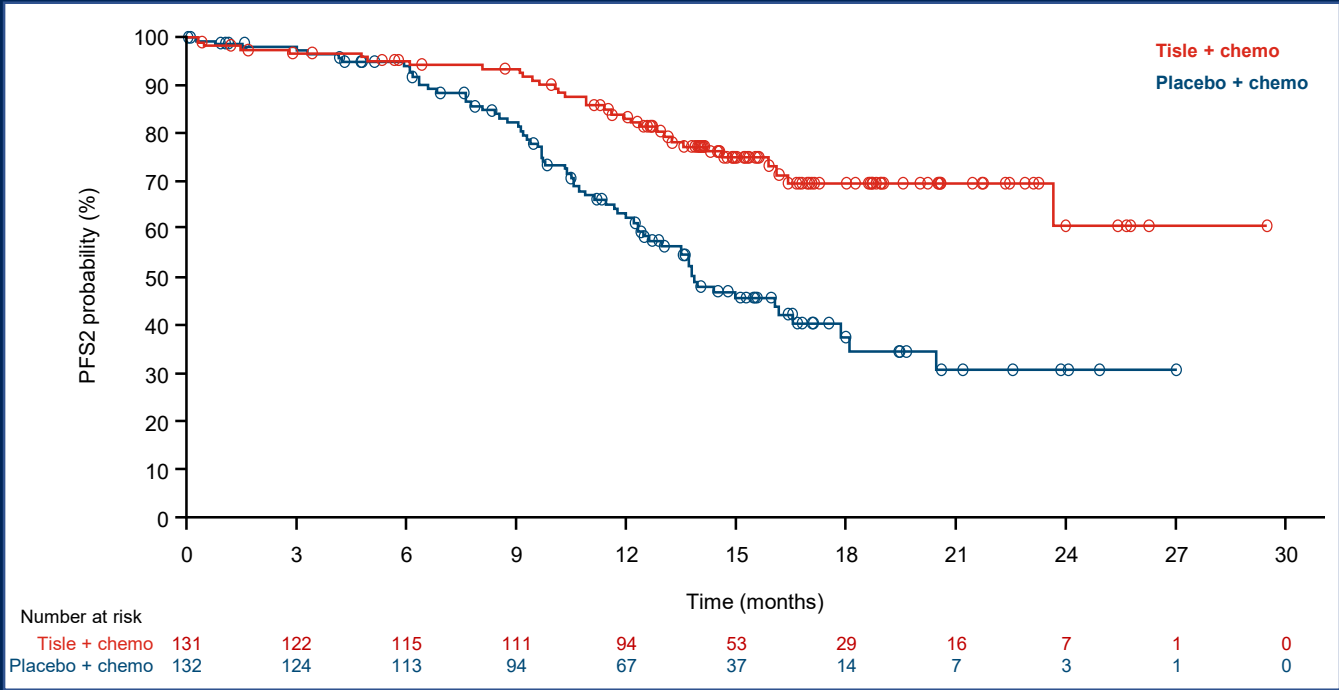
	Tisle + chemo (n=131)	Placebo + chemo (n=132)
Death, n (%) Censored, n (%)	23 (17.6) 108 (82.4)	35 (26.5) 97 (73.5)
Median follow-up, months	15.4	15.6
Median OS (95% CI), months	NR (23.7, NR)	23.0 (19.8, NR)
Stratified HR† (95% CI)	0.60 (0.35, 1.01)	
OS rate, % (95% CI) 6 months 9 months 12 months	 95.3 (89.9, 97.9) 94.5 (88.8, 97.3) 89.6 (82.8, 93.8)	 97.6 (92.9, 99.2) 92.6 (86.3, 96.1) 86.4 (78.8, 91.5)
Crossover to tisle monotherapy, n (%)	–	65 (49.2)

A numerical OS benefit was observed in the tislelizumab + chemotherapy arm vs the placebo + chemotherapy arm; final OS data are still immature

OS in the ITT population
*Data cutoff: September 30, 2021; †Stratified by gender and liver metastases
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NR, not reached; OS, overall survival; tisle, tislelizumab

Tislelizumab + chemotherapy demonstrated a substantial improvement in PFS2 vs placebo + chemotherapy

