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Original Research

Impact of early tumor shrinkage and depth of response on the outcomes of panitumumab-based maintenance in patients with *RAS* wild-type metastatic colorectal cancer

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Abstract ***Background:*** In patients with metastatic colorectal cancer (mCRC) receiving highly active first-line combination treatments, early tumor shrinkage (ETS) and depth of response (DoR) are associated with survival, but their influence on outcomes during maintenance therapy is unknown. The *Valentino* study showed inferior PFS in 229 *RAS* wild-type mCRC patients randomized to panitumumab plus FOLFOX followed by maintenance with panitumumab vs. panitumumab + 5-FU/LV.

Patients and methods: After blinded independent central review of ETS (≥20% reduction of the sum of target lesions) and DoR in patients enrolled in *Valentino*, the prognostic and predictive role of such parameters was investigated, along with their combination with PRESSING panel (uncommon genomic alterations associated with anti-EGFRs resistance beyond *RAS* and *BRAF*).

Results: One hundred and ninety-six patients were included (ETS in 132 [67.3%], median DoR: 44.1%). Both ETS and DoR ≥34% were associated with longer mPFS ($p = 0.010$ and $p < 0.001$) and mOS ($p = 0.006$ and $p < 0.001$). The PFS benefit of 5-FU/LV added to panitumumab maintenance, reported in the study, was independent from ETS and DoR status (interaction tests NS for both PFS and OS). However, outcomes were extremely poor in patients who received single-agent panitumumab and had no-ETS (mPFS and mOS: 7.7 and 18.7 months) or DoR < 34% (mPFS and mOS: 6.5 and 18 months). Combining PRESSING panel ('molecular hyperselection') and response dynamics allowed to stratify both PFS ($p < 0.001$ and $p < 0.001$ for ETS and DoR, respectively) and OS ($p < 0.001$ and $p = 0.017$ for ETS and DoR, respectively).

Conclusions: ETS and DoR allow on-treatment anticipation of outcomes following an anti-EGFR-based strategy planning de-escalation, and poor radiological response may guide enrolment in crossover strategy trials. As *in vivo* markers of drug sensitivity, ETS and DoR may be integrated with several patient- and tumor-related factors to wisely drive decision-making on upfront treatment duration and intensity.

1. Introduction

Regarding the upfront treatment of patients with metastatic colorectal cancer (mCRC), novel radiological parameters were investigated with the aim to implement RECIST-defined response metrics and to measure longitudinal changes in tumour burden in terms of rapidity (e.g., early tumor shrinkage [ETS], time-to-response, time-to-tumour growth) and magnitude (e.g., depth of response [DoR]) [1–3]. The clinical importance of ETS and DoR stems from their significant correlation with survival outcomes, as an optimal cytoreduction after first-line induction therapy may positively impact the subsequent disease course and increase the chance of postprogression exposure to a continuum of effective options [3]. The optimal choice of upfront therapy is therefore of paramount importance, independently from the conversion intent to secondary resection of metastases or from the urgent need to palliate the symptoms related to high disease burden. Noteworthy, both FOLFOXIRI plus bevacizumab and doublets plus anti-EGFR agents (the latter regimens in patients with *RAS* wild-type mCRC) are highly active first-line regimens with maximal effects on ETS and DoR, which may translate in clinically meaningful increase of post-progression survival (PPS) and overall survival (OS). In particular, FOLFOXIRI plus bevacizumab was able to achieve higher percentage of ETS and better DoR as compared to doublet chemotherapy plus bevacizumab [4], and the same results were achieved by doublets plus anti-EGFRs compared to chemotherapy alone or with bevacizumab in *(K)RAS* wild-type subgroup [2,5].

Noteworthy, available evidence suggests that both ETS and DoR are useful and strong on-treatment prognostic parameters, but they are not predictive of the efficacy of a specific treatment regimen with regard to either chemotherapy intensity or the class of monoclonal antibody [4,5]. Therefore, despite the likely association of ETS and DoR with enhanced tumor sensitivity to the chosen combination treatment, their implementation in the clinical practice has been limited by the lack of clinical trials testing the modification of treatment strategy upon evidence of poor radiological response.

Regarding maintenance therapy of patients with mCRC, bevacizumab plus 5-FU/LV is regarded as the optimal choice after bevacizumab-based induction regimens for its significant effect on PFS [6]. Even though the role of anti-EGFR-based maintenance therapies is less established, the *Valentino* trial suggested that patients randomized to 4-month induction therapy with

Table 1
Baseline characteristics in the overall population, and according to treatment response parameters of early tumor shrinkage (as a continuous variable and according to the −20% literature cutoff) and depth of response (as a continuous variable).

