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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

Li Zhang, MD[1]

on behalf of Yunpeng Yang,[1] Jianji Pan,[2] Xiaozhong Chen,[3] Yan Sun,[4] Hui Wang,[5] Shenhong Qu,[6] Nianyong Chen,[7] Lizhu Lin,[8] Siyang Wang,[9] Qitao Yu,[10] Guihua Wang,[11] Feng Lei,[12] Jiyu Wen,[13] Chenqi Chen,[14] Yanjie Wu,[14] Shiangjiin Leaw,[14] Wenfeng Fang[1]

[1]Sun Yat-sen University Cancer Center, Guangzhou, China; [2]Fujian Cancer Hospital, Fuzhou, China; [3]Zhejiang Cancer Hospital, Hangzhou, China; [4]Beijing Cancer Hospital, Beijing, China; [5]Hunan Cancer Hospital, Changsha, China; [6]The People's Hospital of Guangxi Zhuang Autonomous Region, Otolaryngology Department, Nanning, China; [7]West China Hospital of Sichuan University, Chengdu, China; [8]The First Affiliated Hospital of Guangzhou Traditional Chinese Medicine University, Guangzhou, China; [9]The Fifth Affiliated Hospital Sun Yat-sen University, Zhuhai, China; [10]The Affiliated Cancer Hospital of Guangxi Medical University, Nanning, China; [11]Changsha Central Hospital, Changsha, China; [12]The People's Hospital of Zhongshan City, Zhongshan, China; [13]Affiliated Hospital of Guangdong Medical University, Zhanjiang, China; [14]BeiGene (Shanghai) Co., Ltd., Shanghai, China

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)

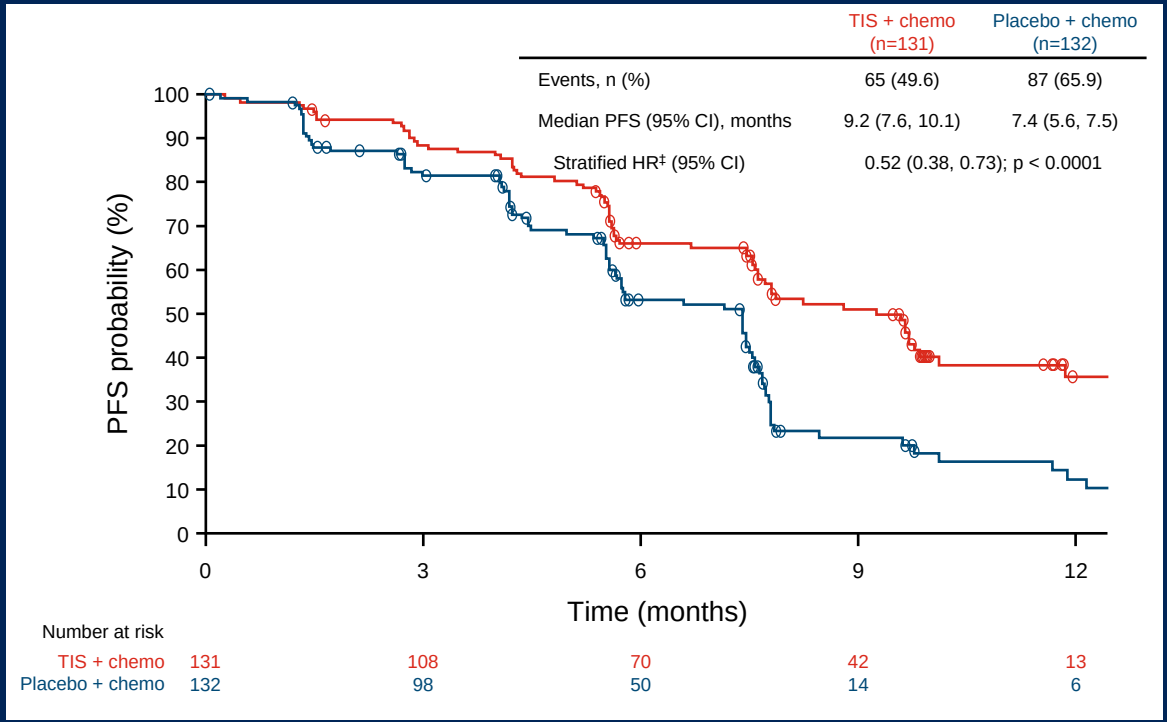
Primary endpoint: IRC-assessed PFS in the ITT population
Secondary endpoints include OS, investigator assessed PFS2, and safety
Exploratory endpoints include biomarker analyses such as PD-L1 expression and gene expression profiling