Median follow-up: 15.5 months*



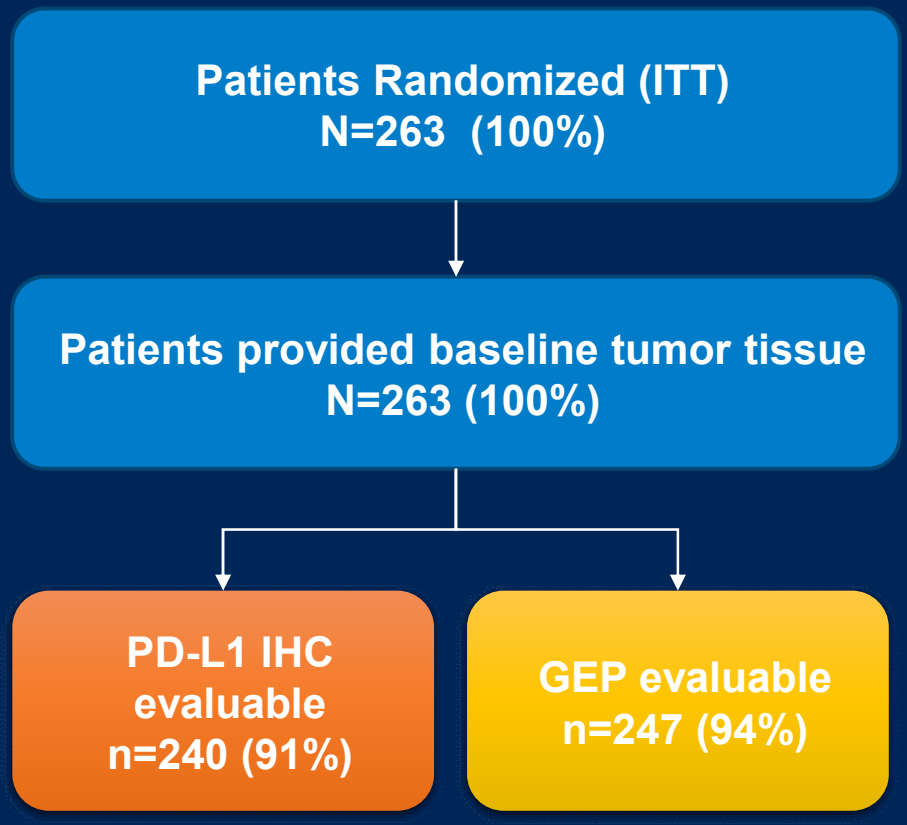
	Tisle + chemo (n=131)	Placebo + chemo (n=132)
PFS2 events, n (%)	32 (24.4)	65 (49.2)
Median PFS2 (95% CI), months	NR (23.7, NR)	13.9 (12.5, 17.9)
Unstratified HR (95% CI)	0.38 (0.25, 0.58)	
PFS2 rate, % (95% CI)		
6 months	95.3 (89.8, 97.9)	94.4 (88.6, 97.3)
9 months	93.6 (87.7, 96.8)	82.4 (74.3, 88.2)
12 months	83.4 (75.4, 88.9)	62.6 (53.1, 70.8)
Crossover to tislelizumab monotherapy, n (%)	–	65 (49.2)

The substantial improvement in PFS2 observed with tislelizumab + chemotherapy vs placebo + chemotherapy indicates that 1L treatment with tislelizumab may improve outcomes of the treatment sequence

Investigator-assessed PFS2 in the ITT population
*Data cutoff: September 30, 2021
1L, first-line; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NR, not reached; PFS2, progression-free survival after next line of treatment; tisle, tislelizumab