		Total	ETS n (%)	No ETS n (%)	p[a]	Median ETS, % reduction (IQR)	p[b]	Median DoR, % reduction (IQR)	p[b]
Age, median (IQR)	<70	147 (75.0)	101 (68.7)	46 (31.3)	0.598	32 (44–15)	0.255	45 (56–23)	0.307
	≥70	49 (25.0)	31 (63.3)	18 (36.7)		28 (38–13)		42 (54–25)	
Sex	Female	133 (67.9)	85 (63.9)	48 (36.1)	0.184	33 (18–49)	0.167	45 (22–67)	0.236
	Male	63 (32.1)	47 (74.6)	16 (25.4)		29 (13–40)		43 (24–53)	
ECOG PS	0	144 (73.5)	97 (67.4)	47 (32.6)	1	30 (14–42)	0.943	45 (29–56)	0.164
	1	52 (26.5)	35 (67.3)	17 (32.7)		31 (15–44)		41 (15–54)	
Prior adjuvant therapy	No	160 (84.7)	108 (67.5)	52 (32.5)	1	31 (15–44)	0.215	45 (24–59)	0.021
	Yes	29 (15.3)	19 (65.5)	10 (34.5)		26 (2–38)		36 (22–44)	
Liver-limited disease	No	127 (64.8)	78 (61.4)	49 (38.6)	0.025	26 (11–40)	0.011	40 (20–52)	<0.001
	Yes	69 (35.2)	54 (78.3)	15 (21.7)		35 (24–44)		51 (40–62)	
Metastases timing	Metachronous	149 (76.0)	106 (71.1)	43 (28.9)	0.066	25 (4–38)	0.024	41 (18–53)	0.048
	Synchronous	47 (24.0)	26 (55.3)	21 (44.7)		32 (16–44)		45 (27–60)	
No of metastatic sites	>1	103 (52.6)	70 (68.0)	33 (32.0)	0.968	26 (15–40)	0.38	41 (22–52)	0.044
	1	93 (47.4)	62 (66.7)	31 (33.3)		32 (12–44)		47 (27–61)	
Primary tumor sidedness	Left	167 (85.2)	115 (68.9)	52 (31.1)	0.384	31 (16–43)	0.459	44 (25–56)	0.399
	Right	29 (14.8)	17 (58.6)	12 (41.4)		26 (3–42)		41 (17–54)	
BRAF status	Wild-type	189 (96.4)	130 (68.8)	59 (31.2)	0.069	31 (16–43)	0.007	45 (24–56)	0.056
	Mutated	7 (3.6)	2 (28.6)	5 (71.4)		7 (0–19)		25 (20–37)	
Pressing status[c]	Negative	137 (76.1)	97 (70.8)	40 (29.2)	0.173	45 (30–56)	0.27	32 (17–44)	0.049
	Positive	43 (23.9)	25 (58.1)	18 (41.9)		41 (18–55)		24 (4–37)	
Arm	Pani + FU/LV	101 (51.5)	67 (66.3)	34 (33.7)	0.874	29 (14–41)	0.427	41 (22–53)	0.211
	Pani	95 (48.5)	65 (68.4)	30 (31.6)		33 (14–45)		46 (24–58)	

List of abbreviations: DoR, depth of response; ETS, early tumor shrinkage; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; PS, performance status; pani, panitumumab.
[a] χ^2 test.
[b] Mann–Whitney test.
[c] Pressing panel encloses molecular characterization of *HER2* and *MET* amplifications, *ALK, ROS1, NTRK1/2/3* and *RET* fusions, *PIK3CA (exon 20)/PTEN/AKT1* mutations, *RAS* mutations with low mutant allele fraction and microsatellite instability.

panitumumab plus FOLFOX followed by maintenance with single-agent panitumumab may achieve inferior PFS compared to those receiving the same induction followed by panitumumab plus 5-FU/LV [7]. Here we conducted a post-hoc analysis of the *Valentino* study, aimed at investigating the prognostic and predictive impact of centrally reviewed ETS and DoR in patients with *RAS* wild-type mCRC randomized to the two panitumumab-based maintenance strategies.

2. Methods

2.1. Study population

The *Valentino* study (NCT02476045) was a multicenter, randomized, open-label, phase 2 trial that investigated the progression-free survival (PFS) noninferiority of maintenance with single-agent panitumumab (arm B) versus panitumumab plus 5-FU/LV (arm A) following an induction treatment with panitumumab plus FOLFOX-4 in patients with *RAS* wild-type mCRC [7]. The trial enrolled 229 (arm A/B: 117/112) patients; main inclusion and exclusion criteria are reported in the Supplemental material (study protocol). CT (or MRI) scans were performed at baseline and every 8 weeks during treatment (independently from delays of treatment cycles) until disease progression, unacceptable toxicity, consent withdrawal or death. Tumor response dynamics were assessed according to RECIST v1.1 criteria.

For this exploratory analysis, we included all randomized patients with measurable disease and at least one post-baseline radiological disease re-assessment. CT scans were centrally collected at the Coordinating Center and submitted to blinded independent central review (BICR) to assess RECIST response, ETS and DoR. Extended molecular data beyond *RAS* and *BRAF* mutational status—including *HER2*/*MET* amplifications, gene fusions, *PIK3CA*/*PTEN* mutations, *RAS* mutations with low mutant allele fraction and microsatellite instability (MSI)—were previously reported [8] and available for the present study population.

Institutional review board and ethics committee's approval was obtained from all participating centers. All the patients provided written informed consent before any study-related procedures.