Statistical analyses
- A total of 181 PFS events is required to provide 82% power to detect a HR of 0.65 for PFS, with a one-sided significance level of 0.025
- Interim analysis occurred when approximately 127 (70% information rate) PFS events were observed in the ITT population
- An updated analysis of PFS, PFS2, and OS was performed based on the latest data cutoff (September 30, 2021) for descriptive purposes

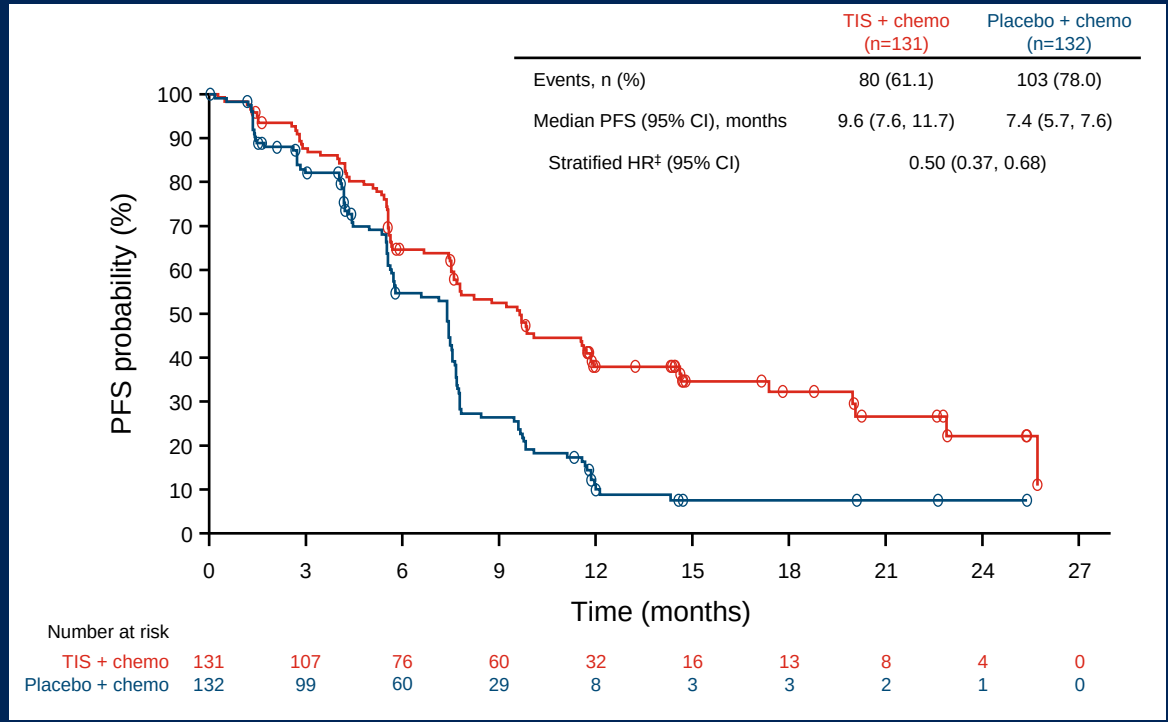
NCT03924986. Patients were recruited from China/Thailand only
*Including immunotherapy for R/M NPC. Patients who have received prior neoadjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for nonmetastatic disease must have experienced a treatment-free interval of ≥ 6 months from the last dose of chemotherapy and/or radiotherapy prior to randomization
D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; 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 v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; R/M NPC, recurrent or metastatic nasopharyngeal cancer
Yang Y, et al. Ann Oncol 2021;32 (Abs 121O) [presented at ESMO IO 2021]

The primary endpoint of PFS was met at the interim analysis, and tislelizumab + chemo continued to demonstrate greater PFS benefit vs placebo + chemo at the updated analysis