Biomarker analysis

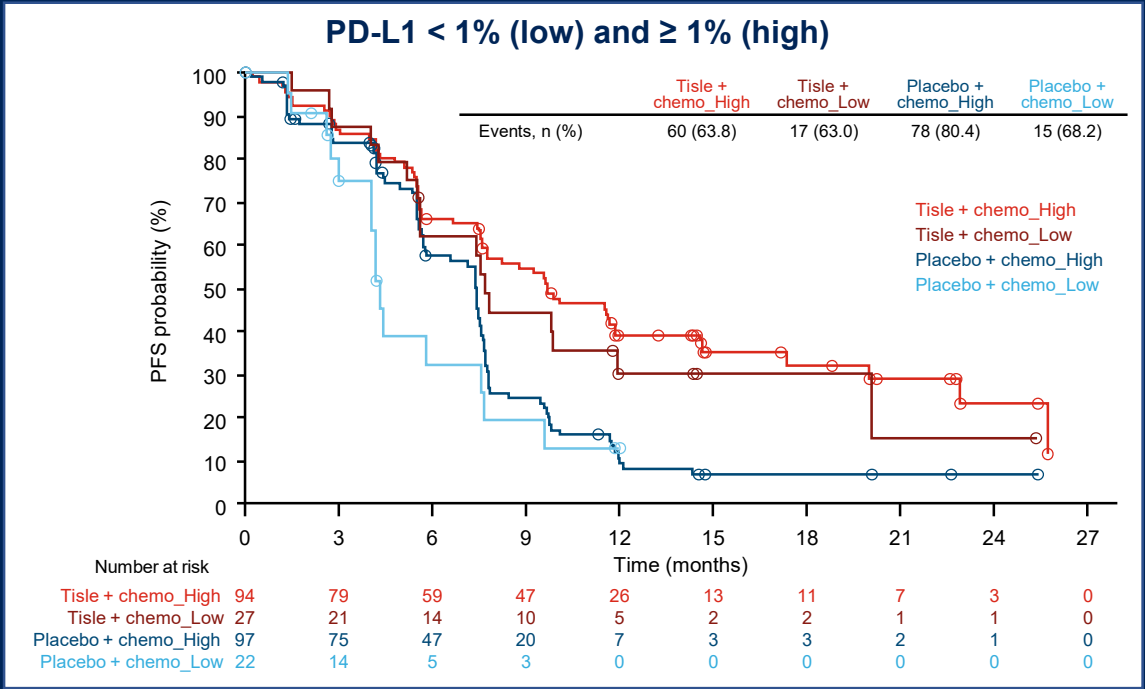
- Biomarker assessments were performed on baseline tumor tissue, including:
  - PD-L1 IHC by Ventana SP263
  - GEP by HTG EdgeSeq Precision Immuno-Oncology Panel - 1392 genes were included
- The biomarker evaluable populations and ITT population had similar baseline characteristics and efficacy outcomes