2.2. Assessment of radiological parameters and tumor response dynamics

For the assessment of ETS and DoR, the longest diameters of the RECIST-defined target lesions were measured and summed for each assessment. According to the literature, ETS was defined as a categorical variable based on either the presence or absence of a 20% or more reduction in the sum of the longest tumor diameters of lesions followed according to RECIST 1.1 criteria at the first tumor assessment after baseline (week 8). DoR was defined as the smallest of the sum of target lesions diameters (compared with baseline), as previously described [4,5].

2.3. Statistical analysis

Progression-free survival (PFS) was defined as the interval from randomization to first objective documentation of progressive disease (PD) or death from any cause, whichever occurred first (censoring at last follow-up for patients alive and without PD). OS was the interval from randomization to death from any cause (censoring at last follow-up for patients alive).

Interquartile ranges were used to report distribution of continuous variables. Confidence intervals were calculated at a 95% level. Chi-squared and Fisher tests were used—depending on samples numerosity—to test the distribution of categorical data. Mann–Whitney U test was used for the comparisons of continuous,

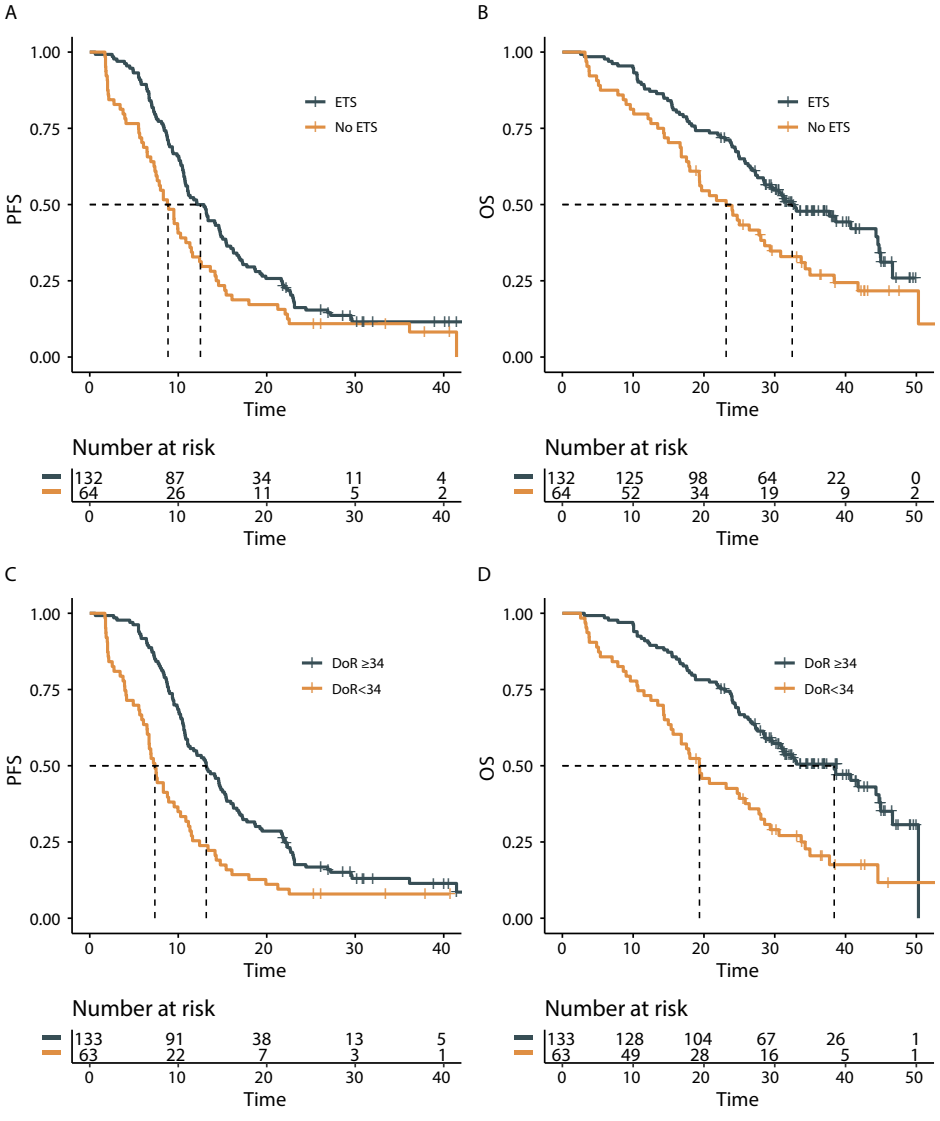

Fig. 1. Prognostic analysis according to ETS and DoR. This figure depicts the Kaplan-Meier curves for progression-free survival and overall survival in patients stratified according to ETS (present or absent in blue and orange, respectively) in panels A and B; DoR status (≥ or <34% cutoff in blue and orange, respectively) in panels C and D. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Predictive analyses according to the randomly allocated treatment arm and early tumor shrinkage or depth of response (34% optimal cutoff).