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



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



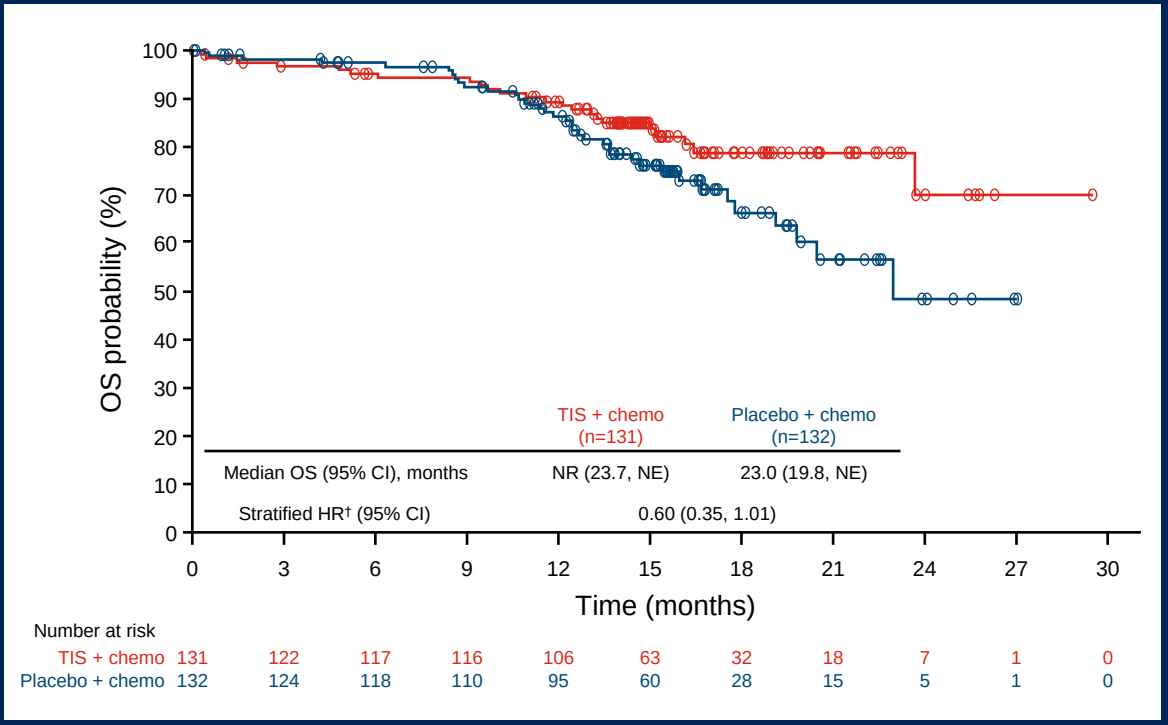
An improvement in PFS for tislelizumab + chemo vs placebo + chemo was observed in all TC PD-L1 expression subgroups (< or ≥ 1% and < or ≥ 10%)†§[2]

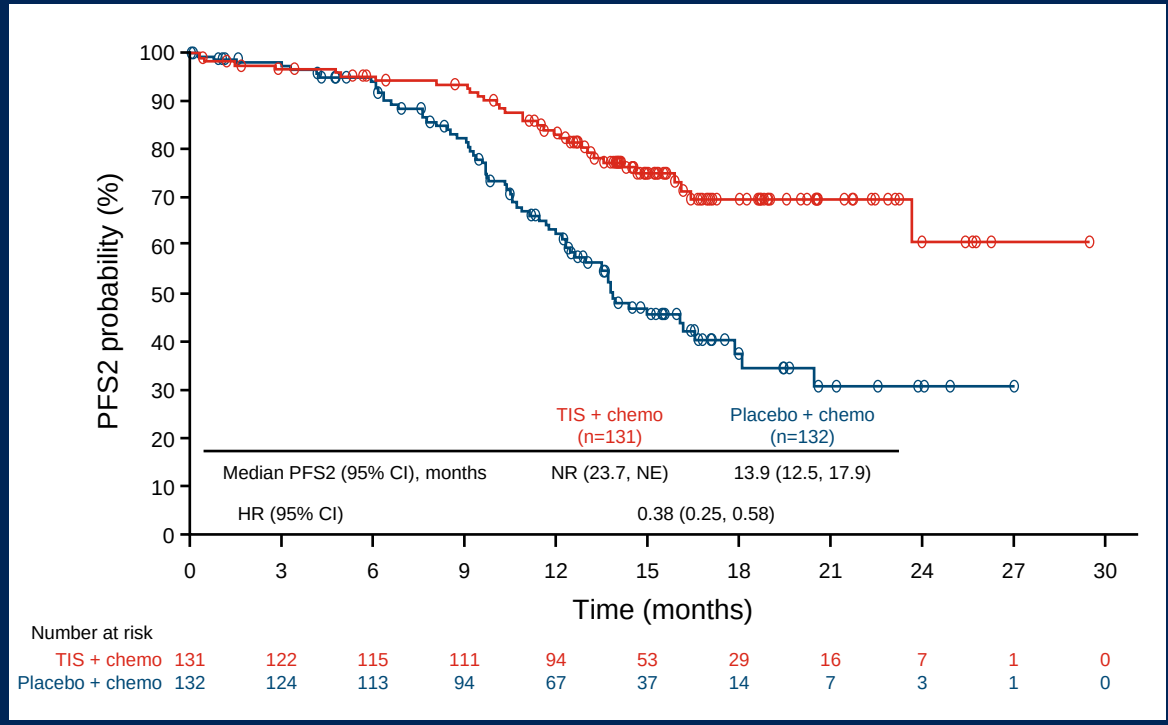
PFS was assessed by an independent review committee in the ITT population. *Data cutoff: March 26, 2021; †Data cutoff: September 30, 2021; ‡Stratified by gender and liver metastases; §Biomarker analyses are *post hoc* and exploratory
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TC, tumor cell; TIS, tislelizumab

