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A Novel Crossover Adjustment Analysis of Overall Survival Results from the Phase 3 ClarIDHy Study of Ivosidenib Versus Placebo in Patients with m*IDH1* Cholangiocarcinoma

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Background

- The global, phase 3, randomised, placebo-controlled ClarIDHy study demonstrated significantly improved progression-free survival (p<0.0001) and a favourable safety profile for ivosidenib (IVO), an oral inhibitor of the mutant isocitrate dehydrogenase 1 (mIDH1) protein, versus placebo (PBO) in patients with previously treated, non-resectable or metastatic m*IDH1* cholangiocarcinoma (CCA)[1]
- As a result of a high crossover rate from PBO to IVO (70%) among patients participating in ClarIDHy, crossover adjustment using the rank preserving structural failure time model (RPSFTM) with re-censoring was applied and showed a significant overall survival (OS) benefit with IVO versus PBO (hazard ratio [HR] 0.49 [95% confidence interval (CI): 0.34, 0.70]; 1-sided p<0.001)[2]
- However, the validity of the RPSFTM method of crossover adjustment has been questioned for later-line therapies without previously proven OS benefit[3]
- Results of an independent analysis of OS data from the ClarIDHy study using alternative crossover adjustment methods are presented

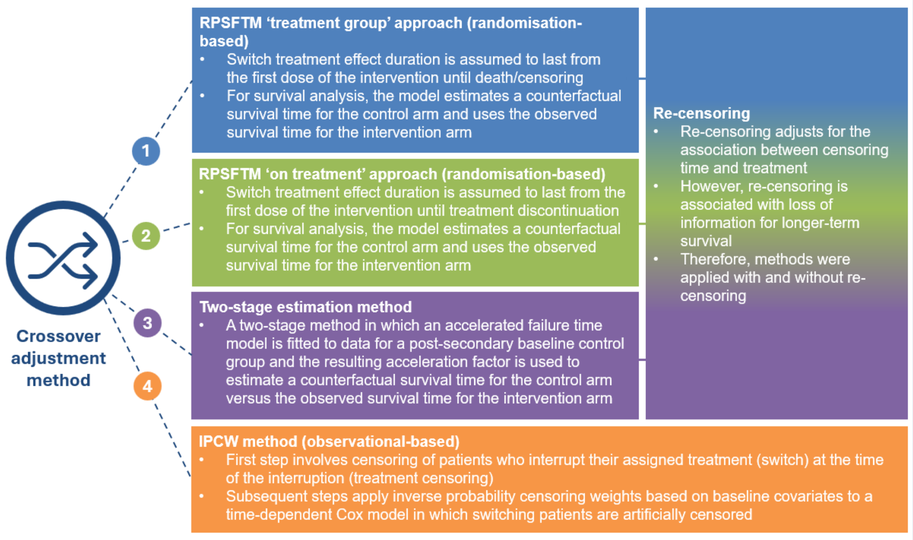
Objectives

- To test the robustness of the RPSFTM-adjusted survival results for IVO versus PBO in the ClarIDHy study

Methods

- In the ClarIDHy study, patients aged ≥18 years with m*IDH*1 CCA were randomised 2:1 to receive IVO 500 mg/day or matched PBO[1,2]
  - Crossover from PBO to IVO was permitted upon disease progression based on radiographic findings[1,2]
- OS was a key secondary study endpoint analysed in the intent-to-treat (ITT) population[2]
- This independent analysis included individual patient data from the ITT population (N=187; IVO, n=126; PBO, n=61) of the ClarIDHy study, and OS is the primary endpoint of this analysis
- Established statistical adjustment methods for crossover and treatment switching – RPSFTM, inverse probability of censoring weighting (IPCW), and two-stage estimation[3,4] – were applied to the patient data from ClarIDHy (Figure 1)

Figure 1: Crossover adjustment methods



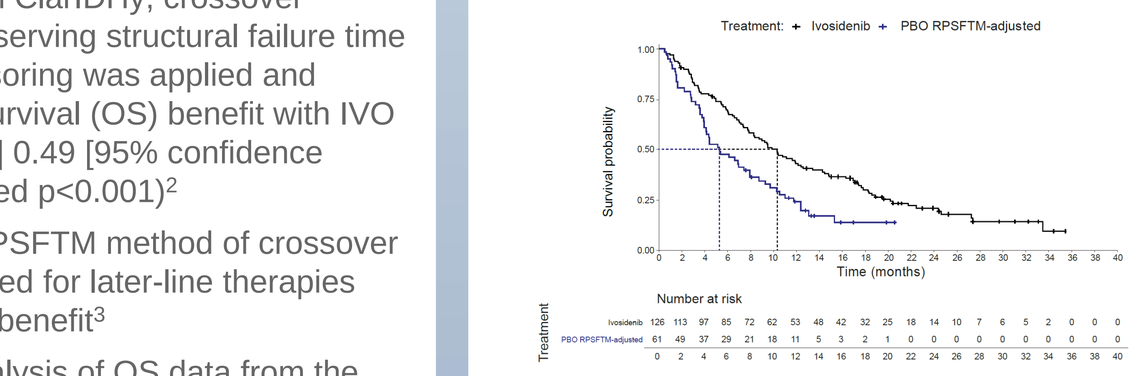
RPSFTM, rank preserving structural failure time model; IPCW, inverse probability of censoring weighting.