	Arm A	Arm B	HR (95% CI)	*p*	Arm A	Arm B	HR (95% CI)	*p*	Interaction *p*
ETS status	ETS				No ETS				
Median PFS, months (95% CI)	13.2 (11.1–17.8)	11.1 (10.1–15)	1.07 (0.74–1.54)	0.720	9.5 (8–15.2)	7.7 (5.5–10.9)	1.57 (0.93–2.66)	0.091	0.175
Median OS, months (95% CI)	30.6 (26.5–45)	33.1 (28.4-NA)	0.92 (0.58–1.46)	0.723	24.7 (20.8-NA)	18.7 (15–35)	1.37 (0.77–2.43)	0.287	0.308
DoR status	DoR ≥ 34%				DoR < 34%				
Median PFS, months (95% CI)	14.6 (12.1–18.7)	11.4 (10.3–15.4)	1.15 (0.8–1.66)	0.447	8 (6.9–13.4)	6.5 (4.1–10)	1.43 (0.85–2.41)	0.175	0.335
Median OS, months (95% CI)	38.6 (28.6–NA)	33.1 (28.4–NA)	1.10 (0.69–1.75)	0.702	19.7 (15.6–28.6)	18 (14.4–35)	0.95 (0.54–1.69)	0.872	0.601

List of abbreviations: ETS, early tumor shrinkage; DoR, depth of response; HR, hazard ratio; CI, confidence interval.

nonparametric data. Univariate and multivariate cox regressions were used to model right-censored variables; features with a $p < 0.1$ in the univariate analyses were used to build the multivariate models. Interaction terms were used to investigate the interplay between multiple predictors. Optimal cutoffs for right-censored variables prediction were calculated using maximization of log-rank statistics. Data were imported and handled in R v 3.6.1 (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria), using ggplot2, maxstat, dplyr, survminer, survival and finalfit packages.

3. Results

3.1. Baseline characteristics

A total number of 196 patients out of the 229 (86%) enrolled in the *Valentino* study were eligible for this analysis. The patients' flow chart is illustrated in Supplementary Fig. 1. Overall, 51.5% and 48.5% patients were treated in arm A and B, respectively. Patients with ETS were 132 (67.3%), with median value of 30.2% (IQR: 14.0-42-6). Median DoR was 44.1% (IQR: 22.9–56.1%). Expectedly, ETS and DoR were significantly associated: patients experiencing ETS had significantly higher median DoR compared to patients without ETS (51.1% vs. 14.4% $p < 0.001$). Baseline cohort characteristics are reported in Table 1 along with corresponding ETS status and median ETS and DoR. No significant associations were observed between baseline characteristics and radiological parameters, except for higher ETS and DoR in patients with liver-limited disease, lower ETS in *BRAF* mutated subgroup and lower DoR in patients exposed to prior adjuvant therapy. Supplementary Fig. 2 shows the waterfall plots of ETS values (panel A) and DoR (panel B) according to the allocated maintenance arm. In details, median ETS was 29% versus 33% in arm A and B, respectively (p = 0.427; Supplementary Fig. 3A), whereas median DoR was 41% versus 46% in arm A and B, respectively ($p = 0.211$; Supplementary Fig. 3B).

At the time of this analysis (cutoff 01 February 2020), the median follow-up was 36.9 months (95% CI: 35.8–41.4). A total number of 175 disease progressions and 122 deaths occurred. Supplementary Fig. 4A and B depict, respectively, the PFS (median: 11.0 months) and OS (median: 28.6 months; 3-year OS: 40.9%) curves in the overall study population.

3.2. Prognostic analyses according to radiological parameters

ETS was associated with a longer PFS (mPFS: 12.5 vs. 8.8 months; HR = 0.66, 95% CI: 0.48–0.91; $p = 0.010$; Fig. 1A), as well as OS (mOS: 32.5 vs. 23.1 months; HR = 0.60, 95% CI: 0.41–0.86; $p = 0.006$; Fig. 1B). Supplementary Fig. 5A–C show the swimmer plot for PFS, PPS and OS according to the ETS status.

Next, using maximization of log-rank statistics, we identified 33.3% and 34.7% as the best DoR cutoffs for the prediction of PFS and OS, respectively; we thus selected the approximated mean (34%) for survival analyses. In detail, DoR ≥34% was associated with a longer PFS (mPFS: 13.1 vs. 7.4 months; HR = 0.51, 95% CI: 0.37–0.70; $p < 0.001$; Fig. 1C), as well as OS (mOS: 38.4 vs. 19.4 months; HR = 0.44, 95% CI: 0.31–0.64; $p < 0.001$; Fig. 1D); Supplementary Fig. 5D–F show the swimmer plot for PFS, PPS and OS according to the DoR status. Supplementary Table 1 shows the results of univariate and multivariate cox