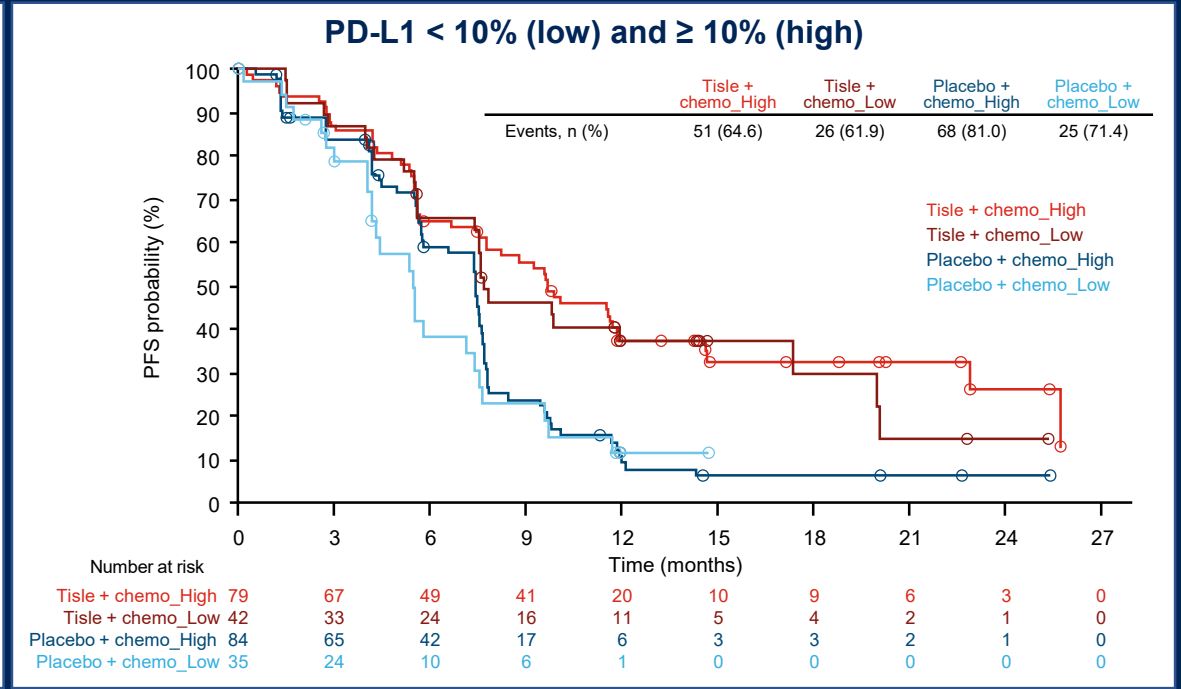


GEP, gene expression profiling; IHC, immunohistochemistry; ITT, intent-to-treat; PD-L1, programmed death ligand 1

The PFS benefit observed with tislelizumab + chemotherapy vs placebo + chemotherapy was regardless of PD-L1 expression

PFS among subgroups defined by TC PD-L1 expression levels (median follow-up: 15.5 months*)

