Evaluating EU HTA PICO Exercise Outcomes: Duration of and Time to Response in Hepatocellular Carcinoma Using Randomization-Preserving Methods with IMbrave150 Data

Launonen A, Jaffer A, Shi L, Belleli R, Blanchet Zumofen M-H, Sibbe M
All authors are employees of F Hoffman-La Roche, Ltd.

BACKGROUND

The European Commission's PICO exercises for Joint Clinical Assessment (JCA) identified duration of response (DoR) and time to response (TTR) as key patient-relevant outcomes in oncology.

Traditional analyses restricted to responders —e.g., themedian DoR among responders—compromise the intention-to-treat (ITT) principle (ICH E9) by selecting patients based on a post-randomization intercurrent event (ICH E9 Addendum), and therefore lack causal interpretation at the trial level.

Restricted Mean(RM) DoR ('i.e.,expected DoR') summarizes the average time in response within a pre-specified time horizon across all randomized patients—non responders contributing as zero—whereas traditional DoR measures time in response conditional on achieving a response.

OBJECTIVE AND PRIOR WORK

Objective: To assess the applicability and interpretability of randomization-preserving methods for DoR and TTR in hepatocellular carcinoma(HCC) using updated data from IMbrave150 trial, quantifying treatment effects in the ITT population over a clinically relevant time horizon within the trial follow-up time.

Prior work:

- RMDoR and PBIR (Probability of Being In Response; randomization-preserving DoR estimand): Huang et al. (2018, 2022); Daletzakis et al. (2025); Weber et al. (2024).
- TTR (competing-risk framework): Weber et al., (2024); Huang et al., (2020).
- IMbrave150: Kudo et al. (2023), Cheng et al. (2022)—ORR 27.3% vs 11.9%; median DoR among responders 18.1 vs 14.9 months (atezolizumab+bevacizumab vs sorafenib)

METHODS

Trial & Population: IMbrave150 (Updated Data), ITT population with measurable disease (RECIST 1.1); atezolizumab+bevacizumab (N=326) vs. sorafenib(N=159)

Estimands:

RMDoR: Defined as the expected DOR restricted to interval [0- τ], where τ is the pre-specified truncation point. Derived as the area between S_{PFS} (time to progression or death) and S_{RPD} (time to first of response/progression/death) (Huang et al. 2022);

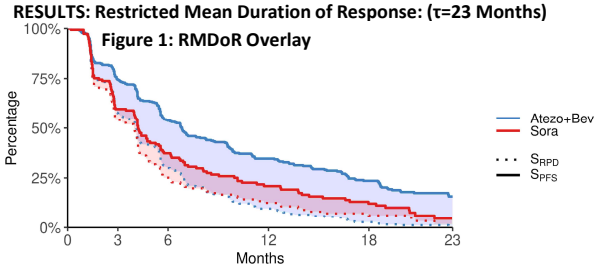
PBIR(t): Derived as $S_{PFS}(t) - S_{RPD}(t)$, representing the probability of being in the response state.

TTR: Estimated using the Cumulative Incidence Function (CIF) to report 3-month cumulative incidence of response and the time to reach 10% cumulative incidence. PBIR serves as a complementary measure for TTR onset and sustainability.

Prespecification: τ=23 months and 10% threshold were pre-specified to balance clinical relevance and data maturity.

RESULTS: Restricted Mean Duration of Response: (τ=23 Months)

Figure 1: RMDoR Overlay



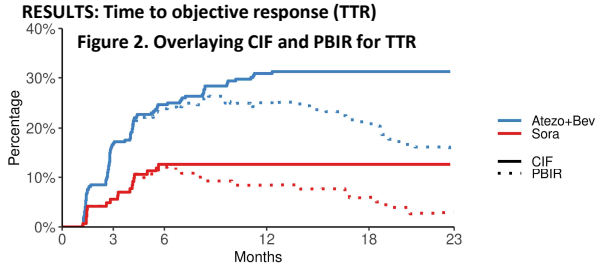
Atezo+Bev vs Sora	RMDoR(τ=23)	p-value(Wald)
Difference	3.00 (95% CI 1.87–4.13)	<0.0001
Ratio	2.92 (95% CI 1.74–4.90)	<0.0001*

During the first 23 months from treatment initiation, patients randomized to atezolizumab+bevacizumab remained in response, on average three months longer—or roughly three times longer—compared to those randomized to sorafenib.

* log scale, SE derived using delta method

RESULTS: Time to objective response (TTR)

Figure 2. Overlaying CIF and PBIR for TTR



Arm	3-month CIF %	Time to 10% CIF
Atezo+Bev	17.0 (95% CI:12.8–21.1)	2.6 months
Sora	5.6 (95% CI:1.8–9.4)	4.2 months
Atezo+Bev vs Sora	11.4 (95% CI: 5.8–17.0)	p-value <0.0001*

Patients randomized to atezolizumab+bevacizumab had a faster onset and higher cumulative incidence of objective response compared to those randomized to sorafenib.

*Fine-Gray test of difference of the CIF curves

CONCLUSIONS

- EU HTA PICO exercises highlight the relevance of DoR and TTR in Oncology.
- Traditional responder-only summaries on DoR and TTR lack causal interpretability.
- RMDoR can support EU HTA PICO requirments while preserving ITT.
- During early follow-up, PBIR and CIF often align; however, PBIR declines as patients progress, while CIF continues to accumulate.
- For TTR, combine CIF-based estimates with PBIR to support EU HTA PICO, as the competing-risk approach may face limited acceptance.
- It is crucial to pre-specify the RMDoR time horizon and TTR thresholds.
- Randomization-preserving analyses indicated that patients randomized to atezolizumab+bevacizumab experienced a longer RMDoR (a difference of 3 months) and faster TTR (2.6 months vs. 4.2 months to reach 10% CIF) compared to those randomized to sorafenib in HCC.

Abbreviations:DoR (Duration of Response), **TTR** (Time to Response), **RMDoR** (Restricted Mean DoR), **ITT** (Intention-to-Treat), **CIF** (Cumulative Incidence Function), **PBIR** (Probability of Being In Response), **ORR** (Objective Response Rate), **PFS** (Progression-Free Survival,i.e time to progression or death), **JCA** (Joint Clinical Assessment), **HCC** (Hepatocellular carcinoma), **KM** (Kaplan–Meier), **RECIST 1.1** (Response Evaluation Criteria in Solid Tumors, version 1.1), **RPD** (time to response, progression or death , i.e first event.)