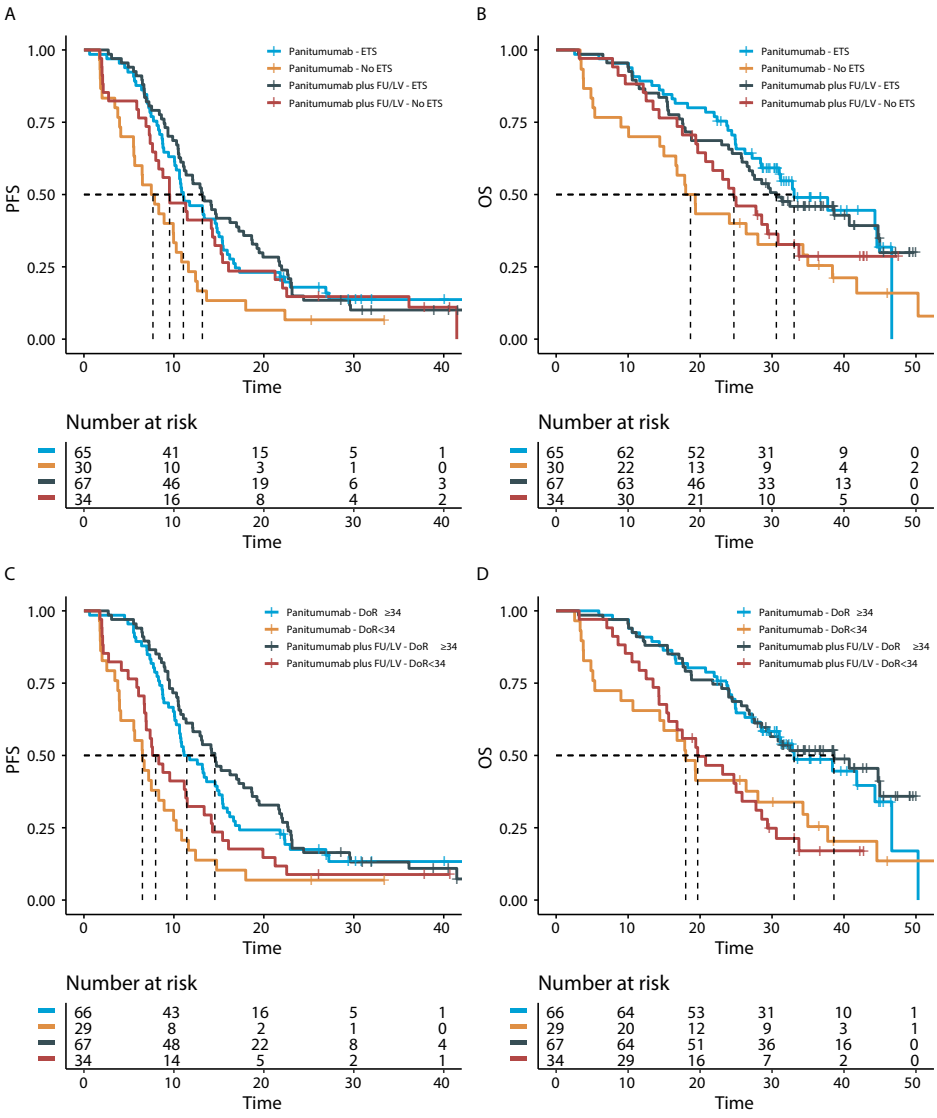

Fig. 2. Predictive analysis according to ETS and DoR. This figure illustrates the Kaplan-Meier curves for progression-free survival and overall survival in patients stratified according to the two different maintenance treatment arms and ETS status in panels A and B, or DoR status (≥ or <34% cu-off) in panels C and D.

models for PFS and OS: DoR, but not ETS, was independently associated with both PFS (HR = 2.08, 95% CI: 1.32–3.28; $p = 0.002$) and OS (HR = 3.07, 1.82–5.18; $p < 0.001$).

3.3. Predictive analyses according to radiological parameters

Results on the predictive role of ETS and DoR according to the two treatment arms are summarized in Table 2. ETS was not significantly associated with differential effect of the two maintenance arms in terms of PFS and OS (p for interaction = 0.175 and 0.308, respectively), although survival outcomes were extremely poor in patients without ETS and randomized to maintenance treatment with panitumumab alone (Fig. 2A and B). Similar results were observed regarding the predictive effect of DoR for both PFS and OS (p for interaction = 0.335 and 0.601, respectively); consistently, the PFS outcome was clearly unsatisfactory in patients with DoR < 34% and randomized to panitumumab alone, whereas OS outcomes were mostly driven by DoR status and not by treatment arm (Fig. 2C and D).