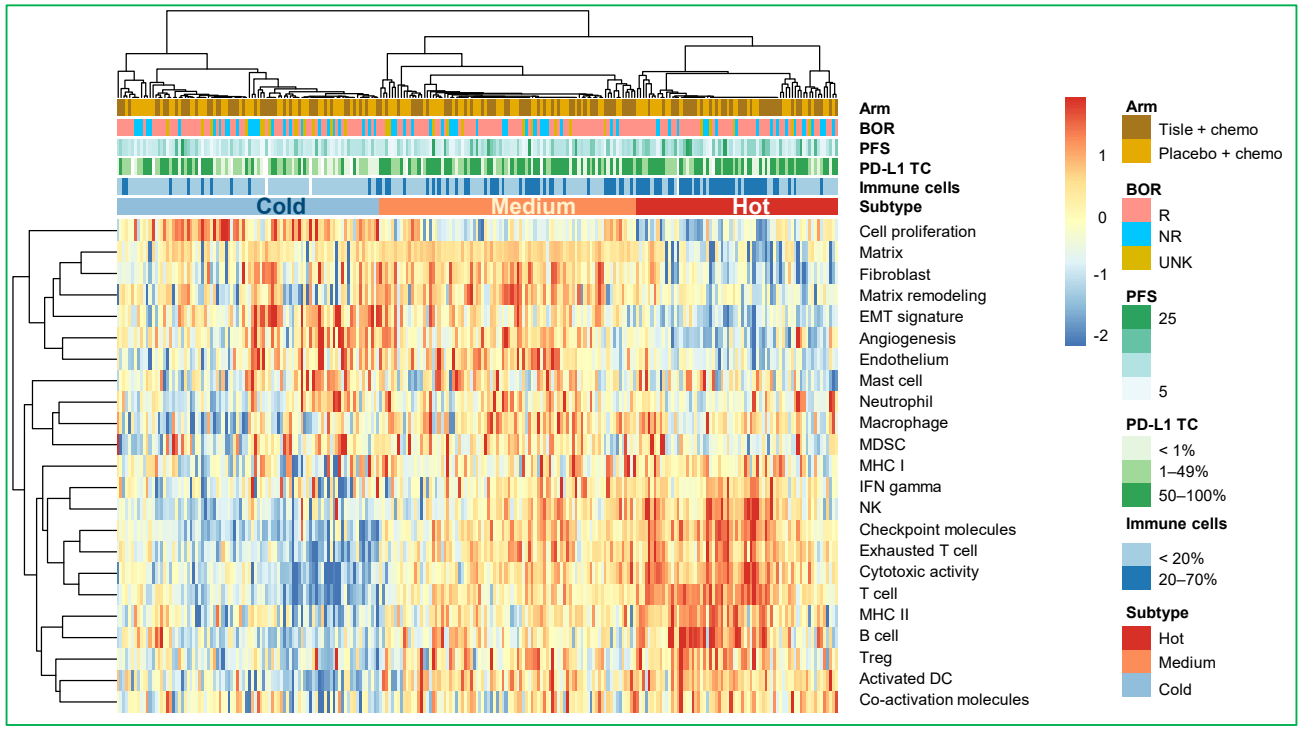


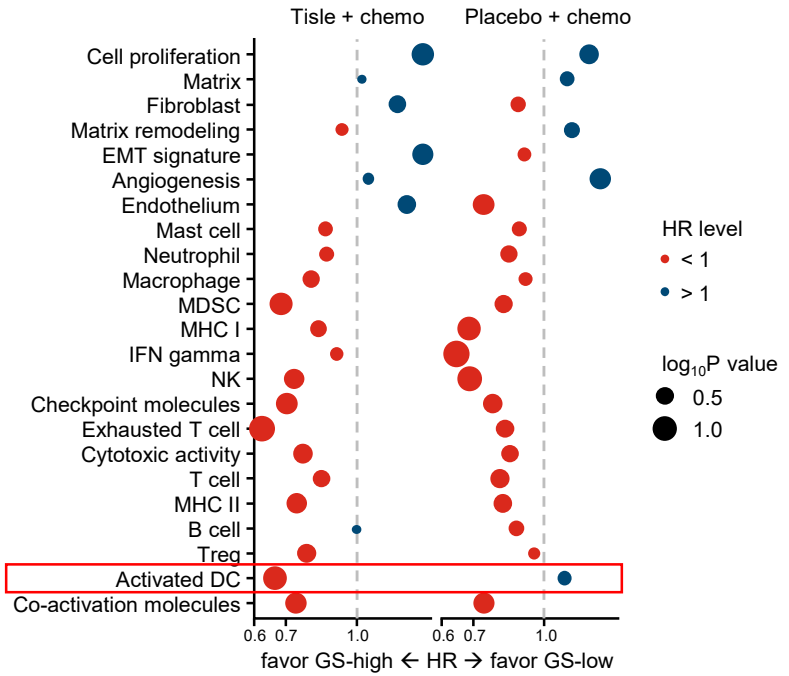


An improvement in PFS for tislelizumab + chemotherapy vs placebo + chemotherapy was observed in all TC PD-L1 expression subgroups (< or ≥ 1% and < or ≥ 10%)

*Data cutoff: September 30, 2021; biomarker analyses are *post hoc* and exploratory
Chemo, chemotherapy; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TC, tumor cell; tisle, tislelizumab

Gene expression profiling identified three gene expression clusters as potential biomarkers for efficacy



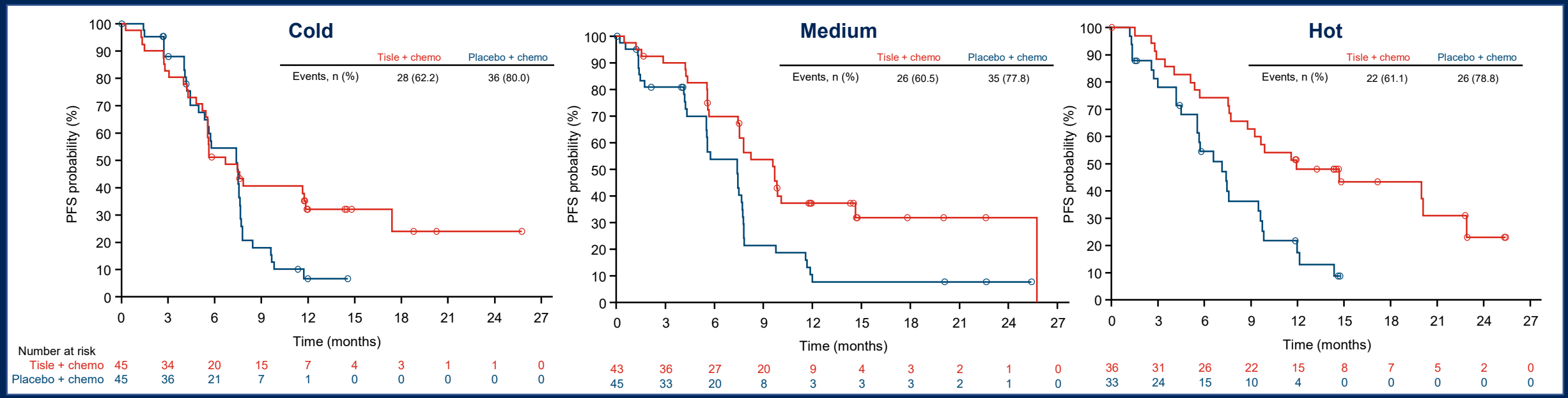


The GEP analysis was performed using GEP signatures (representing both immune and tumor cell characteristics) with unsupervised clustering, and identified three gene expression clusters: ‘cold’, ‘medium’, and ‘hot’

