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Abstract #165

Constructing a Hybrid Control for the MORPHEUS Colorectal Cancer (CRC) Trial Using IMblaze370 Historical Trial Data

Chen Li,[1] Ana Ferro,[1] Shivani K. Mhatre,[2] Danny Lu,[3] Marcus Lawrance,[1] Shi Li,[2] Simon Allen,[2] Jayesh Desai,[4] Marwan Fakih,[5] Tae You Kim,[6] Irmarie Reyes-Rivera,[7] Christelle Lenain,[7] Neil H. Segal[8]

[1]Roche Products Ltd, Welwyn Garden City, United Kingdom; [2]Genentech Inc, South San Francisco, CA, USA; [3]Hoffmann-La Roche Limited, Mississauga, ON, Canada; [4]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [5]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [6]Seoul National University College of Medicine, Seoul, South Korea; [7]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA

INTRODUCTION

- Randomised controlled trials are regarded as the gold standard for evaluating treatment effectiveness, yet regulatory agencies are becoming increasingly receptive to supplementing or replacing control arms with historical data from various sources, including previously completed trials, especially in rare and paediatric disease areas, or life-threatening indications with few treatment options.[1-3] In such scenarios, randomising patients to control arms may be less acceptable due to feasibility.[1] Even in more prevalent diseases or trials with specific eligibility criteria, significant challenges may be encountered during patient recruitment, such as in late-stage cancer trials with requirements for specific biomarker status[2]
- The hybrid control design using relevant individual patient data from historical clinical trials can achieve more patient-centric, cost-effective and accelerated clinical development, as fewer patients are needed to be assigned to a control arm (standard-of-care treatment or placebo)[4,5]
  - This approach may preserve the benefits of randomisation while also strengthening trial evidence by integrating historical data with an evaluation of consistency between current and historical trial data[4,5]
- However, few examples have been established to assess the applicability of such design in supporting early trial development. We present a proof of concept of a hybrid control design within the MORPHEUS-CRC trial
- The MORPHEUS platform consists of multiple, global, open-label, randomised umbrella Phase Ib/II trials designed to accelerate the development of combinations across a wide range of cancer indications by identifying early efficacy signals and establishing proof-of-concept clinical data
  - Each MORPHEUS trial includes a current standard-of-care control arm for improved result confidence, yet the small sample size of the control arm, as with all early-phase trials, may limit the power to detect a treatment effect. Hence, the use of hybrid control design in this setting may improve precision of the treatment efficacy estimates, thereby facilitating more appropriate decision-making to inform later-phase trial development
- In the MORPHEUS-CRC trial (NCT03555149), patients with microsatellite-stable metastatic (m)CRC refractory to first- and second-line standard therapies are randomised to either an experimental combination or the control arm
- IMblaze370 (NCT02788279) was a Phase III, multicentre, open-label, randomised study in patients with mCRC with disease progression who received or were intolerant to ≥ 2 previous systemic chemotherapy regimens[7]
  - IMblaze370 and MORPHEUS-CRC are both randomised studies that enrolled or are enrolling a similar patient population, with a substantial overlap in the eligibility criteria, and that include a standard-of-care control arm, regorafenib[6]
- We constructed a hybrid control arm (regorafenib) for MORPHEUS-CRC by integrating historical control data from the IMblaze370 study, with a comparison against the MORPHEUS-CRC experimental arm atezolizumab + isatuximab

PATIENTS AND METHODS

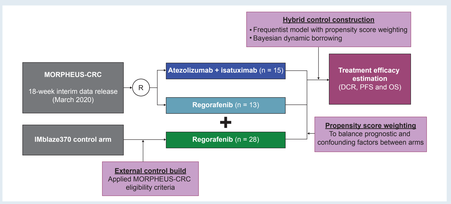
Patients

- Patients in the current control arm (regorafenib) and the experimental arm (atezolizumab + isatuximab) of MORPHEUS-CRC (enrolment: September 2018 to August 2019) were included in this study
- In addition, patients in the control arm of IMblaze370 (enrolment: July 27, 2016, to January 19, 2017) who received regorafenib as third-line (3L) treatment and met the MORPHEUS-CRC eligibility criteria were selected to build an external control arm
- The external control arm was incorporated into the MORPHEUS-CRC control arm to construct the hybrid control arm using a Frequentist or Bayesian dynamic borrowing method[8,9]