3.4. Interplay between radiological parameters and molecular hyperselection

We investigated the association between combined subgroups based on radiological parameters (ETS or

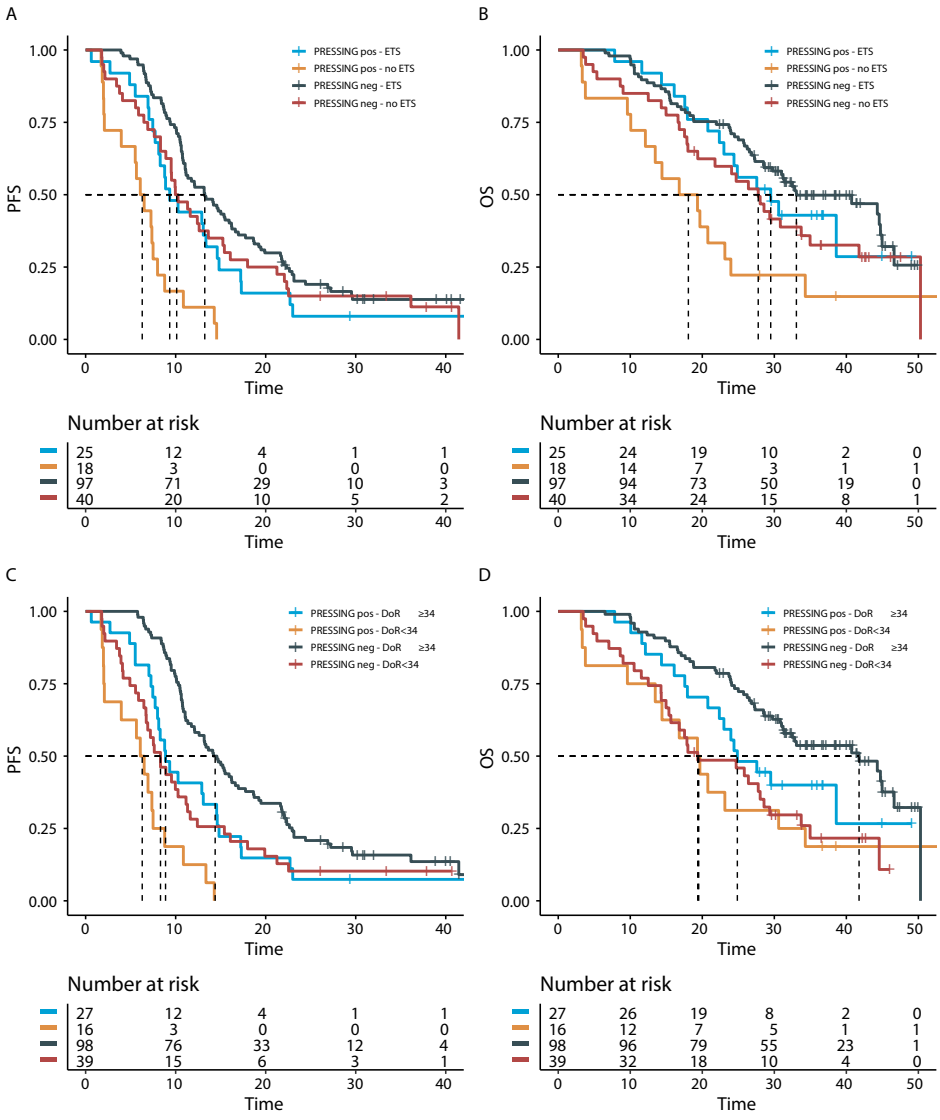

Fig. 3. Prognostic analyses according to the combined assessment of ETS or DoR plus PRESSING panel extended molecular profile. This figure illustrates the Kaplan-Meier curves for progression-free survival and overall survival in patients stratified according to the ETS status in panels A and B, or DoR status (≥ or <34% cutoff) in panels C and D.

DoR) and PRESSING panel, which previously allowed us the baseline prediction of efficacy of EGFR inhibition based on the combination of several uncommon biomarkers of primary resistance to targeted therapy [8,9].

Despite not being associated with ETS, a negative PRESSING panel was associated with a higher DoR ($p = 0.049$; Table 1). As shown in Fig. 3 and Table 3, the combination of response dynamics and molecular hyperselection allowed to stratify both PFS (panels A, C) and OS (panels B, D) and to achieve the maximal mPFS (13.2 and 14.4 months) and mOS (33.1 and 41.8 months) in patients with PRESSING panel negative tumors associated with ETS and DoR ≥ 34%, respectively.

4. Discussion

According to a previously proposed model of tumor dynamics during first-line therapy of patients with mCRC [3], ETS allows the early assessment of treatment sensitivity and it is clearly associated with DoR, which in turn may influence both PPS and OS. Even though the surrogacy of both ETS and DoR for OS has not been established yet [10], both radiological parameters consistently showed their prognostic role in patients with mCRC receiving upfront treatment, with particular regard to highly active regimens such as FOLFOXIRI plus bevacizumab or doublets plus anti-EGFR monoclonal antibodies. Here we confirmed such prognostic role of ETS and DoR in a molecularly selected *RAS*

Table 3
Combined assessment of ETS or DoR with PRESSING panel[a] molecular status and its association with progression-free survival and overall survival based on Cox univariate models.

