Matching-Adjusted Indirect Comparison in Previously Treated KRAS G12C-Mutated Advanced/Metastatic Non-Small Cell Lung Cancer: Adagrasib versus Sotorasib

Poster # CO95

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Background

Disease landscape – Non-small cell lung cancer (NSCLC)

- NSCLC comprises about 80% to 85% of all lung cancer cases.[1]
- The Kirsten Rat Sarcoma viral oncogene (KRAS) is one of the most prevalent genetic mutations in NSCLC (25% to 30% of cases), with G12C being the most frequent variant (40% to 55% of all KRAS mutations).[1]

Adagrasib and sotorasib

- Two new therapies targeting KRAS^{G12C} are approved by the Food and Drug Administration (FDA) for advanced or metastatic NSCLC (a/mNSCLC) patients: sotorasib (May 2021); adagrasib (December 2022).[2,3]
- No head-to-head randomized controlled trial (RCT) exists comparing the two agents.

Objective

The objective of this study was to determine the comparative efficacy and safety of adagrasib versus sotorasib among patients with KRAS^{G12C} mutated a/mNSCLC who have received ≥1 prior line of systemic treatment.

Methods

Evidence base

- Adagrasib received FDA approval based on KRYSTAL-1, a phase 2, single-arm trial (NCT03785249) of a/mNSCLC patients pre-treated with chemoimmunotherapy.[4]
- Sotorasib's initial approval and indication (US and ex-US) was supported by CodeBreaK100 (NCT03600883), a phase 2, single-arm trial of a/mNSCLC patients pretreated with chemotherapy and/or immunotherapy (IO). A confirmatory phase 3 randomized clinical trial (RCT), CodeBreaK200 (NCT04303780), provided additional data in a/mNSCLC patients pretreated with chemoimmunotherapy.[5,6]

Statistical analyses

- Efficacy outcomes across all three trials included objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Safety outcomes included all grade treatment-related adverse events (TRAEs), grade ≥3 TRAEs, and discontinuations due to TRAEs.
- Two separate unanchored matching-adjusted indirect comparisons (MAICs) were conducted, comparing adagrasib studied in KRYSTAL-1 versus sotorasib as investigated in CodeBreaK100 and CodeBreaK200. The analyses were conducted in accordance with NICE (National Institute for Health and Care Excellence) Decision Support Unit Technical Support Document 18,[7] with relevant literature and clinical expert opinion incorporated when selecting for matching variables.
- The base-case analysis for efficacy outcomes matched patients based on age, sex, metastatic disease, Eastern Cooperative Oncology Group performance status (ECOG PS), squamous histology, and smoking status. Following clinical expert consultation, the safety MAIC incorporated only age, sex and ECOG PS as matching variables, as the other variables were not expected to impact safety outcomes.
- Sensitivity analyses investigated the impact of matching for differences in the number of lines of previous systemic treatment (SA1), previous anti-PD-1/L1 treatment (SA2), previous anti-PD-1/L1 treatment and the number of prior lines (SA4), previous treatment with both platinum-based chemotherapy and anti-PD-1/L1 therapy (SA5), time since last prior IO (SA6), sequences of previous treatment [platinum-based chemotherapy and anti-PD-1/L1 treatment] (SA7), and previous exposure to docetaxel (SA8). Sensitivity analysis 3 (SA3) investigated the impact of adding race as a matching variable.
- To estimate relative treatment effects, logistic regression models were employed for binary outcomes (ORR, safety outcomes) and Cox proportional hazards models were used for time-to-event outcomes (OS, PFS).

Study and patient baseline characteristics

- Study and patient characteristics, before matching, are provided in **Table 1**. Differences were observed for the proportion of male patients, ECOG PS, proportion of patients with metastatic disease, and previous treatment.

Results

MAIC for efficacy outcomes

- Adagrasib outcomes improved in the MAIC relative to the naïve comparison, indicating that the prognosis of KRYSTAL-1 patients was potentially unfavourable relative to those in the sotorasib trials.
- Adagrasib demonstrated a significant ORR benefit compared to sotorasib in the CodeBreaK200 MAIC (odds ratio [OR]=2.22, 95% confidence interval [CI] 1.25-3.96; **Figure 1a**). Adagrasib also showed a favorable ORR in the CodeBreaK100 MAIC, but the difference was not statistically significant (OR=1.46, 95%CI 0.81-2.63).
- For PFS, point estimates indicated a benefit for adagrasib in both MAICs (CodeBreaK200 MAIC: hazard ratio [HR]=0.79, 95%CI 0.55-1.12; CodeBreaK100 MAIC: HR=0.77, 95%CI 0.52-1.14; **Figure 1b**).
- Similarly, the point estimate for OS favoured adagrasib in the CodeBreaK200 MAIC (**Figure 1c**); however, differences were not significant (HR=0.81, 95%CI 0.55-1.17). The comparison based on CodeBreaK100 showed that OS was similar between therapies (HR=0.95; 95%CI, 0.63-1.42).
- Sensitivity analyses confirmed the base case, except when time since prior IO was incorporated (OR ORR 1.52, 95%CI 0.70-3.28). This sensitivity analysis (SA6) resulted in extreme weights and a low effective sample size (ESS), explained by differences in the wash-out period.* The ESS ranged from 35.9 to 72.9.