1. Yang Y, et al. Ann Oncol 2021;32 (Abs 121O) [presented at ESMO IO 2021]; 2. Zhang L, et al. J Clin Oncol 2022;40 (Abs 384950) [presented at ASCO Plenary Series, April 2022]

Tislelizumab + chemo demonstrated favorable OS and PFS2 benefit vs placebo + chemo, despite a crossover rate of 49.2%

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



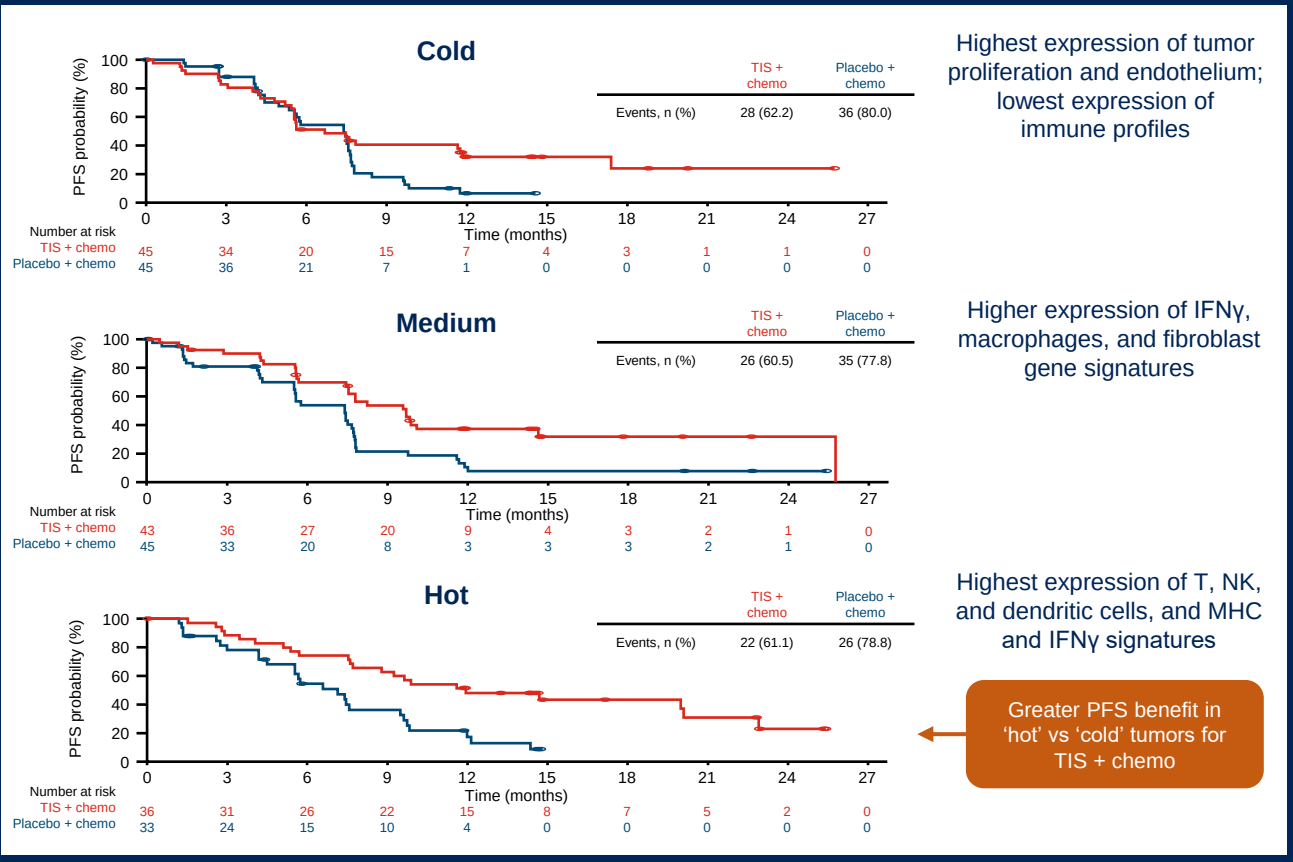


A total of 65 (49.2%) patients in the placebo + chemo arm crossed over to tislelizumab monotherapy after disease progression