	n (%)	Progression-free survival (PFS)			Overall survival (OS)		
ETS Subgroups		mPFS (95%CI)	HR	*p*	mOS (95%CI)	HR	*p*
ETS/PRESSING neg	97 (54%)	13.2 (11.1–16.2)	*Ref*	<0.001	33.1 (29.8–46.6)	*Ref*	0.017
ETS/PRESSING pos	25 (14%)	9.3 (8.1–14.8)	1.55		29.5 (23–NA)	1.2	
no ETS/PRESSING neg	40 (22%)	10.1 (8.9–15.4)	1.33		27.8 (19.4–41.8)	1.49	
no ETS/PRESSING pos	18 (10%)	6.3 (4–8.8)	4.78		18.1 (12.1–34.3)	2.67	
DoR Subgroups		mPFS (95%CI)	HR	*p*	mOS (95%CI)	HR	p
DoR ≥ 34%/PRESSING neg	98 (54%)	14.4 (12.1–17)	*ref*	<0.001	41.8 (31.2–NA)	*ref*	<0.001
DoR ≥ 34%/PRESSING pos	27 (15%)	8.9 (8–14.6)	1.76		24.9 (22.4–NA)	1.58	
DoR < 34%/PRESSING neg	39 (22%)	8.3 (6.7–11.3)	1.9		19.4 (15.6–29.4)	2.38	
DoR < 34%/PRESSING pos	16 (9%)	6.3 (2.1–10.9)	5.16		19.5 (13.5–NA)	2.48	

List of abbreviations: DoR, depth of response; ETS, early tumor shrinkage; HR, hazard ratio; CI, confidence interval.
[a] Pressing panel encloses molecular characterization of *HER2* and *MET* amplifications, *ALK, ROS1, NTRK1/2/3* and *RET* fusions, *PIK3CA (exon 20)/PTEN/AKT1* mutations, *RAS* mutations with low mutant allele fraction and microsatellite instability.

wild-type mCRC population, as previously reported [5]. The novelty of our data relies on the association of modern radiological parameters with the patients' outcomes after panitumumab-based maintenance treatment. Of note, phase 3 trials on the role of bevacizumab-based maintenance therapy enrolled patients who achieved disease control after a 4/6-month induction administered prior to randomization. Therefore, ETS and DoR were neither prospectively collected nor retrospectively reviewed in previously reported maintenance trials. Conversely, the *Valentino* study randomized eligible patients prior to induction treatment, and such a trial design provided the unique opportunity to investigate the impact of ETS and DoR, assessed by BICR during the study treatment, on the long-term efficacy of panitumumab-based maintenance therapy. Interestingly, patients randomized to maintenance therapy with panitumumab alone and with no-ETS or poorer DoR showed extremely unsatisfactory PFS and, limitedly to the absence of ETS, such suboptimal maintenance therapy was also associated with poor OS. Therefore, our results highlight that fluoropyrimidine-based maintenance therapy may be useful to rescue early treatment failures in the subgroup of patients with primary resistance (or relatively lower sensitivity) to anti-EGFR therapy, as potentially anticipated by unfavorable tumor dynamics. However, it is crucial to highlight that the PFS benefit of adding 5-FU/LV in the maintenance phase is independent from response dynamics and the continuation of fluoropyrimidine-based therapy until disease progression may be beneficial also in the subgroup of patients with initial treatment sensitivity, also thanks to the delay of acquired resistance to EGFR inhibition.

The key importance of ETS lies in its rapid availability at 6/8 weeks, which makes it capable to anticipate both PFS and OS and thus to guide the decision making on optimal first-line treatment duration and de-escalation strategies. Importantly, ETS may be adopted by future trials as an early eligibility criterion to select patients eligible for de-escalation or 'stop&go' strategies with available or investigational options.

Finally, we recently showed that the assessment of a panel of rare and multiple genomic drivers of primary resistance to anti-EGFRs (PRESSING panel) was significantly associated with outcomes in the subgroup of patients with *RAS* and *BRAF* wild-type mCRC enrolled in the *Valentino* study [7,8]. However, even after such a molecular hyperselection, a non-negligible subset of patients may show relatively poor outcomes after upfront anti-EGFR-based treatment due to nongenomic stromal resistance, specific gene expression profiles, transcriptional regulation mechanisms or relatively faster selection of pre-existing resistant tumor subclones—being all of these mechanisms are still far from clinical availability and validation [11,12]. Given that radiological response dynamics are immediately available for physicians, here we showed the nonoverlapping effects of both molecular hyperselection and modern radiological parameters, which can be used in combination to identify subgroups of patients with significantly different outcomes. Although PRESSING panel status was not associated with ETS, but only with DoR (partly because of the low number of patients and the confounding effects of the association of chemotherapy to panitumumab), the combined assessment of independent variables may be of value, as previously shown for ETS and anti-EGFR-related skin toxicity [13].

The present study has some clear limitations. Subgroup analyses—which are inherently limited—were conducted only in the trial patients with measurable disease and were not preplanned. Both ETS and DoR are not baseline variables and DoR is time-dependent, thus challenging their clinical usefulness for the choice of upfront therapy. Moreover, our optimized cutoff of DoR will need prospective validation to prove its

efficacy in PFS and OS prediction. Finally, patients with disease progression during induction treatment and thus not receiving the planned maintenance strategy were included in the intention-to-treat population of the *Valentino* study and subsequent post-hoc analyses including the present one. However, the percentage of such patients was perfectly balanced in the two maintenance arms [7], and the ETS and DoR outcomes in the *Valentino* study were in line with the hallmark study in the literature [5].

