EE505

Predictive Analysis Comparing Economic and Clinical Consequences of Treatment-Related Hepatotoxicity in Patients with KRAS^{G12C}-Mutated Advanced Non-Small Cell Lung Cancer Treated Post-Immunotherapy

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Background

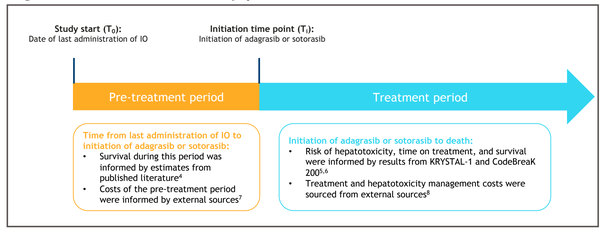
- Two KRAS^{G12C} inhibitors, adagrasib and sotorasib, have been approved for patients with KRAS^{G12C}-mutated locally advanced or metastatic non-small cell lung cancer (aNSCLC) who have received at least one prior systemic therapy.
- Emerging evidence suggests an increased risk of high-grade, treatment-related hepatotoxicity with sotorasib when initiated within 90 days post-immunotherapy (IO); however, the same has not been observed for adagrasib. This is hypothesized to result from differences in pharmacokinetic/pharmacodynamic profiles.[3-5]
- This study explored the potential economic and clinical consequences of high-grade treatment-related hepatotoxicity with adagrasib and sotorasib.

Methods

Study overview

- Patients with KRAS^{G12C}-mutated aNSCLC enrolled in the KRYSTAL-1/CodeBreaK 200 trials informed the analysis.
  - Outcomes for those with IO in their most recent line of therapy (LOT) were used; however, survival was only reported for the overall population from CodeBreaK 200.
- A schematic of the study is presented in **Figure 1**.
  - The starting point was last administration of prior IO (T_0) in the most recent LOT (first or later [1L+]), which represented the beginning of the pre-treatment period.
  - Transition to the treatment period was at the initiation time point (T_i), which corresponded to the start of treatment with either adagrasib or sotorasib.
- A partitioned survival framework with a weekly cycle length and a lifetime time horizon was adopted; the overall hazard function was a piecewise combination of the functions for the pre-treatment and treatment periods, with these joined according to the specified initiation time point (fixed for adagrasib and variable for sotorasib).

Figure 1. Overview of study periods



Abbreviation: IO, immunotherapy.

Summary of model inputs

- Real-world survival data for patients with KRAS^{G12C}-mutated aNSCLC who received prior IO as their most recent LOT and who also met all inclusion/exclusion criteria for the adagrasib and sotorasib trials was unavailable.
  - Thus, survival during the pre-treatment period was informed by estimates from Shokoohi et al. 2022, a real-world study of treatment patterns and outcomes for aNSCLC patients.[6]
  - Two separate patient populations receiving either chemotherapy (base case) or best supportive care (BSC; sensitivity) in any LOT were used in the model.
- Clinical data during the treatment period, including grade ≥3 hepatotoxicity rates (**Table 1**), time on treatment, as well as survival within and beyond the trial period were informed by KRYSTAL-1 and CodeBreaK 200.[7,8]
- As only individual patient data were available for adagrasib and aggregate data for sotorasib, a multi-step approach was employed to model survival for the two therapies in a population who received IO in their most recent LOT, prior to receiving either KRAS^{G12C} inhibitor (adagrasib or sotorasib).
  - First, patients in KRYSTAL-1 (N=116) were matched to those in CodeBreaK 200 (N=169) using propensity score weights from a logistic regression model. This accounted for between-study differences in patient characteristics; parametric distributions were then fitted to the reweighted cohort of patients with IO immediately prior to receiving adagrasib in KRYSTAL-1 (n=77). The best fitting model was used to estimate survival during the treatment period for adagrasib.
  - Based upon the reweighted population from KRYSTAL-1, a hazard ratio was estimated between those who received an IO agent in their most recent LOT and the overall population.
  - This correction factor (i.e., hazard ratio) was then applied to the best fitting parametric distribution for sotorasib based on the full population in CodeBreaK 200 to approximate survival in patients with IO in their most recent LOT prior to receiving sotorasib.
- The model included routine care costs during the pre-treatment period, as well as drug acquisition, disease monitoring, hepatotoxicity and other treatment-related adverse event (TRAE) management costs, all informed by external sources.[9-11]

Table 1. Hepatotoxicity in patients with IO in their most recent LOT

Time since last administration of IO	Adagrasib (n=77)			Sotorasib (n=149)		
	N	Any grade, n (%)	Grade ≥ 3, n (%)	N	Any grade, n (%)	Grade ≥ 3, n (%)
<1.58 months	30	16 (53.3)	4 (13.3)	36	12 (33.3)	12 (33.3)
[1.58 - 2.59) months	21	8 (38.1)	1 (4.8)	38	13 (34.2)	9 (23.7)
[2.60 - 6.20) months	14	4 (28.6)	2 (14.3)	36	8 (22.2)	5 (13.9)
> 6.20 months	12	4 (33.3)	0 (0.0)	39	5 (12.8)	3 (7.7)

Abbreviations: IO, immunotherapy; LOT, line of therapy.