Study Design

- The study overview is presented in Fig. 1

Figure 1. Study overview for the construction of a hybrid control



DCR, disease control rate; OS, overall survival; PFS, progression-free survival.

Outcomes

- The outcomes evaluated in this study were (1) DCR, defined as the proportion of patients with complete or partial response at any time during the trial or stable disease for ≥ 12 or ≥ 16 weeks in the MORPHEUS-CRC or the IMblaze370 trial, respectively; (2) PFS, defined as the time from trial randomisation to the occurrence of disease progression or death (whichever occurs first) or end of trial follow-up and (3) OS, defined as the time from trial randomisation to the occurrence of death or end of trial follow-up
- Disease progression was determined by clinical investigators according to the Response Evaluation Criteria in Solid Tumours version 1.1
- The time interval for response assessment was every 6 and 8 weeks in MORPHEUS-CRC and IMblaze370, respectively
  - Hence, the DCR in the IMblaze370 trial at 12 weeks was inferred using tumour overall response assessment at 8 and 16 weeks. Specifically, if a patient at 8 weeks showed progressive disease (PD) in the IMblaze370 trial, then the response for that patient at 12 weeks was defined as PD; if a patient at both 8 and 16 weeks showed stable disease, then the response for that patient at 12 weeks was defined as stable disease; otherwise, a patient's response was set as unknown.
- PFS and OS in the external control arm were truncated to match the maximum PFS and OS, respectively, of the MORPHEUS trial

Propensity Score Estimation

- Propensity score (PS) with standardised mortality ratio (SMR) weighting method was used to adjust for imbalances of pre-defined prognostic and/or confounding factors between the MORPHEUS-CRC experimental arm and the external control arm
- PS was estimated using a multivariate logistic regression model adjusted for pre-defined covariates, including age, sex, presence of liver metastases, time from metastatic diagnosis to baseline (> 18 vs ≤ 18 months) and Eastern Cooperative Oncology Group (ECOG) performance status
- PS was calculated for each patient, representing a patient's probability of being in the MORPHEUS-CRC experimental arm, depending on the selected pre-specified covariates
- Covariate selection depended on the potential clinical importance with respect to the prognostic impact of the covariate in the metastatic refractory setting, data availability and model convergence
- Balance was assessed with standardised mean difference (SMD), in which covariates with an SMD of < 0.25 were deemed sufficiently balanced

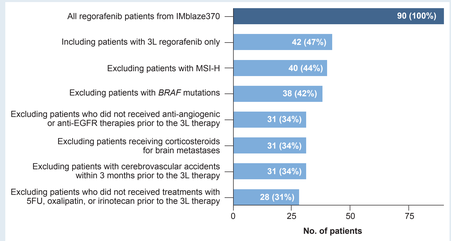
Statistical Analysis

- Baseline demographic and clinical characteristics were separately summarised for the external control and MORPHEUS-CRC control and experimental arms
- Experimental treatment efficacies were estimated by comparing the MORPHEUS-CRC experimental arm with the MORPHEUS-CRC control arm or hybrid control arm separately in a Frequentist or Bayesian framework
  - Survival (PFS and OS) was determined using Kaplan-Meier (KM) estimates with SMR weighting, with median PFS point estimates and corresponding 95% CIs summarised for each arm along the KM curves

RESULTS

- Fig. 2 shows the IMblaze370 control cohort attrition for the selection of patients included in the external control arm

Figure 2. IMblaze370 control cohort attrition



5FU, fluorouracil; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; EGFR, epidermal growth factor receptor; MSI-H, microsatellite instability–high.