Data cutoff: September 30, 2021; biomarker analyses are *post hoc* and exploratory
BOR, best overall response; chemo, chemotherapy; DC, dendritic cell; EMT, epithelial-mesenchymal transition; GEP, gene expression profile; GS, gene signature; HR, hazard ratio; IFN, interferon; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; NK, natural killer; NR, non-response; PD-L1, programmed death-ligand 1; PFS, progression-free survival; R, response; TC, tumor cell; tisle, tislelizumab; TME, tumor microenvironment; Treg, regulatory T cell; UNK, unknown

A greater PFS benefit was observed in patients with a "hot" tumor microenvironment

PFS among subgroups by expression cluster (median follow-up: 15.5 months*)



Highest expression of tumor proliferation and endothelium; lowest expression of immune profiles

Higher expression of IFNγ, macrophages, and fibroblast gene signatures

Highest expression of T, NK and dendritic cells, and MHC and IFNγ signatures

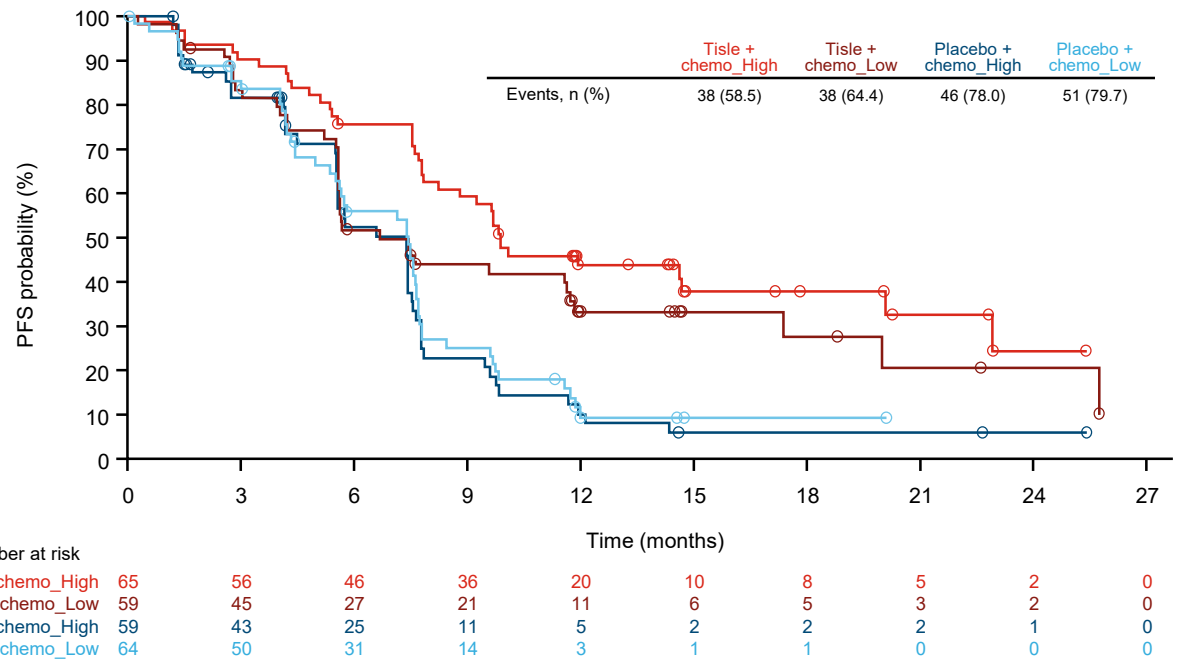
A 'hot' tumor immune profile was characterized by the highest expression of immune cells, including dendritic cells, and was associated with a greater PFS benefit vs 'cold' tumors for tislelizumab + chemotherapy