Summary of model outputs

- A primary analysis was conducted to compare grade ≥3 treatment-related hepatotoxicity-management costs associated with adagrasib and sotorasib from a US third-party payer perspective; differences in total costs were also estimated.
- In the base case, costs were compared assuming both therapies were initiated after a 28-day washout-period post last administration of IO.
- Varying initiation times for sotorasib were also evaluated: 2.60 months and 4.41 months.
  - 2.60 months was the median time from last administration of prior IO for sotorasib from CodeBreaK 200.
  - 4.41 months was the mid-point of the third quartile of the time intervals (**Table 1**), where the risk of severe hepatotoxicity can be considered similar between the two therapies.
- A secondary analysis was conducted to compare life years gained (LYG) associated with adagrasib versus sotorasib under the same set of initiation times as the primary analysis.

Scenario analyses

- Various scenario analyses were also conducted for the primary analysis:
  - Scenario 1: Using adjusted hepatotoxicity risk rates based on a matching-adjusted indirect comparison (MAIC) of KRYSTAL-1 to CodeBreaK 200.
  - Scenario 2: Using alternative sources for hepatotoxicity management costs (i.e., using increased ALT or AST as a proxy).
  - Scenario 3,4,5: Using alternative survival for the pre-treatment period (BSC).

Results

Primary analysis

- In the base case, after a 28-day washout-period, adagrasib was associated with lower hepatotoxicity management costs versus sotorasib ($2,095.57 versus $5,246.80; net savings of $3,151.23); this cost-saving decreased with increasing time/delayed start in initiating sotorasib post-IO (**Figure 2**).
- In terms of total costs, adagrasib was associated with higher costs when compared to sotorasib (**Table 2**), primarily driven by differences in drug acquisition costs and longer time on therapy (estimated based on the median duration of adagrasib [5.70 months] and sotorasib [4.58 months] in KRYSTAL-1 and CodeBreaK 200, respectively).

Figure 2. Estimated hepatotoxicity management costs at different initiation times for sotorasib

Notes: The cost of managing drug induced liver injury was assumed to represent those for managing grade ≥3 hepatoxicity; cost data were updated post abstract submission.

Table 2. Estimated total costs* at different sotorasib initiation times

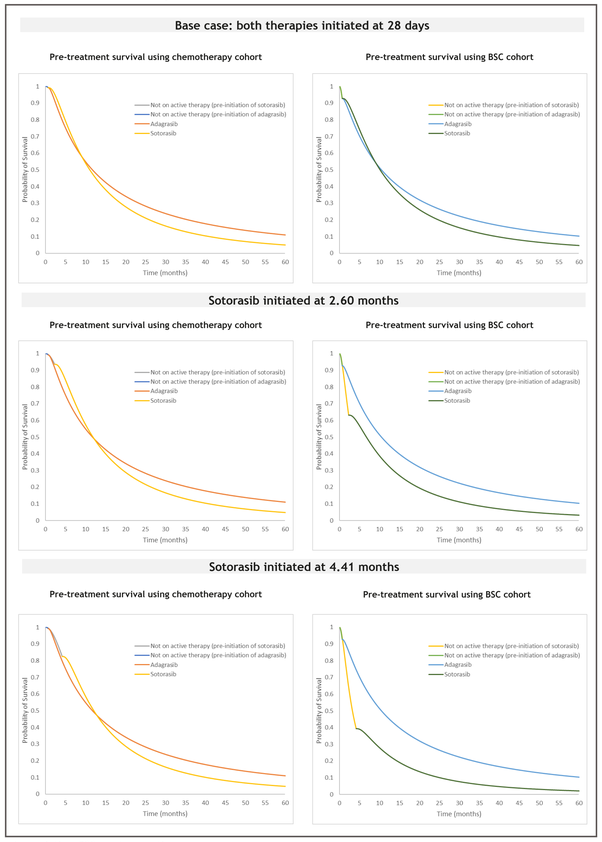
Interventions	Initiation time of sotorasib		
	28 days	2.60 months	4.41 months
Adagrasib**	$102,335.65		
Sotorasib	$95,975.37	$91,200.60	$81,711.33
Cost difference	**$6,360.28**	**$11,135.04**	**$20,624.31**

*Total costs included those for routine care during the pre-treatment period, as well as drug acquisition, disease monitoring, hepatotoxicity and other TRAE management costs. **The initiation time for adagrasib was fixed to 28 days.