- Of the 90 patients who received regorafenib in IMblaze370, 28 were included in the external control arm
- Baseline demographics and disease characteristics in each cohort are summarised in Table 1

Table 1. Comparison of the baseline demographic and clinical characteristics between the external control derived from IMblaze370 and the MORPHEUS-CRC control and experimental arms before covariate balancing

	IMblaze370 EC (n = 28)	MORPHEUS-CRC		*P* value (EC vs atezo + isa)	SMD (EC vs atezo + isa)
		Atezo + isa (n = 15)	Regorafenib (n = 13)		
Age, mean (SD), y	57.0 (9.6)	52.2 (12.0)	59.5 (10.5)	0.18	0.45
Sex, n (%)					
Female	12 (43)	6 (40)	7 (54)	0.86	0.06
Male	16 (57)	9 (60)	6 (46)		
Race, n (%)					
White	21 (84)	10 (71)	8 (67)	0.36	0.31
Non-white	4 (16)	4 (29)	4 (33)		
Unknown	3	1	1		
Region, n (%)					
North America	6 (21)	11 (73)	6 (46)	0.002	1.50
Europe	17 (61)	1 (7)	2 (15)		
Asia and/or Australia	5 (18)	3 (20)	5 (38)		
Time from metastatic diagnosis to baseline, n (%)					
< 18 mo	7 (25)	7 (47)	4 (31)	0.16	0.46
≥ 18 mo	21 (75)	8 (53)	8 (62)		
Unknown	0	1	0		
ECOG performance status, n (%)					
0	13 (46)	5 (33)	6 (46)	0.42	0.27
1	15 (54)	10 (67)	7 (54)		
***RAS* mutation status, n (%)**					
Wild type	10 (38)	6 (40)	8 (62)	0.92	0.03
Mutant	16 (62)	9 (60)	5 (38)		
Unknown	2	0	0		
Liver metastases, n (%)					
No	10 (36)	6 (40)	4 (31)	0.79	0.09
Yes	18 (64)	9 (60)	9 (69)		

Statistical differences between the EC and the MORPHEUS experimental arm (atezo + isa) were assessed using (1) *P* values calculated via 2-tailed χ^2 (or Fisher exact) tests for all categorical variables or the Wilcoxon rank-sum test for the age variable or (2) SMD.
atezo, atezolizumab; EC, external control (regorafenib); isa, isatuximab; *RAS*, Rat sarcoma proto-oncogene, GTPase; SD, standard deviation.

- Between patients in the EC and those in MORPHEUS-CRC, there was no major difference in baseline demographic and disease characteristics, including age, sex, race, time from metastatic diagnosis to baseline, ECOG performance status, *RAS* mutational status and presence of liver metastases
- A lower percentage of EC patients was enrolled from Asia or Australia compared with MORPHEUS-CRC patients

Efficacy

- Treatment efficacy of atezolizumab + isatuximab vs regorafenib was evaluated by comparing DCR, PFS and OS of the MORPHEUS-CRC experimental arm with the MORPHEUS-CRC control arm, IMblaze370-derived external control arm and hybrid control arm separately (Table 2; Figs. 3 and 4)

Table 2. DCR estimation in the original data sets without weighting

n (%)	IMblaze370	MORPHEUS-CRC	
	EC (n = 28)	Atezo + isa (n = 15)	Regorafenib (n = 13)
DCR[a]	6 (21)	2 (13)	2 (15)
Stable disease[b]	6 (21)	2 (13)	2 (15)
Progressive disease[b]	17 (61)	11 (73)	9 (69)
Responders	0	0	0
Unknown[c]	5 (18)	2 (13)	2 (15)

[a]Criteria for disease control is either response and/or stable disease or better for at least 12 weeks. [b]Patients were classified as achieving stable disease or progressive disease if assessment was at least 12 weeks from randomization. [c]Patients were classified as missing if no post-baseline response at the corresponding assessments were available.