*Data cutoff: September 30, 2021; biomarker analyses are *post-hoc* and exploratory
Chemo, chemotherapy; IFN, interferon; MHC, major histocompatibility complex; NK, natural killer; PFS, progression-free survival; tisle, tislelizumab

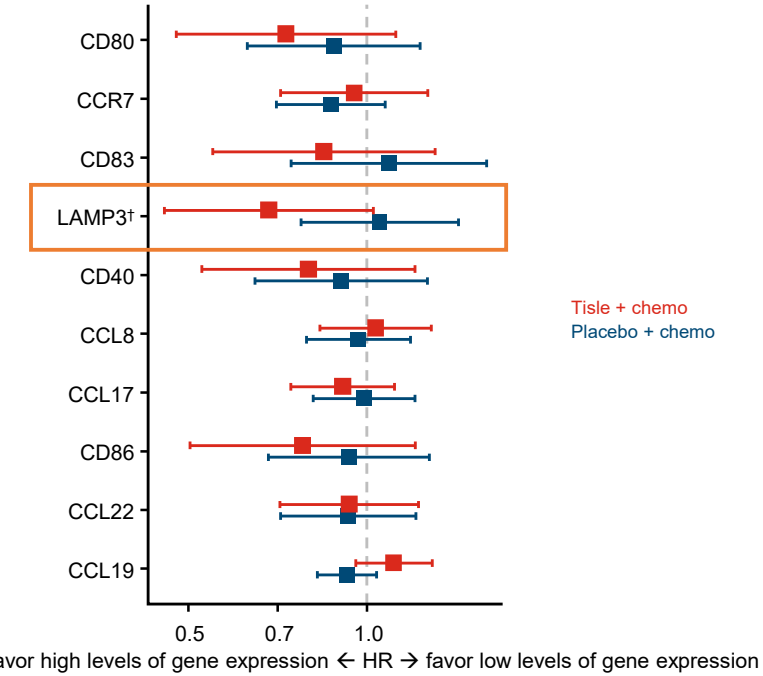
PRESENTED BY: Li Zhang

Enhanced PFS benefit was observed in patients with a high activated DC signature

PFS by levels of DC signature*



PFS by levels of gene expression



The PFS benefit of tislelizumab + chemotherapy was highest in patients with an activated DC signature, advocating the use of a DC signature as a potential biomarker tool

Data cutoff: September 30, 2021; biomarker analyses are *post hoc* and exploratory

*Patients with high levels of DC signature included those with DC levels above the median cutoff value. Patients with low levels of DC signature included those with DC levels below the median cutoff value; †LAMP3 is a classic DC activation marker[1]

Chemo, chemotherapy; DC, dendritic cell; HR, hazard ratio; LAMP3, lysosomal associated membrane protein 3; PFS, progression-free survival; tisle, tislelizumab