PFS2 was investigator assessed. Both OS and PFS2 were assessed 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; NE, not estimable; NR, not reached; OS, overall survival; PD-L1, programmed death-ligand 1; PFS2, progression-free survival after next line of treatment; TIS, tislelizumab

Gene expression profiling identified three gene expression clusters and an activated DC signature as potential biomarkers for efficacy

PFS by gene expression cluster



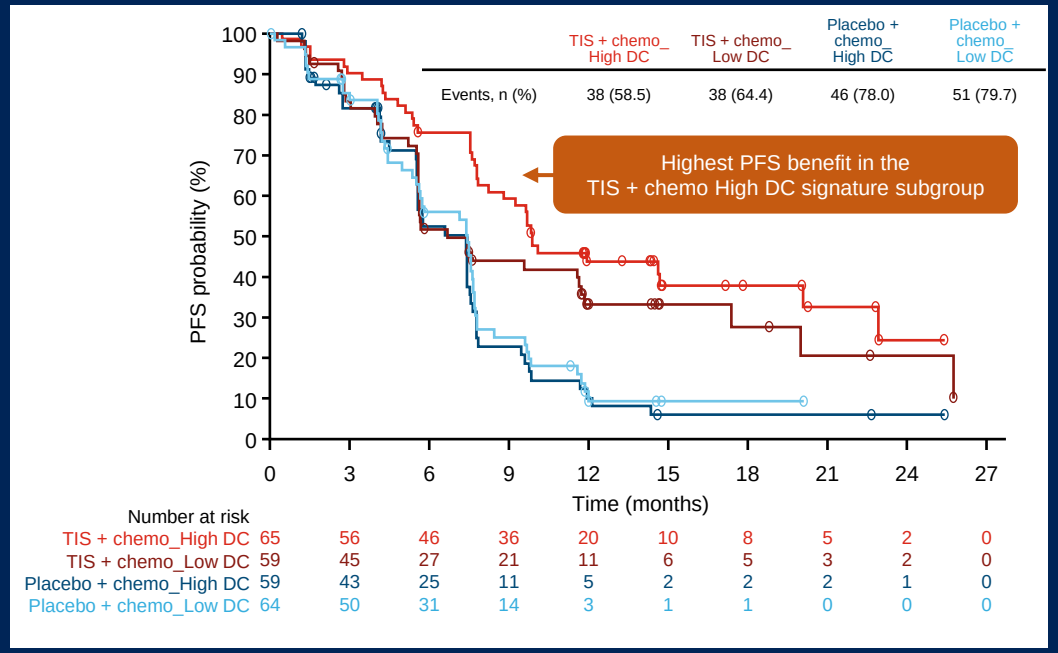
Highest expression of tumor proliferation and endothelium; lowest expression of immune profiles

Higher expression of IFNγ, macrophages, and fibroblast gene signatures

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

Greater PFS benefit in 'hot' vs 'cold' tumors for TIS + chemo

PFS by levels of DC signature*



Further analysis revealed ***LAMP3***, a classic DC activation marker[1], was associated with PFS benefit with tislelizumab + chemo

Updated analysis; data cutoff: September 30, 2021; biomarker analyses are *post hoc* and exploratory. *High DC signature ≥ median cutoff value; low DC signature < median cutoff value
Chemo, chemotherapy; DC, dendritic cell; IFN, interferon; LAMP3, lysosomal associated membrane protein 3; MHC, major histocompatibility complex; NK, natural killer; PFS, progression-free survival; TIS, tislelizumab