- DCR was higher in the external control arm than the MORPHEUS-CRC control arm (odds ratio [OR], 0.83 [95% CI: 0.20, 1.97]; τ mean = 13.15)

Figure 3. (A) PFS and (B) OS with SMR weighting by treatment arms

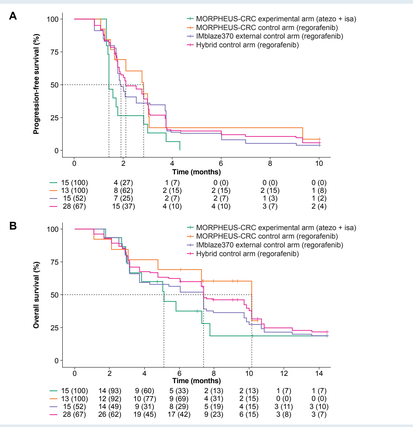


Table 3. Median PFS and OS

Arm	Survival, median (95% CI), mo	
	PFS	OS
MORPHEUS-CRC CC (regorafenib)	2.83 (1.64, NA)	10.15 (4.76, NA)
MORPHEUS-CRC EXP (atezo + isa)	1.41 (1.41, 2.99)	5.13 (3.12, NA)
EC (regorafenib)	1.91 (1.74, 3.75)	7.39 (3.15, 10.71)
HC (regorafenib)	2.10 (1.77, 3.09)	7.39 (4.76, 10.87)

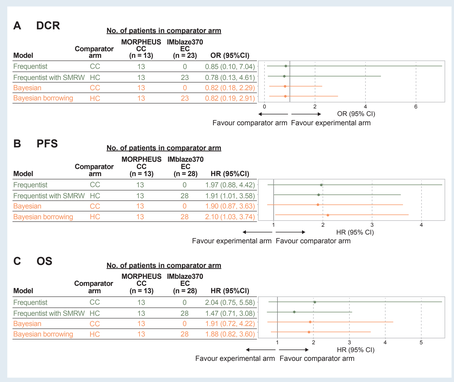
CC, current control; EXP, experimental; HC, hybrid control; NA, not applicable.

- The MORPHEUS-CRC control was comparable to the external control in terms of PFS (hazard ratio [HR], 1.04 [95% CI: 0.67, 1.63]; τ mean = 3.52×10^5) and OS (HR, 1.00 [95% CI: 0.66, 1.38]; τ mean = 7.48×10^5)

DISCUSSION

- The Frequentist approach with SMRW was generally more effective in terms of improving the precision of treatment effect estimates. However, it is more likely to be biased due to residual imbalance of a priori selection of confounding factors or unmeasured confounding factors
- The Bayesian dynamic borrowing method can automatically detect potential dissimilarities and adapt the decision of borrowing based on the estimation of the commensurability parameter. In this study, the application of a weakly informative prior distribution on the commensurability parameter provided an advantage of borrowing at a conservative level to reduce the inflation of type 1 error rate but at the cost of potentially over-attenuating the influence of historical control data on treatment effect estimation
- Due to the small sample size in MORPHEUS-CRC, PS models were unable to accommodate other factors with potential prognostic impact on CRC, such as *RAS* mutation status and tumour sidedness, leading to potential bias in the treatment effect estimates. In consideration of this, we applied a Bayesian method independent of PS adjustment, which counteracts the limitations from the Frequentist models with PS weighting; we also used the Frequentist model to benchmark the prior settings for the Bayesian models
- Despite similar trial populations and randomized designs of IMblaze370 and MORPHEUS-CRC, the 2 trial recruitment periods are different—the historical trial was initiated ≈ 2 years before the current trial, which may introduce some heterogeneity between the 2 control arms. For example, during the 2-year period prior to MORPHEUS-CRC trial initiation, optimisation of regorafenib dosing[11] and better management of toxicities were incorporated into the MORPHEUS-CRC trial, which may have translated into better outcomes in control patients in MORPHEUS compared with those in IMblaze370. This potential source of heterogeneity may not be fully addressed, although by design, any unknown differences between the 2 trials have been embedded in the Bayesian commensurability prior setting
- Definitions of the clinical outcomes varied in terms of response assessment frequencies (6 vs 8 weeks), and this led to missing DCR values in the external control cohort. Such variations exerted minimal effects on PFS and OS as cumulative survival probability distributions between the external control and the current control cohorts were comparable, especially after balancing of the baseline covariates

