Transportability of RATIONALE-315 Trial Outcomes Assessing Perioperative Tislelizumab to the European Patient Population With Resectable Non-Small Cell Lung Cancer

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INTRODUCTION

- RATIONALE-315 was a randomized, placebo-controlled, phase 3 trial conducted at 50 sites across China that compared the efficacy and safety of neoadjuvant tislelizumab (TIS) or placebo (PBO) in combination with neoadjuvant platinum-based chemotherapy (nCT) followed by surgery and adjuvant TIS (TIS arm) or PBO (PBO arm) in patients with resectable stage II-IIIA squamous or nonsquamous non-small cell lung cancer (NSCLC)[1]
- RATIONALE-315 demonstrated that perioperative TIS combination therapy showed a clinically meaningful and statistically significant improvement in efficacy and a manageable safety profile compared with the control arm[1]
- As RATIONALE-315 was exclusively conducted in Chinese patients, this study aimed to assess the transportability of RATIONALE-315 to the European patient population in resectable NSCLC

METHODS

- A statistical analysis of the RATIONALE-315 trial data, supported by protocol-driven targeted literature reviews (TLRs), was conducted to estimate the relative treatment effect of the TIS arm in the European population
- Three TLRs were conducted to identify relevant peer-reviewed articles. The first TLR (real-world evidence [RWE] TLR) focused on identifying publications reporting on baseline characteristics of stage II-IIIA NSCLC patients in European real-world populations. The second and third TLRs supplemented the RWE TLR by identifying randomized controlled trials (RCT TLR) and effect modifier (EM TLR) studies in resectable NSCLC, aiming to obtain a comprehensive list of EMs
- Final selected studies were used to define the target European populations for estimating the transportability of the treatment effects observed in RATIONALE-315
- Outcome regression analyses were conducted on RATIONALE-315 individual patient data to estimate the transportability of treatment effects observed in RATIONALE-315 to the identified European target populations
  - The outcomes used for the analysis were event-free survival (EFS), major pathological response (MPR), and pathological complete response (pCR)

RESULTS

- After screening 178 articles and eight grey literature sources (**Supplemental Figure 1**), 10 RWE studies that reported baseline characteristics in European resectable NSCLC patients were identified (**Supplemental Table 1**)

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- These studies underwent further scrutiny based on the availability of patient characteristics identified as potential EMs; with two studies (Dalvi et al 2023[2]; Couñago et al 2019[3]) ultimately deemed relevant for the statistical analyses
  - Dalvi et al 2023 fulfilled all PICOS criteria and provided data on all EMs, except PD-L1 and lymph node station
  - Couñago et al 2019 met all PICOS criteria. However, this study only included patients with stage IIIa NSCLC and did not provide information on *EGFR* mutations and *ALK* gene translocations, along with not reporting sufficient information required for adjustment on ECOG
- It was not feasible to adjust for race or region because RATIONALE-315 included Chinese patients exclusively; however, although this is a limitation of the analyses, the bias is expected to be limited as the available evidence from the TLRs suggests that race/region is not a strong EM for outcomes in resectable NSCLC
- The baseline characteristics for patients with NSCLC enrolled in RATIONALE-315, Dalvi et al 2023, and Couñago 2019 are presented in **Table 1**

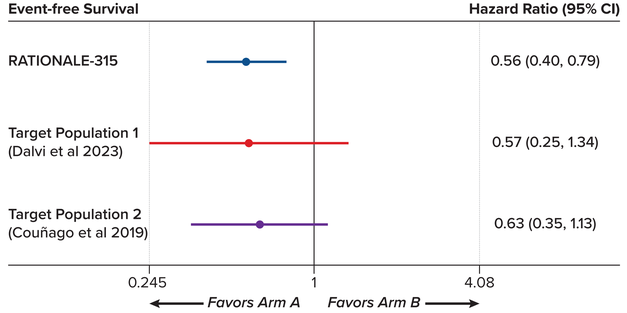
Table 1. Patient Characteristics at Baseline in RATIONALE-315 and Target European Populations

	RATIONALE-315[1]	Target Population 1 (Based on Dalvi 2023)[2]	Target Population 2 (Based on Couñago 2019)[3]
Treatment	Neoadjuvant TIS and nCT + surgery + adjuvant TIS vs PBO and nCT + surgery + adjuvant PBO	Adjuvant CT[a]	Neoadjuvant therapy + surgery (100%) + adjuvant therapy (43.2%)[b,c]
Sample size (N)	N=453	N=372	N=118
Age (years), median	62	64	62
Other categories		18-59: 36% 60-69: 43.3% ≥70: 20.7%	≤60: 42.4% >60: 57.6%
Sex (%)			
Male	90.5%	49.5%	79.7%
Female	9.5%	50.5%	20.3%
Disease stage (%)			
IB	0.2%	58.97%[d]	0%
II	40.4%		0%
IIIA	58.5%[e]	41.03%[d]	100%
IIIB	0.9%[e]		0%
Histology (%)			
Squamous	78.1%	32.5%	42.6%
Nonsquamous	21%	60.5%	57.4%
Other	0.9%	7%	0%
Smoking status (%)			
Former	84.5%	96%[d]	46.6%
Current			3.4%
Never	15.5%	4%[d]	50%
ECOG PS (%)			
0	65.5%[d]	59.2%[d]	NA
1+	34.5%[d]	40.8%[d]	

[a]In this study, 3.6% of patients had *EGFR*-positive mutation and 95.1% had negative *EGFR* mutation.
[b]Neoadjuvant therapy, n (%), CRT: 66 (56%), CT: 52 (44%). CT was a platinum-based doublet in 93.2% of cases. Postoperative adjuvant therapy, n (%): 51 (43.2%).
[c]Among patients receiving adjuvant therapy, n (%), only adjuvant chemotherapy: 20 (39.2%); only radiotherapy (45-50 Gy): 20 (39.2%); both: 11 (21.6%).
[d]Proportions calculated using only non-missing records.
[e]Patients in RATIONALE-315 classified as IIIA and IIIB were combined into IIIA as in IRT for randomization.
Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance score; NA, not available; nCT, neoadjuvant platinum-based chemotherapy; PBO, placebo; TIS, tislelizumab.