1. Nishimura J, et al. Esophagus 2019;16:333–4

Clinical implications of RATIONALE-309

- RATIONALE-309 met its primary endpoint at the interim analysis
- The results of RATIONALE-309 are consistent with other Phase 3 RCTs in R/M NPC*[1,2]
  - Combined, these three studies provide robust support for the use of a PD-1 inhibitor + chemo for 1L R/M NPC
- This is the first analysis of PFS2 in 1L R/M NPC and the observed PFS2 benefit supports the use of tislelizumab + chemo first in the treatment sequence
- Biomarker analyses identified three unique gene expression clusters representing hot and cold tumors. Further analysis identified an activated DC signature as a potential biomarker for efficacy‡
  - In addition, the DC activation marker *LAMP3*[3] was found to be most associated with tislelizumab + chemo PFS benefit‡
- The safety profile of tislelizumab + chemo was manageable in the interim analysis and consistent with prior reports (presented previously)[4,5]

PFS and OS in Phase 3 RCTs in R/M NPC*

	RATIONALE-309†		JUPITER-02[1]		CAPTAIN-1st[2]	
	TIS + chemo (n=131)	Placebo + chemo (n=132)	Tori + chemo (n=146)	Placebo + chemo (n=143)	Cam + chemo (n=134)	Placebo + chemo (n=129)
PFS events, n (%)	80 (61.1)	103 (78.0)	49 (33.6)	79 (55.2)	78 (58.2)	100 (77.5)
Median PFS (95% CI), months	9.6 (7.6, 11.7)	7.4 (5.7, 7.6)	11.7 (11.0, NE)	8.0 (7.0, 9.5)	10.8 (8.5, 13.6)	6.9 (5.9, 7.9)
HR (95% CI)	0.50 (0.37, 0.68)		0.52 (0.36, 0.74)		0.51 (0.37, 0.69)	
Median OS (95% CI), months	NR (23.7, NE)	23.0 (19.8, NR)	NE (NE, NE)	NE (22.8, NE)	NR	22.6 (19.2, NR)
HR (95% CI)	0.60 (0.35, 1.01)		0.60 (0.36, 1.00)		0.67 (0.41, 1.11)	

*Cross-trial comparisons should be interpreted with caution; †Data cutoff: September 30, 2021; median follow-up 15.5 months; ‡Biomarker analyses are *post hoc* and exploratory
1L, first-line; cam, camrelizumab; Chemo, chemotherapy; CI, confidence interval; DC, dendritic cell; HR, hazard ratio; LAMP3, lysosomal associated membrane protein 3; NE, not estimable; NR, not reached; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; PFS2, progression-free survival after next line of treatment; RCT, randomized controlled trial; R/M NPC, recurrent or metastatic nasopharyngeal cancer; TIS, tislelizumab; tori, toripalimab

1. Mai HQ, et al. Nat Med 2021;27:1536–43; 2. Yang Y, et al. Lancet Oncol 2021;22:1162–74; 3. Nishimura J, et al. Esophagus 2019;16:333–4; 4. Yang Y, et al. Ann Oncol 2021;32 (Abs 121O) [presented at ESMO IO 2021];
5. Zhang L, et al. J Clin Oncol 2022;40 (Abs 384950) [presented at ASCO Plenary Series, April 2022]

Questions for future research

- Most patients in RATIONALE-309, JUPITER-02, and CAPTAIN-1st had non-keratinizing NPC and a high level of baseline EBV DNA[1–3]
  - More research is needed in patients with keratinizing NPC and those with a low level of baseline EBV DNA[4]
- Further research is warranted to assess the biomarker potential of the activated DC signature found in this study
- Studies investigating the use of PD-1 inhibitors for the treatment of early-stage NPC are ongoing[5–8]

PD-1 inhibitors have the potential to transform the treatment algorithm for patients with R/M NPC. This updated analysis of RATIONALE-309 supports the use of tislelizumab + chemo as a 1L treatment for R/M NPC

1L, first-line; DC, dendritic cell; EBV, Epstein-Barr virus; NPC, nasopharyngeal cancer; PD-1, programmed cell death protein 1; R/M NPC, recurrent or metastatic nasopharyngeal cancer

1. Yang Y, et al. Ann Oncol 2021;32 (Abs 121O) [presented at ESMO IO 2021]; 2. Yang Y, et al. Lancet Oncol 2021;22(8):1162–74; 3. Mai HQ, et al. Nat Med 2021;27(9):1536–43; 4. Young LW and Dawson CW. Chin J Cancer 2014;33(12):581–90; 5. ClinicalTrials.gov. NCT04557020; 6. ClinicalTrials.gov. NCT05229315; 7. ClinicalTrials.gov. NCT03925090; 8. ClinicalTrials.gov. NCT04833257

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View a patient lay summary of the RATIONALE-309 study here: