

Cost per Responder Analysis Comparing Adagrasib and Sotorasib in Patients with KRAS G12C-Mutated Previously Treated Non-Small Cell Lung Cancer (NSCLC)

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Background

Disease landscape - 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 mutation (40% to 55% of all KRAS mutations).^{2,3}

Adagrasib and sotorasib

- Two new therapies targeting KRAS^{G12C} have been approved by the Food and Drug Administration for previously treated advanced or metastatic NSCLC (a/mNSCLC) patients: sotorasib (May 2021) and adagrasib (December 2022).^{4,5}
- Among patients with KRAS G12C-mutated a/mNSCLC previously treated with chemoimmunotherapy, adagrasib demonstrated an objective response rate (ORR) of 42.9% in the KRYSTAL-1 phase 2 single-arm trial.⁶ Sotorasib demonstrated an ORR of 37.0% in the phase 2 CodeBreak100 trial, and subsequently a lower 28.1% ORR in the phase 3 randomized clinical trial (RCT) CodeBreak200.^{7,8}
- Currently there are no head-to-head clinical trial or real-world data comparing adagrasib and sotorasib, with limited understanding of the comparative effectiveness within the KRAS^{G12C} inhibitor class.

Objective

- To assess comparative efficiency, a cost-effectiveness model was developed to estimate and compare the costs per response of adagrasib versus sotorasib.

Methods

Approach

- ORRs and treatment-related adverse events (TRAEs) were adjusted for differences in baseline characteristics between KRYSTAL-1 and CodeBreak200 using matching-adjusted indirect comparisons (MAICs).⁹
- MAICs used individual patient-level data (IPD) from KRYSTAL-1 and aggregated data published from CodeBreak200 to estimate the odds ratios (ORs) of response and of Grade ≥3 TRAEs. ORR results are shown in Table 1.
- Model inputs included treatment-related direct medical costs: drug acquisition, monitoring and TRAE management (Table 2). Treatment costs for adagrasib and sotorasib were based on current wholesale acquisition costs, median treatment duration (5.7 and 4.6 months) and relative dose intensity (RDI, 76.5% and 89.2%) as observed in clinical trials.^{6,7,8} Bottle wastage was included, rounding up to the next integer number of bottles required to treat a patient. Management costs of grade ≥3 TRAEs occurring in ≥5% patients were incorporated.

Model outcomes

- The average cost per response was calculated as the ratio between total treatment-related costs and ORR for each treatment, indicating the expected cost to achieve one response, with the lowest cost associated to the most efficient intervention.
- The number needed to treat (NNT) for an additional objective response was calculated as the reciprocal of the ORR difference. The NNT measures the “expected number of patients who need to receive the experimental rather than the comparator intervention for one additional patient to experience an event” (i.e., an objective response).¹⁰

Sensitivity analyses

- Sensitivity analyses included: (1) adagrasib WAC price prior to the August 2023 increase (original launch price), (2) exclusion of bottle wastage, (3) TRAEs occurring in at least 1% of patients (instead of 5%), (4) an assumption where treatment duration is equal to median progression-free survival (PFS) instead of median treatment duration, and (5) using the unadjusted (naïve) ORR for adagrasib.
- A structural sensitivity analysis using adagrasib MAICs matching KRYSTAL-1 patients to the CodeBreak100 population was also carried out (6). ORRs are reported in Table 1.
- A threshold (tipping point) analysis was performed to identify at which price sotorasib would be associated with the same cost per response as adagrasib.

Table 1. Adagrasib vs sotorasib: Naïve vs MAIC ORR

MAIC analysis set	Intervention	Naïve comparison		MAIC-adjusted comparison	
		Response rate	Odds ratio (95% CI)	Response rate	Odds ratio (95% CI)
CodeBreak200 vs KRYSTAL-1	Adagrasib	42.9%	1.922	46.5%	2.222
	Sotorasib	28.1%	(1.16, 3.17)	28.1%	(1.25, 3.96)
CodeBreak100 vs KRYSTAL-1*	Adagrasib	42.9%	1.272	46.2%	1.462
	Sotorasib	37.0%	(0.75, 2.14)	37.0%	(0.81, 2.63)

CI, confidence interval; MAIC, matching-adjusted indirect comparison. *CodeBreak100 used in sensitivity analysis only.

Table 2. Total cost per intervention (average per patient cost)

Cost category	Adagrasib	Sotorasib
Drug acquisition cost	\$104,576.25	\$100,552.65
Monitoring cost	\$47.72	\$51.13
TRAE management cost	\$1,336.93	\$1,897.82
Average cost per patient	\$105,960.90	\$102,501.60

TRAE, treatment-related adverse event.

Results

- The total cost for one patient to achieve one objective response was \$227,987 with adagrasib and \$364,774 with sotorasib. As shown in Figure 2, \$136,787 would be saved per response achieved with adagrasib instead of sotorasib.
- Average treatment costs were comparable (\$105,961 adagrasib; \$102,502 sotorasib), \$3,459 (3%) more per patient with adagrasib even though treatment duration of adagrasib was 24% longer than sotorasib. MAIC-adjusted ORRs, favoring adagrasib (46.5%) over sotorasib (28.1%), were the primary driver in cost per responder differences (Figure 1).
- The NNT was 5.44, i.e., for every 6 patients treated, one additional objective response is expected with adagrasib compared to sotorasib.
- A tipping point analysis demonstrated that the price of sotorasib would need to decrease by 38% to obtain the same cost per response of adagrasib.

Figure 1. MAIC-adjusted objective response rates

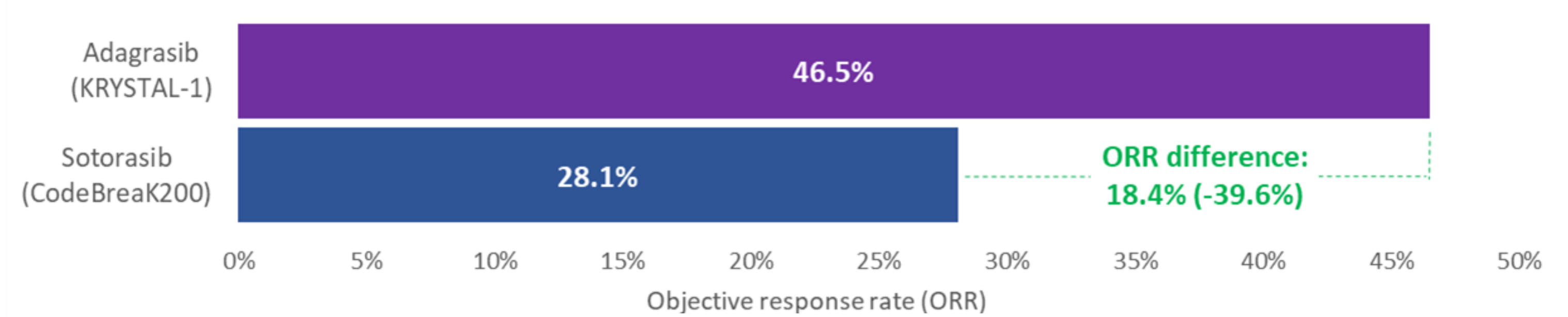
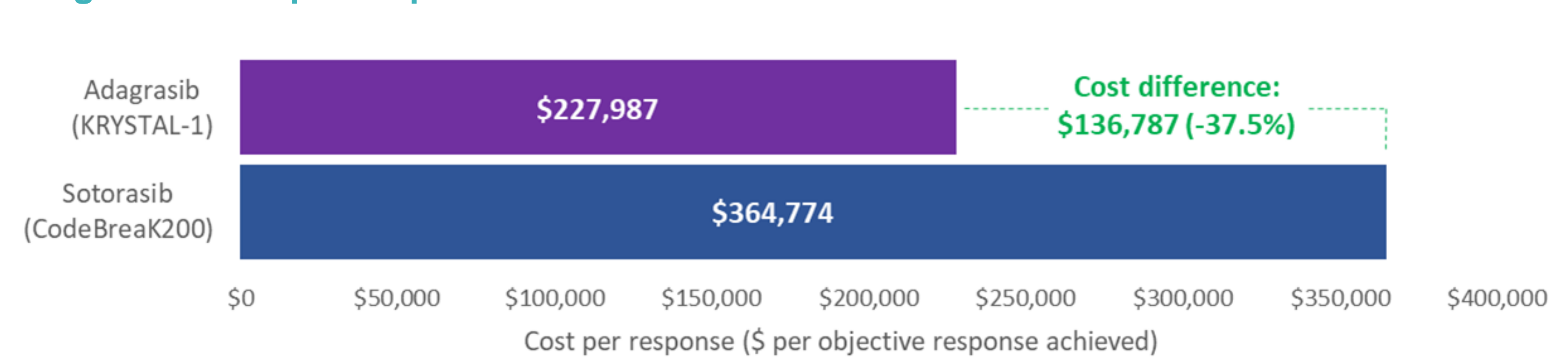


Figure 2. Cost per response model results



Sensitivity analyses

- The results of sensitivity analyses on key model assumptions, reported in Table 3, align with the base case without major variability.
- In the CodeBreak100 scenario, the difference between adagrasib and sotorasib in cost per response was \$42,961, favoring adagrasib. This analysis was superseded with the availability of CodeBreak200 data.

Table 3. Sensitivity analysis results

Scenario analysis	Expected cost per response		
	Adagrasib	Sotorasib	Difference
Base case	\$227,987	\$364,774	\$136,787
1) Adagrasib price before August 2023	\$215,451	\$364,774	\$149,323
2) Exclusion of bottle wastage	\$202,070	\$303,580	\$101,510
3) TRAEs inclusion threshold 1%	\$240,488	\$367,185	\$126,697
4) Treatment duration equal to median PFS	\$273,003	\$436,383	\$163,380
5) Naïve ORR comparison	\$246,787	\$364,774	\$117,987
6) CodeBreak100 MAIC	\$230,506	\$273,468	\$42,961

MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; ORR, objective response rate; TRAE, treatment-related adverse event.

Conclusions

- At a comparable cost, adagrasib is a more effective and cost-efficient option compared to sotorasib, expected to save \$136,787 per response achieved.
- Treating 6 patients with adagrasib instead of sotorasib results in an additional clinical response. The NNT is meaningful, as NNTs lower than 10 versus placebo are generally considered clinically acceptable.¹¹
- Additional confirmation of the MAIC leveraging results from the phase 3 KRYSTAL-12 RCT comparing adagrasib and docetaxel is needed to increase the reliability of the analyses.

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