- In RATIONALE-315, the perioperative TIS arm improved EFS versus the PBO arm, with a stratified hazard ratio (HR) of 0.56, 95% CI: 0.40-0.79[1]
- The predicted results for the target European population 1 (HR: 0.57 [95% CI: 0.25-1.34]) and target population 2 (HR: 0.63 [0.35-1.13]) were comparable to the EFS HR for RATIONALE-315 (**Figure 1**)

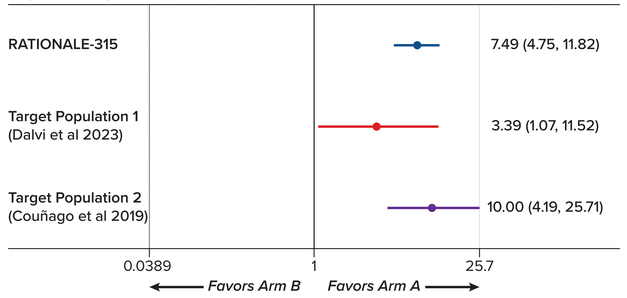
Figure 1. EFS Treatment Effect of TIS Arm vs PBO Arm Observed in RATIONALE-315 and Predicted in Two European Populations



Arm A: tislelizumab (200 mg Q3W) plus chemotherapy followed by surgery and adjuvant tislelizumab (400 mg Q6W); Arm B: placebo plus chemotherapy followed by surgery and adjuvant placebo.

- The MPR, as assessed by blinded independent pathology review (BIPR), reported in RATIONALE-315 was significantly higher in the TIS arm versus PBO arm (odds ratio [OR]: 7.49 [4.75-11.82])[1]; this was aligned with the predicted MPR results in population 1 (OR: 3.39 [1.07-11.52]) and population 2 (OR: 10 [4.19-25.71]) (**Figure 2**)

Figure 2. Major Pathologic Response Treatment Effect of TIS Arm vs PBO Arm Observed in RATIONALE-315 and Predicted in Two European Populations



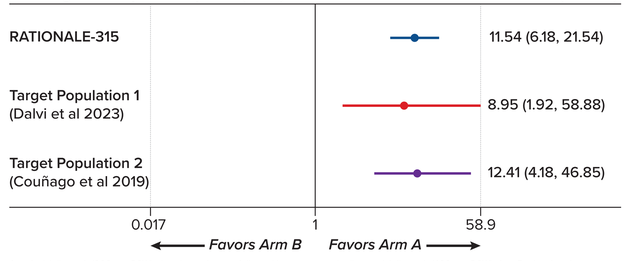
Arm A: tislelizumab (200 mg Q3W) plus chemotherapy followed by surgery and adjuvant tislelizumab (400mg Q6W); Arm B: placebo plus chemotherapy followed by surgery and adjuvant placebo.

CONCLUSIONS

- Transportability analyses, which assess whether treatment effectiveness from a clinical trial can be generalized to a different population of interest, can be used in the absence of clinical data specific to the population of interest. Since the RATIONALE-315 trial was exclusively conducted in a Chinese population, a transportability analysis was performed to determine if the treatment effects observed in the trial could be applicable to a European patient population
- The statistical analysis conducted revealed that the effect (EFS, MPR, and pCR) of the TIS arm versus the PBO arm demonstrated in the RATIONALE-315 trial is applicable to the European patient population
- Limitations of the evidence include the influence of other factors (eg, performance status, genetic characteristics), the lack of safety data from European RWE studies, and the absence of comparisons between Asian and European patient RWE data from multinational studies. Additionally, the limited number of studies per treatment setting restricts the ability to compare findings across different treatment settings
  - Furthermore, adjustments for race/region as EMs were not feasible; however, the bias from not adjusting for these factors is expected to be limited, as available evidence suggests they are not strong EMs for outcomes in resectable NSCLC
  - None of the identified RWE studies reported on PD-L1 status, thus it was not possible to include PD-L1 status in the statistical analysis

- Similar results were observed for pCR, as assessed by blinded independent pathology review, in RATIONALE-315, and were significantly higher in the TIS arm than in the PBO arm (OR=11.54, [95% CI: 6.18-21.54]); this was aligned with the predicted ORs for both European target populations (population 1: OR=8.95, [95% CI: 1.92-58.88]; population 2: OR=12.41, [95% CI: 4.18-46.85]) (**Figure 3**)

Figure 3. Pathological Complete Response Treatment Effect of TIS Arm vs PBO Arm Observed in RATIONALE-315 and Predicted in Two European Populations



Arm A: tislelizumab (200 mg Q3W) plus chemotherapy followed by surgery and adjuvant tislelizumab (400 mg Q6W); Arm B: placebo plus chemotherapy followed by surgery and adjuvant placebo.

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DISCLOSURES

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