Figure 4. (A) DCR, (B) PFS and (C) OS of atezolizumab + isatuximab vs regorafenib using MORPHEUS-CRC current control or hybrid control arm



RCT, randomised controlled trial; SMRW, standardised mortality ratio weighting.

- The hybrid control design in the Frequentist framework showed estimates that were comparable to those of the MORPHEUS-CRC current control arm for DCR, PFS and OS, with greater precision (smaller 95% CI range) for all 3 endpoints
- The hybrid control design in the Bayesian framework also showed similar estimates compared with the MORPHEUS-CRC control arm for all 3 efficacy outcomes
  - Precision was improved only for the PFS and OS, indicating a higher degree of commensurability between the external and MORPHEUS-CRC current control arms on PFS and OS (Fig. 3), leading to an effective borrowing of power
  - Precision improvement was not observed for DCR, due to a larger amount of dissimilarity between the external and MORPHEUS-CRC current control arms (Table 2)

CONCLUSIONS

- This proof-of-concept study showed that a hybrid control design using historical trial data from the IMblaze370 clinical trial recapitulated the results obtained with the MORPHEUS-CRC control arm with generally greater precision (i.e., narrower CIs for treatment effect estimates)
- Our work also demonstrated the feasibility of supplementing an internal control arm with data from a historical trial–derived external control arm
- Hybrid control designs could increase trial attractiveness by favouring randomisation to potentially transformative experimental arms, as well as accelerating clinical development
- Therefore, further work is warranted to investigate this approach in other mCRC settings, as well as other cancer indications

REFERENCES

1. Schmidli H, et al. *Clin Pharmacol Ther* 2020;107:806-16.
2. Ghadessi M, et al. *Orphanet J Rare Dis* 2020;15:69.
3. Lim J, et al. *Ther Innov Regul Sci* 2018;52:546-59.
4. Hobbs BP, et al. *Biometrics* 2011;67:1047-56.
5. Zhu M, et al. *Contemp Clin Trials* 2020;94:105856.
6. Desai J, et al. ASCO GI 2021 [abstract 82].
7. Eng C, et al. *Lancet Oncol* 2019;20:849-61.
8. Rosenbaum PR, et al. *Biometrika* 1983;70:41-55.
9. Pocock SJ. *J Chronic Dis* 1976;29:175-88.
10. Stuart EA. *J Clin Epidemiol* 2013;66:S84-90.
11. Bekaii-Saab TS, et al. *Lancet Oncol* 2019;20:1070-82.

DISCLOSURES

- Dr Segal is an advisor for Amgen, AstraZeneca, Bristol Myers Squibb, CStone Pharmaceuticals, F. Hoffmann-La Roche, Genentech, Gritstone Oncology, GSK, Immunocore, PureTech Ventures, Pieris Pharmaceuticals, PsiOxus Therapeutics, Revitope Oncology, Synlogic and TRM Oncology and received research funding from AstraZeneca, Bristol Myers Squibb, F. Hoffmann-La Roche, Genentech, Immunocore, Incyte, Merck and Pfizer.

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https://bit.ly/3bUFyfM
Dr Neil H. Segal: segaln@mskcc.org