Poster MSR75

CORRELATE: Assessing dose effect using targeted maximum likelihood estimation (TMLE)

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BACKGROUND

- CORRELATE (NCT02042144) was a prospective, observational, multicenter study conducted in 13 countries across Europe, Asia and Latin America and funded by Bayer
- The trial recruited patients with mCRC previously treated with approved therapies other than regorafenib, and for whom the decision to treat with regorafenib was made by the treating physician according to the local health authority approved label
- The primary objective was to assess treatment-emergent adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03
- The secondary outcomes included OS and progression-free survival (PFS) with regorafenib in routine clinical practice settings
- The frequency of tumor evaluations was not defined, and assessments were conducted according to the treating physician's routine practice
  - The study sample size was 1037 patients who were treated between 9 April 2014 and 21 July 2017
  - The final analysis cut-off date was December 15, 2017
- In CORRELATE approx. 43% of patients had an initial regorafenib dose lower than the registered 160mg daily, i.e., mainly 120 mg and 80 mg
  - Regardless of the starting dose, many patients had dose adjustments during the treatment
- US and European health care professionals note that in clinical practice:
  - It is not uncommon to start the regorafenib treatment lower than the registered dose[1]
  - Dose adjustments are made during the treatment according to patient's ability to tolerate

Table 1. Initial dose and treatment modification and duration[1]

Variable	160 mg (n=591)	120 mg (n=315)	80 mg (n=127)
Duration of treatment in months Mean(SD)	3.2 (2.9)	3.3 (3.3)	3.2 (3.0)
Dose Reduction n (%)	278(47)	107 (34)	28 (22)
Dose Interruption/delay n (%)	293 (50)	149 (47)	58 (46)
Dose Re-escalation n (%)	40 (7)	59 (19)	61 (48)
Dose Escalation n (%)	0	47 (15)	61 (48)
No Modification	205 (35)	115 (37)	38 (30)
Time to first dose modification in days median (range)	21 (1-403)	26 (1-242)	19 (3-133)

OBJECTIVES

- The objective of this exploratory analysis is to investigate treatment patterns in practice, and statistically compare the efficacy of flexible dosing in an observational study (aka the cohort) with long follow-ups.

METHODS

- Targeted Maximum Likelihood Estimation (TMLE) is a doubly robust approach in analyzing observational data, which allows for the application of a suite of models for estimating a parameter of interest.
- Longitudinal TMLE was used accounting for the time-varying adverse events and treatment to estimate marginal survival of the cohort who would have been treated with lower doses at the beginning and escalated to 160 mg versus if they were treated with 160mg during their entire time.
- Sequence analysis provided insight on the different patterns of treatments in the real world.
- The following baseline factors used for adjustment

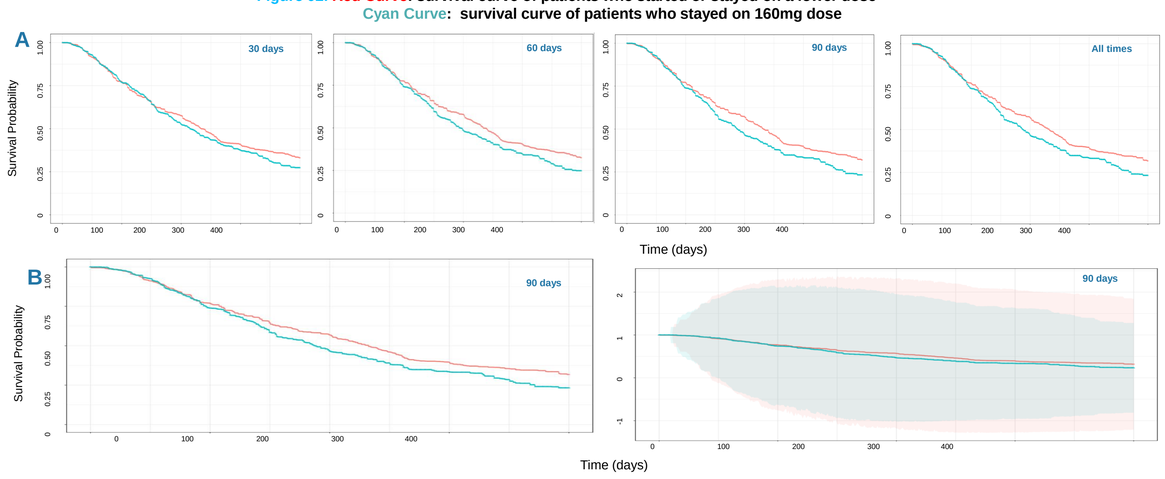
Table 2. Baseline variables for adjustments

