Efficacy of retreatment with anti-EGFRs in mCRC is not predictable by clinical factors related to prior lines of therapy: A multi-institutional analysis.

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Study background and design

- Retrospective analyses and phase II studies suggest that administering an anti-EGFR in advanced lines may be effective in mCRC patients who achieved benefit from a 1st-line anti-EGFR containing regimen.

  Santini et al., Ann Oncol 2012
  Cremolini et al., Jama Oncol 2018

- The identification of clinical features associated with benefit from anti-EGFR re-treatment in patients experiencing PD during 1st-line anti-EGFR (rechallenge) or after its interruption (reintroduction), is a major clinical need.

RECHALLENGE		REINTRODUCTION
Reproposal, after an intervening treatment, of the same therapy to which tumor has already proved to be resistant	≠	Reproposal of a treatment that was interrupted when the disease had not progressed

Patients and Methods

Demographics and disease characteristics

Characteristic. % patients	N=86
Sex (M / F)	63 / 37
Median Age (range)	64 (20 – 82)
ECOG PS (0 / 1-2 / NA)	53 / 37 / 10
Synchronous Metastases (Y / N)	66 / 34
Prior Adjuvant CT (Y / N)	26 / 74
Primary Tumor Site (right / left / rectum)	23 / 64 / 13
Number Metastatic Sites (1 / >1/ NA)	27 / 72 / 1
Resected Primary (Y / N)	88 / 12
Rechallenge / Reintroduction	65 / 35
Median N° lines before re-tx (range)	1 (1 - 7)

Clinical Outcomes

ORR	19.8 %
DCR	46.5 %
mPFS	3.8 mos
mOS	10.2 mos

Patients and Methods

A real-life data-base including a total of 5530 patients treated at 6 institutions from December 2010 to October 2018 was queried.
Patients were

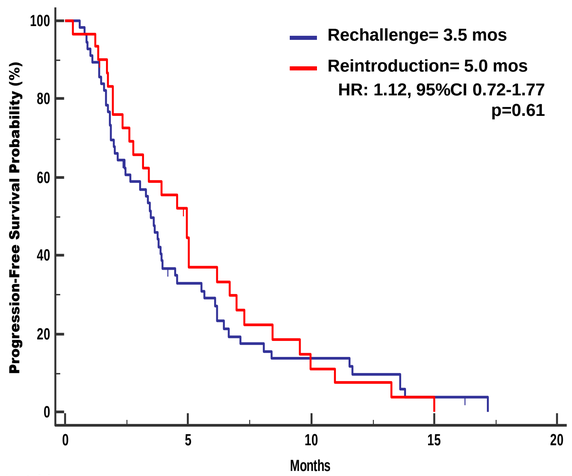
- Retreated with anti-EGFRs, with
- *RAS*/*BRAF* wild-type status on tissue samples
- Had received a 1st-line anti-EGFR-based treatment
- At least SD as best response,
- At least one further line of therapy before anti-EGFR re-treatment, were included.

The association with RECIST response (RR), PFS and OS was investigated for the following variables:

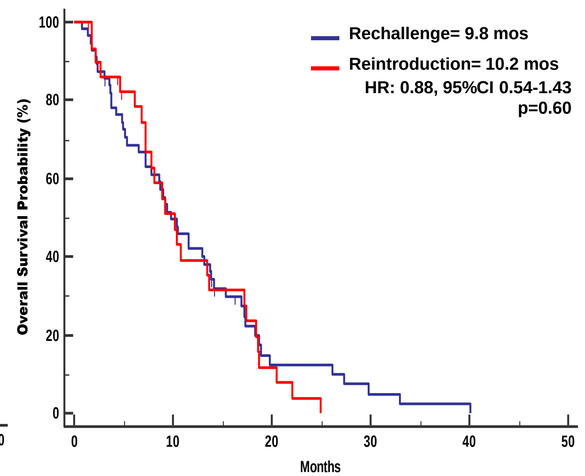
- 1st line Response Rate (PR or CR vs SD or PD)
- PFS during 1st-line;
- Time from the last anti-EGFR administration to 1st-line PD (i.e. reintroduction vs rechallenge);
- Reason for anti-EGFR discontinuation in 1st-line (PD vs. other);
- Number of anti-EGFR-free lines of therapy before re-treatment;
- Anti-EGFR free interval (time between the last anti-EGFR administration in 1st-line and the time of re-treatment);
- Primary tumor side;
- Time from the diagnosis of metastatic disease to re-treatment (≥ vs. < 18 months).

Results

Progression-Free Survival



Overall Survival



Results

Characteristics, % patients	N=86	RR OR [95% CI]	RR p	PFS HR [95% CI]	PFS p	OS HR [95% CI]	OS p
1° line Response Rate (CR-RP / SD-PD)	92 / 8	1.68 [0.19-15.0]	0.64	0.72 [0.29-1.75]	0.40	1.53 [0.75-3.09]	0.28
1° line PFS (≥ vs. < 12 months)	47 / 53	0.98 [0.33-2.86]	0.97	0.86 [0.53-1.43]	0.55	0.89 [0.57-1.40]	0.62
Time last anti-EGFR to 1° PD (Reintroduction/ Rechallenge)	35 / 65	1.17 [0.38-3.62]	0.78	0.89 [0.56-1.39]	0.61	1.13 [0.70-1.84]	0.60
Reason for discontinuation (PD / Other)	65 / 35	0.66 [0.22-2.00]	0.46	1.31 [0.84-2.04]	0.23	0.99 [0.62-1.60]	0.99
N° anti-EGFR free lines before re-tx (1 / >1)	71 / 29	0.41 [0.13-1.27]	0.12	0.86 [0.53-1.43]	0.55	1.10 [0.67-1.80]	0.71
Anti-EGFR Free Interval (≥ vs.< 15 months)	50 / 50	3.42 [0.98-10.87]	0.061	0.94 [0.61-1.46]	0.79	0.860 [0.54-1.35]	0.50
Primary Tumor side (left / right)	23 / 77	0.69 [0.21-2.28]	0.54	0.79 [0.46-1.34]	0.33	0.50 [0.26-0.93]	0.0052
Time from diagnosis of mCRC to re-tx (≥ vs. < 18 months)	77 / 23	2.77 [0.57-13.41]	0.21	0.98 [0.58-1.64]	0.93	0.60 [0.32-1.13]	0.054

Conclusions

Clinical factors that are generally believed to affect the efficacy of anti-EGFR re-treatments are not confirmed in our series. Therefore, clinicians should not rely on those characteristics in their decision-making on anti-EGFR re-treatment, and adequate studies for implementing liquid biopsy in clinical practice are urgently needed.

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