- For application of RPSFTM, data on the dates of randomisation, switch, death/censor, data cut-off and treatment discontinuation for each patient were required
- For IPCW and two-stage estimation, additional baseline data and time-dependent variables were collected
- For all crossover adjustment methods:
  - Kaplan-Meier curves of estimated survival in the adjusted counterfactual dataset for the PBO arm and observed survival in the IVO arm were generated
  - Estimated HRs and associated 95% CIs were calculated for IVO versus PBO using Cox proportional hazards regression modelling and are presented as mortality risk reduction (MRR) estimates

Results

- The two-stage estimation method was deemed unviable for crossover adjustment as too few patients in ClarIDHy did not switch from PBO to IVO after achieving secondary baseline survival (43 switchers vs 6 non-switchers). Therefore, results are not shown for this method
- IVO prolonged median OS by 5.1 months and was associated with an adjusted MRR of 48% compared with PBO using the RPSFTM 'treatment group' method without re-censoring (HR 0.52 [95% CI: 0.37, 0.75]; Figure 2)

Figure 2: Kaplan-Meier survival analysis based on the RPSFTM 'treatment group' method (without re-censoring; ITT population)



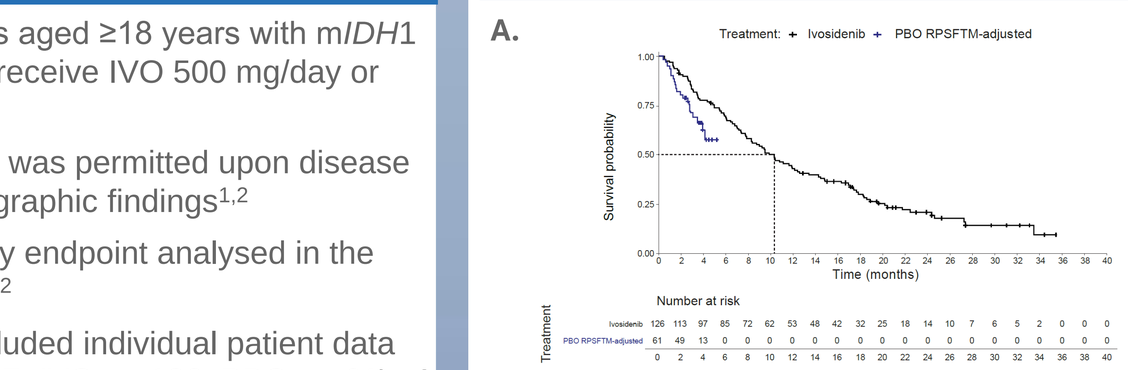
OS (without re-censoring)	IVO (n=126)	PBO (n=61)
Events, n (%)	100 (79.4)	50 (82.0)
Censored, n (%)	26 (20.6)	11 (18.0)
Median (95% CI), months	10.3 (7.8, 12.4)	5.2 (3.9, 7.9)
HR (95% CI)	0.52 (0.37, 0.75)	

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; IVO, ivosidenib; OS, overall survival; PBO, placebo; RPSFTM, rank preserving structural failure time model.

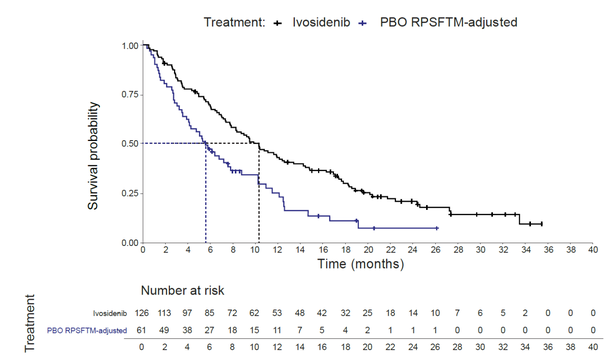
- When the RPSFTM 'on treatment' approach was applied with re-censoring, median OS was not reached in the PBO arm, and IVO was associated with an adjusted MRR of 51% versus PBO (HR 0.49 [95% CI: 0.28, 0.87]; Figure 3A), which is similar to the MRR using the RPSFTM 'treatment group' method
- Without re-censoring, the RPSFTM 'on treatment' approach demonstrated an increase in median OS of 4.8 months for IVO versus PBO, with an MRR of 48% (HR 0.52 [95% CI: 0.36, 0.74]; Figure 3B)

Figure 3: Kaplan-Meier survival analysis based on the RPSFTM 'on treatment' method with (A) and without (B) re-censoring (ITT population)

A.



