ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN CANCER HORIZONS

ORIGINAL RESEARCH

Impact of age and gender on the efficacy and safety of upfront therapy with panitumumab plus FOLFOX followed by panitumumab-based maintenance: a pre-specified subgroup analysis of the Valentino study

A. Raimondi[1†], G. Fucà[1†], A. G. Leone[1], S. Lonardi[2], C. Antoniotti[3], V. Smiroldo[4], A. Amatu[5], M. Tampellini[6], G. Ritorto[7], R. Murialdo[8], M. Clavarezza[9], A. Zaniboni[10], R. Berenato[11], M. Ratti[12], S. Corallo[1], F. Morano[1], M. Di Bartolomeo[1], M. Di Maio[13] & F. Pietrantonio[1*]

[1]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [2]Medical Oncology Unit 3, Department of Oncology, Istituto Oncologico Veneto—IRCCS, Padua; [3]Unit of Medical Oncology, Azienda Ospedaliero-Universitaria Pisana, Pisa; [4]Medical Oncology and Hematology Unit, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Rozzano; [5]Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Milan; [6]Department of Oncology, AOU San Luigi di Orbassano, University of Torino, Orbassano; [7]SSD ColoRectal Cancer Unit, Oncology Department, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza, Torino; [8]Department of Internal Medicine, University of Genoa and IRCCS AOU San Martino-IST, Genoa; [9]Medical Oncology Unit, Ente Ospedaliero Ospedali Galliera, Genoa; [10]Medical Oncology Unit, Fondazione Poliambulanza, Brescia; [11]Medical Oncology Unit, A.O. Papardo, Messina; [12]Medical Oncology Unit, ASST Ospedale di Cremona, Cremona; [13]Department of Oncology, University of Turin, Ordine Mauriziano Hospital, Torino, Italy

Available online 17 August 2021

Background: The safety and efficacy outcome of elderly metastatic colorectal cancer (mCRC) patients fit enough to receive combination chemotherapy plus biological agents is an issue of growing interest. Also, gender-specific differential toxicity and efficacy of anti-epidermal growth factor receptor (EGFR)-based upfront treatments need to be explored.

Patients and methods: Valentino was a multicenter, randomized, phase II trial, investigating two panitumumab-based maintenance strategies following first-line panitumumab plus FOLFOX in *RAS* wild-type mCRC patients. We carried out a subgroup analysis, aimed at assessing the differences in efficacy, safety and quality of life (QoL) according to age ($<$70 versus $\geq$70 years) and gender (male versus female). Efficacy endpoints were progression-free survival (PFS), overall survival (OS) and overall response rate (ORR); safety endpoints were rates of any grade and grade 3/4 adverse events (AEs).

Results: No significant differences in terms of PFS, OS and ORR were observed between patients aged $<$70 or $\geq$70 years and the effect of the maintenance treatment arm on survival outcomes was similar in the two subgroups. The safety profile of both induction and maintenance treatment and the impact on QoL were similar in elderly and younger patients. No significant differences in PFS, OS, ORR or clinical benefit rate were observed according to gender. A significantly higher rate of overall grade 3/4 AEs ($P = 0.008$) and of grade 3/4 thrombocytopenia ($P = 0.017$), any grade and grade 3/4 neutropenia ($P < 0.0001$) and any grade conjunctivitis ($P = 0.033$) was reported in female as compared to male patients. Conversely, we reported a significantly higher incidence of any grade skin rash ($P = 0.0007$) and hypomagnesemia ($P = 0.029$) in male patients.

Conclusions: The upfront choice of an anti-EGFR-based doublet chemotherapy followed by a maintenance strategy represents a valuable option in *RAS* wild-type mCRC irrespective of gender and age, though a careful evaluation of patients to maximize the risk/benefit ratio is warranted.

Key words: colorectal cancer, metastasis, age, gender, anti-EGFR

INTRODUCTION

In patients with *RAS* and *BRAF* wild-type metastatic colorectal cancer (mCRC), the upfront combination of doublet chemotherapy with the anti-epidermal growth factor receptor (anti-EGFR) agents cetuximab or panitumumab is regarded as a valuable option and it is recommended by all major guidelines.[1] However, limited evidence-based data are available on the optimal duration of anti-EGFR-based

*Correspondence to: Dr Filippo Pietrantonio, Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, via Giacomo Venezian 1, 20133 Milan, Italy. Tel: +39-02-23903807; Fax: +39-0223902149
E-mail: filippo.pietrantonio@istitutotumori.mi.it (F. Pietrantonio).

† Both authors are considered co-first authors.

first-line regimens and the role of maintenance therapy in this setting.[2-5]

Several retrospective data and non-randomized trials showed the efficacy and manageable toxicity profile of anti-EGFR monotherapy in frail elderly patients deemed unfit for chemotherapy, whereas capecitabine plus bevacizumab is an evidence-based option independent from the molecular profile.[6] When focusing on elderly patients eligible for combination chemotherapy, it must be pointed out that the geriatric population was clearly under-represented in first-line trials, although CRC is predominantly diagnosed in older adults. Thus, the generalizability of trial results to the overall population of patients with mCRC is an open question. On top of this, subgroup analyses of pivotal trials, such as CRYSTAL and PRIME, often adopted the age cut-off of 65 years because of the limited numerosity of patients aged $\geq$70 years.[7,8] Finally, the safety of anti-EGFR-based maintenance strategies in the elderly population is still unknown.