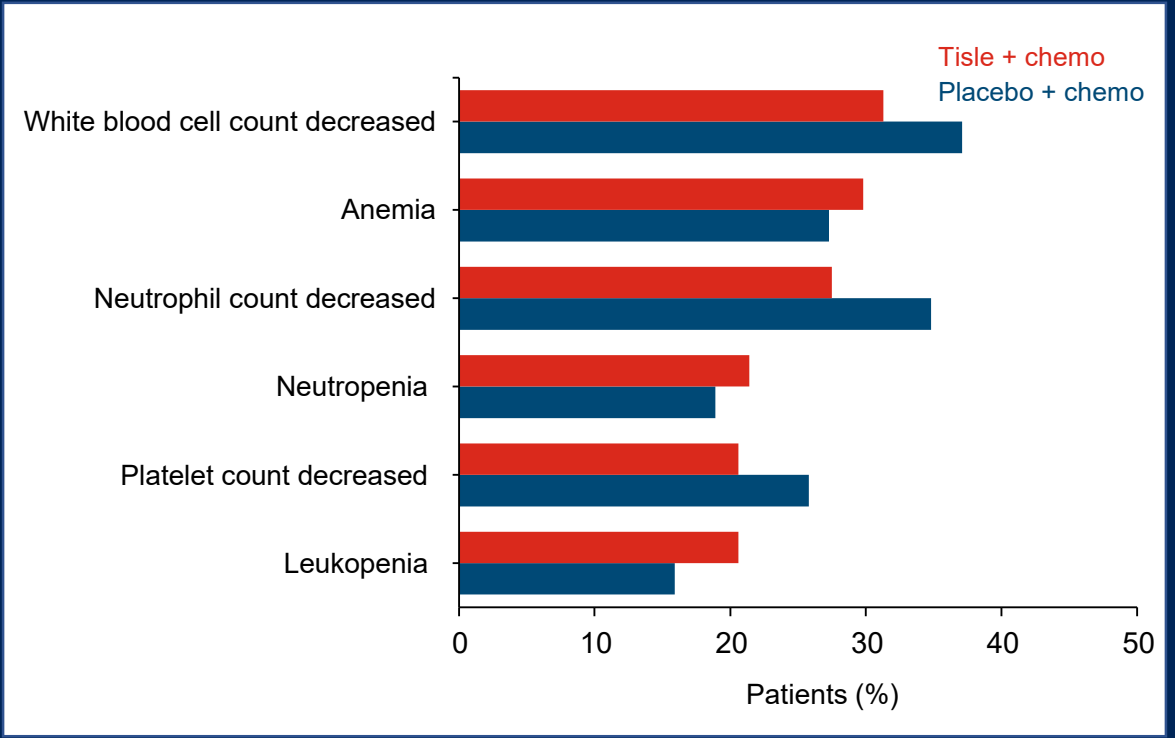
1. Nishimura J et al. Esophagus 2019; 16:333–34

The safety profile of tislelizumab + chemotherapy was manageable in the interim analysis and consistent with previous reports

Safety population (median follow-up: 10.0 months)

n (%)	Tisle + chemo (n=131)	Placebo + chemo (n=132)
TEAE	131 (100.0)	131 (99.2)
≥ Grade 3	106 (80.9)	108 (81.8)
Serious TEAE	36 (27.5)	44 (33.3)
≥ Grade 3	30 (22.9)	35 (26.5)
TEAE leading to death	5 (3.8)	2 (1.5)
TEAE leading to permanent discontinuation of all treatments*	2 (1.5)	3 (2.3)
Immune-mediated TEAE	24 (18.3)	NA
≥ Grade 3	3 (2.3)	NA
Deaths	18 (13.7)	16 (12.1)

TEAEs (≥ 20% of patients with ≥ Grade 3 events)



Data cutoff: March 26, 2021
*This category included patients who discontinued tislelizumab or placebo, cisplatin, and gemcitabine because of an adverse event
Chemo, chemotherapy; NA, not applicable; TEAE, treatment-emergent adverse event; tisle, tislelizumab
Yang Y, et al. Ann Oncol 2021;32 (Abs 121O) [presented at ESMO IO 2021]

Conclusion

- At the latest data cutoff (median follow-up: 15.5 months), PFS remained consistent with the interim data analysis and demonstrated a clinically meaningful improvement for tislelizumab + chemotherapy vs placebo + chemotherapy
  - HR (95% CI)=0.50 (0.37, 0.68); median PFS: 9.6 vs 7.4 months, respectively
- A numerical OS benefit was observed in the tislelizumab + chemotherapy arm vs placebo + chemotherapy arm; final OS data are still immature
- PFS2 was substantially improved for patients treated with tislelizumab + chemotherapy vs placebo + chemotherapy
- The PFS benefit of tislelizumab + chemotherapy was greatest in the 'hot' tumor microenvironment cluster as defined by GEP
  - DC activation was positively correlated with PFS benefit and may serve as a potential biomarker for predicting efficacy; further research is warranted
- The safety profile of tislelizumab + chemotherapy at the interim analysis was consistent with the known risks of each treatment agent and no new safety signals were identified[1]

This updated analysis of the RATIONALE-309 study indicates that tislelizumab + chemotherapy may become a standard-of-care 1L therapy for patients with R/M NPC

1L, first-line; CI, confidence interval; DC, dendritic cell; HR, hazard ratio; GEP, gene expression profile; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival after next line of treatment; R/M NPC, recurrent or metastatic nasopharyngeal cancer

1. Yang Y, et al. Ann Oncol 2021;32 (Abs 121O) [presented at ESMO IO 2021]

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