Secondary analysis

- Estimated survival from the model is presented in **Figure 3**.
- Adagrasib was associated with positive LYG across all sotorasib initiation time points when survival of patients on chemotherapy was used to inform the pre-treatment period (**Table 3**).
  - Limited variation in the results across the different sotorasib time points (LYG = 0.47-0.51) was observed given that survival observed for patients on chemotherapy was similar to that which was estimated for patients who received prior-IO in their most recent LOT from KRYSTAL-1 and CodeBreaK 200.
- Using BSC survival for the pre-treatment period led to steady increases in LYG for adagrasib relative to the base case i.e., more variation in survival across the sotorasib initiation times (LYG = 0.48-1.11).

Figure 3. Estimated survival with chemotherapy versus BSC informing the pre-treatment period



Abbreviation: BSC, best supportive care.

Table 3. Estimated life years at different sotorasib initiation times

Interventions	Time of initiation of sotorasib		
	28 days	2.60 months	4.41 months
Using survival of patients on chemotherapy			
Adagrasib*	2.09		
Sotorasib	1.58	1.62	1.59
Life-years gained	**0.51**	**0.47**	**0.50**
Using survival of patients on BSC			
Adagrasib*	1.95		
Sotorasib	1.48	1.13	0.85
Life-years gained	**0.48**	**0.82**	**1.11**

*The initiation time for adagrasib was fixed to 28 days. *Abbreviation:* BSC, best supportive care.

Scenario analyses

- Results from the scenario analyses are presented in **Table 4.**
- Utilizing proportions of patients experiencing grade ≥3 hepatotoxicity from the MAIC led to a slight increase in the difference in hepatotoxicity management costs (-$3,925.91); a decrease in the difference was observed when using costs based on ALT or AST increases (-$946.51).
- Using the BSC assumption for the pre-treatment period led to decreases in the differences in hepatotoxicity management costs.

Table 4. Results from scenario analyses (adagrasib versus sotorasib)

Scenarios	Difference in grade ≥3 treatment- related hepatotoxicity management costs
Scenario 1 • Using adjusted hepatotoxicity risk based on MAIC • Initiating sotorasib after 28 days	-$3,925.91
Scenario 2 • Using increased ALT and AST as proxy to estimate hepatotoxicity management costs • Initiating sotorasib after 28 days	-$946.51
Scenario 3 • Using alternative survival of patients on BSC • Initiating sotorasib after 28 days	-$2,941.49
Scenario 4 • Using alternative survival of patients on BSC • Initiating sotorasib after 2.60 months	-$422.35
Scenario 5 • Using alternative survival of patients on BSC • Initiating sotorasib after 4.41 months	$1,088.57

Note: For all scenarios, the initiation time for adagrasib was fixed to 28 days. For scenario 1, 2, 3 the initiation time for sotorasib was also to 28 days. *Abbreviations:* ALT, Alanine transaminase; AST, Aspartate transaminase.

Discussion

- This analysis was conducted using results from the pivotal trials of adagrasib and sotorasib as well as published sources; the available data required a number of assumptions to be made which means the results may not be fully reflective of what can be expected in real-world clinical practice.
- A cohort modelling approach was adopted, whereby costs and outcomes were analyzed at the cohort level without accounting for specific costs and outcomes of individual patients.
  - This choice of model was driven primarily by a lack of data availability, particularly for (1) survival in patients with KRAS^{G12C}-mutated aNSCLC from last administration of IO (1L+) as well as (2) effect of time from last administration of IO on the efficacy of sotorasib, given that subgroup data were not presented in CodeBreaK 200.
- These limitations would be partially addressed via a patient level simulation model.
  - Such an analysis may be possible in the future using real-world data, such as that from an ongoing retrospective, observational study of treatment patterns for patients with metastatic NSCLC, including a subgroup with KRAS^{G12C} mutations.[12]

Conclusions

- When adagrasib and sotorasib are initiated at the same time relative to prior IO, adagrasib may offer benefits from an economic perspective due to lower grade ≥3 hepatotoxicity management costs.
- Furthermore, for patients who initiate adagrasib sooner, as a result of lower hepatotoxicity risk, additional clinical benefit may be realized from extended survival.

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