Variables	Variables
Starting dose	Baseline EQ5D index score
Number of prior treatments	Primary site of cancer
Baseline BMI	Histology
Time since first metastatic disease to first study treatment	Primary tumor status at start of therapy
Lung only metastasis	Prior Procedures
KRAS mutation	Prior Anti VEGFn therapy
Stage at initial diagnosis	Baseline ECOG 2 categories
Age at the baseline	Gender

RESULTS

- We applied Longitudinal Survival TMLE using glmnet model2, which is a doubly robust method by modeling the outcome and correcting the potential bias using the treatment strategy model, to compare the treatment groups. We observed that the survival curves of the lower dose treated patients regardless of how long they stayed on the lower dose and then escalated or not escalated to the higher dose are not significantly different, as the 95% CI overlap in all cases (B, right, only one case is shown). We noticed, though, the 30 days on a lower dose (A, left, red) survival curve is a bit close to 160 mg fixed survival curve in comparison to other cases (A, left, blue).

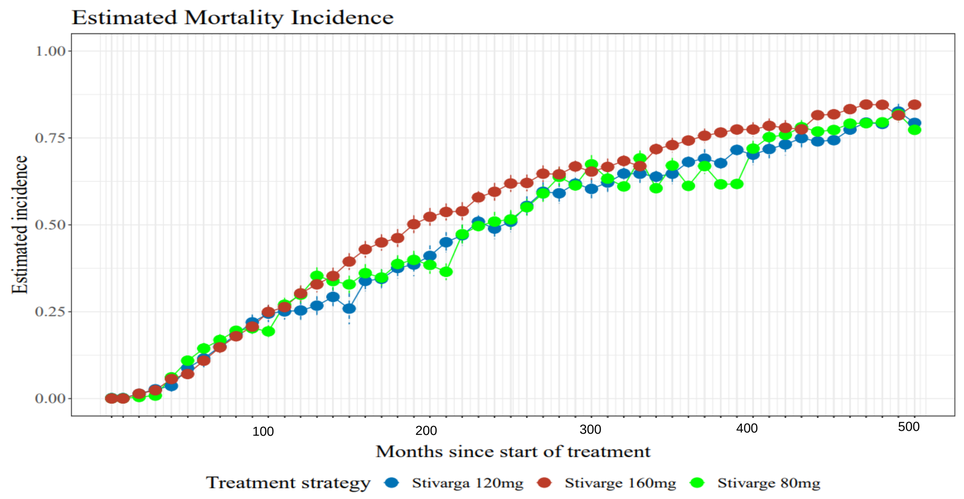
Figure 02. Red Curve: survival curve of patients who started or stayed on a lower dose
Cyan Curve: survival curve of patients who stayed on 160mg dose



RESULTS (CONTINUED)