MAIC for safety outcomes

- The risk of grade ≥3 TRAEs was higher for adagrasib in both CodeBreaK200 and CodeBreaK100 MAICs (OR=1.50, 95%CI 0.87-2.57; OR=2.83, 95%CI 1.56-5.12, respectively); however, discontinuations due to TRAEs were less common in adagrasib-treated patients (OR=0.69, 95%CI 0.26-1.80; and OR=0.98, 95%CI 0.33-2.87, respectively), indicating that TRAEs were manageable and that most patients were able to continue adagrasib treatment. Sensitivity analyses confirmed these findings. The ESS ranged between 40.3 and 94.0 across the various comparisons.

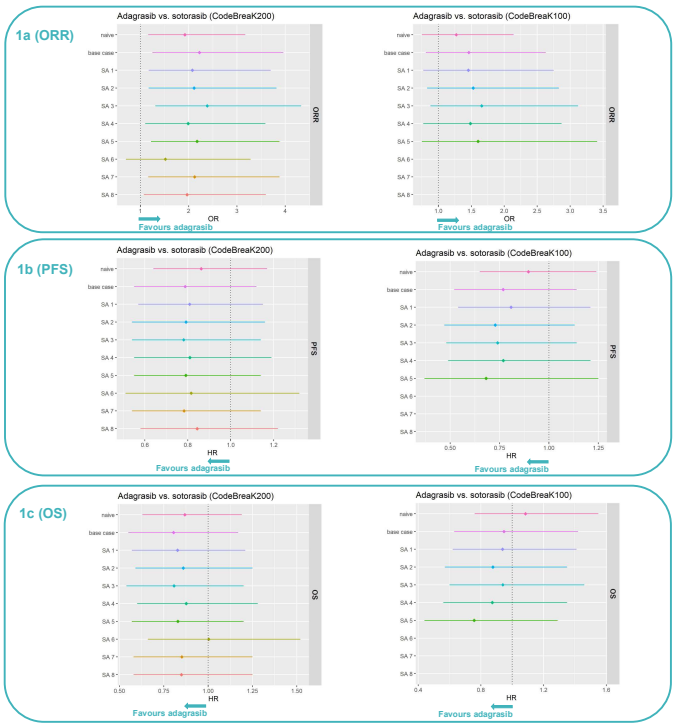
*The wash-out period was 14 days in KRYSTAL-1 and 28 days in CodeBreaK200, implying that time since last prior IO was on average shorter in KRYSTAL-1. Patients who benefited initiating adagrasib earlier in KRYSTAL-1 were downweighted in SA6.

Table 1. Baseline patient characteristics before matching

Characteristic	KRYSTAL-1	CodeBreaK100	CodeBreaK200
Treatment	Adagrasib, 600mg bid	Sotorasib, 960mg qd	Sotorasib, 960mg qd[a]
Sample size	116	126	171
Age, median (range)	64.0 (25-89)	63.5 (37-80)	64.0 (32-88)
Male sex, n (%)	51 (44.0)	63 (50.0)	109 (63.7)
ECOG PS 1[b], n (%)	97 (83.6)	88 (69.8)	112 (65.5)
Current or former smoker, n (%)	111 (95.7)	117 (92.9)	166 (97.1)
Squamous histology, n (%)	3 (2.6)	1 (0.8)	1 (0.6)
Metastatic disease, n (%)	103 (88.8)	122 (96.8)	162 (94.7)
Number of prior lines, n (%)	1: 50 (43.1) 2: 40 (34.5) 3: 12 (10.3) 4+: 14 (12.1)	1: 54 (42.9) 2: 44 (34.9) 3: 28 (22.2)	1: 77 (45.5) 2: 65 (38.0) 3+: 29 (17.0)
Prior anti-PD-1/L1 therapy, n (%)	114 (98.3)	115 (91.3)	167 (97.7)
Prior anti-PD-1/L1 and platinum-based chemotherapy, n (%)	114 (98.3)	102 (81.0)	167 (97.7)

[a]Although docetaxel monotherapy was investigated in CodeBreaK200, this arm was not the focus of this comparison. [b]Only patients with ECOG 0-1 were eligible for inclusion in the trials.
Anti-PD-1/L1, programmed cell death ligand 1; bid, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; qd, once a day.

Figure 1. Forest plots for efficacy comparisons of adagrasib versus sotorasib



Matching variables base case: age, gender, smoking, ECOG, disease stage at treatment initiation/randomization, and histology. Sensitivity analyses (SAs) matched for the base case variables and the following - SA1: the number of prior lines of treatments, SA 2: prior anti-PD-1/L1 therapy, SA3: percentage of Asian patients, SA4: the number of prior lines of treatments and prior anti-PD-1/L1 therapy, SA5: prior anti-PD-1/L1 treatment and platinum-based chemotherapy, SA6: time since last prior IO; SA7: platinum and IO sequences; SA8: prior docetaxel exposure. SA 6-8 were not feasible for the CodeBreaK100 MAIC. **Abbreviations:** ECOG, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SA, sensitivity analysis.

Discussion

- A limitation of this analysis concerns uncertainty of the treatment effects estimates. Additionally, although matching used commonly reported prognostic factors in NSCLC, the accuracy of an unanchored MAIC relies on incorporating all prognostic factors, which is known to be a strong and often unrealistic assumption.[7]
- Additional data from KRYSTAL-12 (NCT04685135), a confirmatory RCT investigating adagrasib, will allow for anchored comparisons and can further inform the comparison of adagrasib versus sotorasib.[8] Real world data may also provide additional clarity in understanding the comparative effectiveness of these two agents.

Conclusion

- This MAIC suggests differences may exist between KRAS^{G12C} inhibitors in a/mNSCLC, with adagrasib demonstrating consistent potential advantages over sotorasib across efficacy endpoints in patients pretreated with standard-of-care chemoimmunotherapy.

References

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