B.



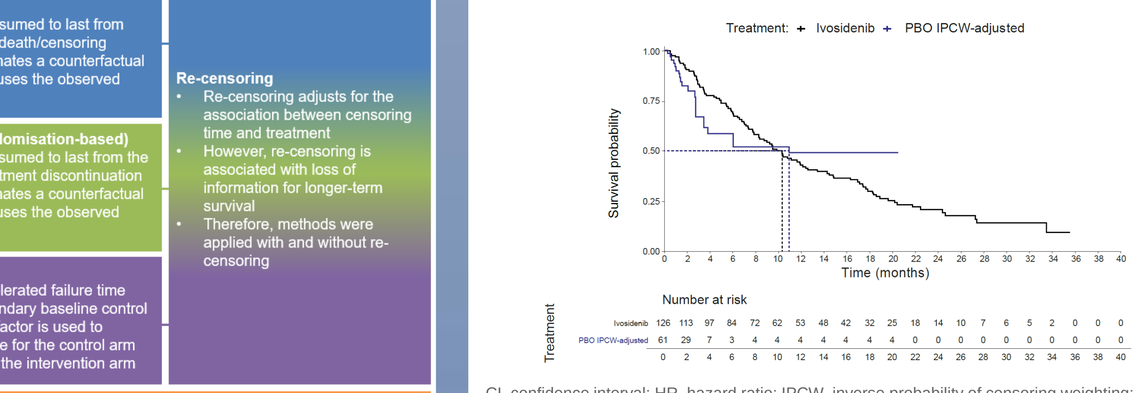
OS (with re-censoring)	IVO (n=126)	PBO (n=61)
Events, n (%)	100 (79.4)	21 (34.4)
Censored, n (%)	26 (20.6)	40 (65.6)
Median (95% CI), months	10.3 (7.8, 12.4)	NR (3.5, NR)
HR (95% CI)	0.49 (0.28, 0.87)	

OS (without re-censoring)	IVO (n=126)	PBO (n=61)
Events, n (%)	100 (79.4)	50 (82.0)
Censored, n (%)	26 (20.6)	11 (18.0)
Median (95% CI), months	10.3 (7.8, 12.4)	5.5 (4.0, 7.8)
HR (95% CI)	0.52 (0.36, 0.74)	

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; IVO, ivosidenib; NR, not reached; OS, overall survival; PBO, placebo; RPSFTM, rank preserving structural failure time model.

- The IPCW-adjusted analysis showed that IVO was associated with an MRR of 26% versus PBO (HR 0.74 [95% CI: 0.35, 1.56]; Figure 4)

Figure 4: Kaplan-Meier survival analysis based on the IPCW method (ITT population)



OS	IVO vs PBO
Events, n	117
Censored, n	70
HR (95% CI)	0.74 (0.35, 1.56)

CI, confidence interval; HR, hazard ratio; IPCW, inverse probability of censoring weighting; ITT, intent-to-treat; IVO, ivosidenib; OS, overall survival; PBO, placebo.

Study limitations

- The IPCW method is limited by the 'no unmeasured confounders' assumption, which can affect estimation stability with wide CIs for randomised controlled trials with small sample sizes. However, this assumption can usually be addressed by ensuring that crucial covariates are included in the model as undertaken in this independent analysis

Conclusions

- **In this independent analysis of data from ClarIDHy, IVO was associated with MRR compared with PBO in adult patients with previously treated, locally advanced or metastatic m*IDH1* CCA, regardless of the crossover adjustment method employed**
- **These results are consistent with previously published RPSFTM-adjusted survival findings from the ClarIDHy study,[2] and the three methods used here for crossover adjustment provided similar outcomes to each other**
- **These data support and validate IVO as an effective treatment among patients with this aggressive, life-threatening disease**

References: 1. Abou-Alfa GK, et al. Lancet Oncol. 2020;21:796-807. 2. Zhu AX, et al. JAMA Oncol. 2021;7:1669-1677. 3. Prasad V, et al. Trials. 2023;24:373. 4. Latimer NR, et al. Statistical Meth Med Res. 2020;29:2900-2918

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