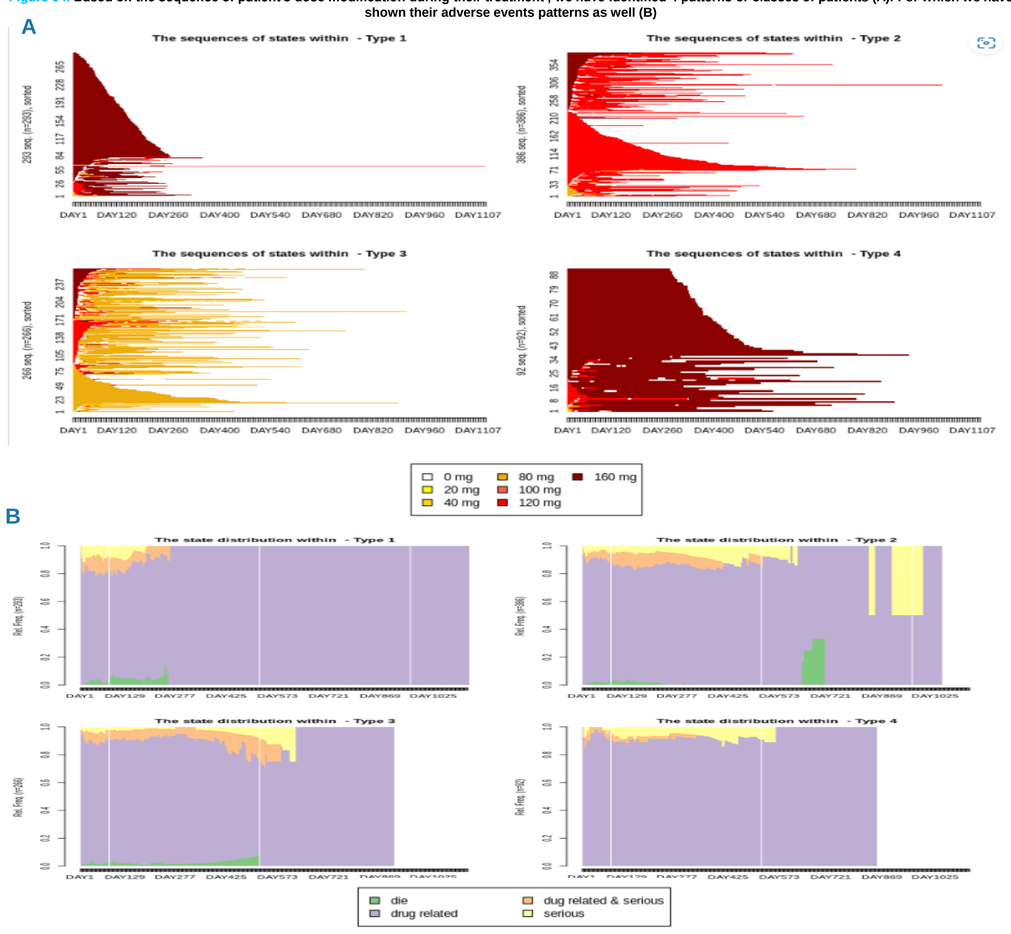
- We also separated different doses by feeding a categorical treatment model using another Longitudinal Survival TMLE package[3], which estimates are the weighted average of glm and random forest models estimates (SuperLearner[4]), to compare the outcomes of the cohort if they would have stayed in different treatment groups for 500 days. The result was very similar to what we observed before.

Figure 03. Red Curve: survival curve of patients who stayed on 160mg dose
Blue Curve: survival curve of patients who stayed on 120mg dose
Green Curve: survival curve of patients who stayed on 80mg dose



- Sequence analysis[5] revealed that most patients that started on 160-mg adjusted to lower doses for a longer time in comparison to those who remained on 160-mg. Among patients started on or shortly adjusted to 160 mg, 293 patients stayed on 160-mg for ~113 days, and 92 of them lasted for ~410 days with no death events for at least 300 days (B, bottom right). While 652 patients started or adjusted to lower dose lasted on lower dose for ~230 days.

Figure 04. Based on the sequence of patient's dose modification during their treatment , we have identified 4 patterns or classes of patients (A). For which we have shown their adverse events patterns as well (B)



SUMMARY

- Using a doubly robust methods (TMLE) to estimate the survival rate among patients in CORRELATE:
  - Estimating patients' outcomes for hypothetical scenarios using the observed Correlate data, we demonstrated that the benefit of flexible dosing (starting with lower dose and switching to 160 mg) has a trend towards a better survival rate, even though it was not statistically significantly than the fixed 160 mg dose.
- Sequence analysis revealed that in practice, most patients that started on 160-mg adjusted to lower doses for a longer time in comparison to 160-mg.
  - Among patients who started on or shortly adjusted to 160-mg, 293 patients stayed on 160-mg for ~113 days, and 92 of them lasted for ~410 days.
  - While 652 patients started or adjusted to lower dose lasted on lower dose for ~230 days.

CONCLUSION

Results of this exploratory analysis are consistent with ReDOS and REARRANGE studies and suggested that using a flexible dose regimen has a comparable survival outcome to treatment with approved dose. For some patients, flexible dose regimen may result in longer time on the treatment.

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