In conclusion, we showed that ETS and DoR may be useful and readily available radiological parameters that may be integrated with several other patient- and tumor-related factors to personalize the treatment strategy and the continuum of care of individual patients with mCRC.

Author contribution

Paolo Manca, Salvatore Corallo, Maria Di Bartolomeo, Filippo de Braud, Giuseppina Calareso, Federica Morano, Filippo Pietrantonio: conception and design, data interpretation and analysis. All authors: data acquisition and analysis, manuscript writing and final approval.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Declaration of interests: FP has received honoraria for speaker activities and participation in advisory boards from Sanofi, Amgen, Bayer, Merck-Serono, Lilly, Roche, Servier, and research grants from BMS. SL has received honoraria for speaker activities and participation in advisory boards from Amgen, Bayer, Merck-Serono, Roche, Servier, Bristol-Myers Squibb. CC has received honoraria for speaker activities and participation in advisory boards from Roche, Amgen, Bayer, Servier, Merck-Serono and research grants from Merck Serono. LR has received honoraria for speaker activities and participation in advisory boards from AstraZeneca, AbbVie, Amgen, ArQule, Basilea, Bayer, Celgene, Eisai, Exelixis, Gilead, Hengrui Therapeutics, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Nerviano Medical Sciences, Roche, Sanofi, and research grants to her Institution from Agios, ARMO BioSciences, AstraZeneca, BeiGene, Eisai, Lilly, Exelixis, FibroGen, Incyte, Ipsen, Merck Sharp & Dohme. AZ has received honoraria for speaker activities and participation in advisory boards from Sanofi, Amgen, Bayer, Merck-Serono, Roche. PR has received honoraria for speaker activities and participation in advisory boards from Servier, Amgen, Roche and Merck. MDB has received honoraria for speaker activities and participation in advisory boards from Amgen, Roche, Lilly, Servier, MSD. FM has received honoraria for speaker activities from Servier. FDB has received honoraria for speaker activities and participation in advisory boards from Amgen, Roche, Novartis, Incyte, Celgene. All other authors declared no disclosures.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.11.017.

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References

[1] Claret L, Girard P, Hoff PM, et al. Model-based prediction of phase III overall survival in colorectal cancer on the basis of phase II tumor dynamics. J Clin Oncol 2009;27:4103–8.

[2] Piessevaux H, Buyse M, Schlichting M, et al. Use of early tumor shrinkage to predict long-term outcome in metastatic colorectal cancer treated with cetuximab. J Clin Oncol 2013;31:3764–75.

[3] Heinemann V, Stintzing S, Modest DP, et al. Early tumour shrinkage (ETS) and depth of response (DpR) in the treatment of patients with metastatic colorectal cancer (mCRC). Eur J Canc 2015;51:1927–36.

[4] Cremolini C, Loupakis F, Antoniotti C, et al. Early tumor shrinkage and depth of response predict long-term outcome in metastatic colorectal cancer patients treated with first-line chemotherapy plus bevacizumab: results from phase III TRIBE trial by the Gruppo Oncologico del Nord ovest. Ann Oncol 2015; 26:1188–94.

[5] Stintzing S, Modest DP, Rossius L, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. Lancet Oncol 2016;17:1426–34.

[6] Yoshino T, Arnold D, Taniguchi H, et al. Pan-asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol 2018;29: 44–70.

[7] Pietrantonio F, Morano F, Corallo S, et al. Maintenance therapy with panitumumab alone vs panitumumab plus fluorouracil-leucovorin in patients with RAS wild-type metastatic colorectal cancer: a phase 2 randomized clinical trial. JAMA Oncol 2019;5: 1268–75.

[8] Morano F, Corallo S, Lonardi S, et al. Negative hyperselection of patients with RAS and BRAF wild-type metastatic colorectal cancer who received panitumumab-based maintenance therapy. J Clin Oncol 2019;37:3099–110.

[9] Cremolini C, Morano F, Moretto R, et al. Negative hyperselection of metastatic colorectal cancer patients for anti-EGFR monoclonal antibodies: the PRESSING case-control study. Ann Oncol 2017;28:3009–14.

[10] Petrelli F, Pietrantonio F, Cremolini C, et al. Early tumour shrinkage as a prognostic factor and surrogate end-point in colorectal cancer: a systematic review and pooled-analysis. Eur J Canc 2015 May;51:800–7.

[11] Woolston A, Khan K, Spain G, et al. Genomic and transcriptomic determinants of therapy resistance and immune landscape evolution during anti-EGFR treatment in colorectal cancer. Canc Cell 2019;36:35–50.

[12] Pietrantonio F, Vernieri C, Siravegna G, et al. Heterogeneity of acquired resistance to anti-EGFR monoclonal antibodies in patients with metastatic colorectal cancer. Clin Canc Res 2017;23: 2414–22.

[13] Holch JW, Held S, Stintzing S, et al. Relation of cetuximab-induced skin toxicity and early tumor shrinkage in metastatic colorectal cancer patients: results of the randomized phase 3 trial FIRE-3 (AIO KRK0306). Ann Oncol 2020;31:72–8.