Only few retrospective data are currently available about the toxicity profiles and outcomes of standard systemic regimens in mCRC according to patients' gender. Specifically, females with different solid tumors suffer from a higher incidence of chemotherapy-related adverse events (AEs),[9-11] but the impact of gender differences on efficacy and toxicity of upfront anti-EGFR-based therapy is another paramount issue with limited available data.[12]

In this study, we investigated the impact of age and gender on the safety and efficacy of upfront therapy with panitumumab plus FOLFOX followed by panitumumab-based maintenance in patients with *RAS* wild-type mCRC enrolled in the Valentino study.[13]

PATIENTS AND METHODS

Study design and trial population

The Valentino study (NCT02476045) was a multicenter, randomized, open-label, phase II trial designed to investigate the non-inferiority in terms of progression-free survival (PFS) of maintenance with single-agent panitumumab (arm B) versus panitumumab plus 5-fluorouracil/leucovorin (5-FU/LV) (arm A) after a 4-month induction with panitumumab plus FOLFOX-4 in patients affected by *RAS* wild-type mCRC as a first-line treatment. The results of the trial demonstrated that maintenance with single-agent panitumumab was inferior to panitumumab plus 5-FU/LV, although endowed with a slightly reduced toxicity burden.[13]

The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice. Institutional review board and ethics committee approval was obtained from all participating centers. All patients provided written informed consent before any study-related procedures.

Age and gender subgroup analysis

We carried out a subgroup analysis of the trial, aimed at assessing the differences in terms of efficacy, safety and quality of life (QoL) according to age ($<$70 versus $\geq$70 years) and gender (male versus female).

The trial enrolled 229 (arm A/B: 117/112) patients. For the present analysis, we included all randomized patients in the efficacy dataset, whereas only patients who received at least one dose of study treatment were included in the safety dataset. The outcome measures of the efficacy endpoint were PFS, overall survival (OS) and response rate according to RECIST v1.1, while those of the safety endpoint were the rates of occurrence of any grade and grade 3/4 overall and singular AEs in patients stratified according to age and gender in the intention-to-treat and per-protocol population overall or per treatment arm. Extended molecular data beyond *RAS* and *BRAF* mutational status—the 'PRESSING panel'—were retrospectively assessed as previously reported.[14] QoL was assessed through patient-reported outcomes (PROs) via questionnaires [European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30), and the colorectal cancer-specific module (EORTC QLQ-CR29) and EuroQol-5D], as previously described.[15] For this secondary analysis, only results of the QLQ-C30 are described.

Statistical analysis

PFS was defined as the time from randomization to disease progression or death from any cause. OS was defined as the time from randomization to death from any cause. In the absence of events, PFS and OS times were censored at the last date when patients were known to be alive. To examine differences between groups, the chi-square test or Fisher's exact test was used for categorical variables, as appropriate, whereas the non-parametric Kruskal—Wallis test was used for continuous variables. To summarize continuous variables, median value with the corresponding range and/or interquartile range (IQR) was provided. The reverse Kaplan—Meier method was used for follow-up time assessment. The Kaplan—Meier method and Cox proportional hazards regression were used for survival analysis. Hazard ratio (HR) with the corresponding 95% confidence interval (CI) was provided for the Cox proportional hazards regression analyses. For the analysis of the global QoL measured by EORTC QLQ-C30, mean changes from baseline to each of the planned timepoints were reported for each subgroup. A positive value represents an improvement for global health status. For comparison between age and gender subgroups at each timepoint, differences from baseline scores were compared by a multivariable linear regression model, using baseline values and study treatment arm as covariates.

The threshold for statistical significance was set to a *P* value of 0.05 and all statistical tests were two-sided. Statistical analyses were carried out using the R software (version 3.5.0; https://www.r-project.org) and the 'survival', 'survminer' and 'dplyr' packages. QoL analysis was carried out using SPSS (version 27.0; IBM Corp., Armonk, NY).

RESULTS

Patients' characteristics

All the 229 patients randomized in the Valentino study were included in the present analysis. Patients' characteristics according to age and gender are illustrated in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100246. Overall, 169 and 60 patients were <70 and ≥70 years of age and 152 and 77 were male and female, respectively. Elderly patients underwent more frequently primary tumor resection ($P = 0.013$) and had more frequently a right-sided primary tumor ($P = 0.010$). No significant associations were observed between gender and the other clinico-pathological characteristics considered.

Efficacy analysis according to age

Median follow-up time was 48.2 months (IQR: 41.4-54.2 months). A total of 205 PFS events and 158 OS events were recorded, for a median PFS of 10.7 months (95% CI 9.9-12.4 months) and a median OS of 27.8 months (95% CI 24.8-32.5 months) in the overall population. No differences were observed for elderly patients compared with younger patients in terms of PFS (median PFS: 10.8 months, 95% CI 9.9-13.0 months, versus 10.7 months, 95% CI 8.8-14.8 months; HR: 1.03, 95% CI: 0.76-1.41; $P = 0.834$) (Figure 1A) and OS (median OS: 25.6 months, 95% CI 20.6-37.4 months, versus 29.1 months, 95% CI 25.2-34.6 months; HR: 1.22, 95% CI 0.87-1.73; $P = 0.248$) (Figure 1B). The effect of the treatment arm on the survival outcomes was similar in elderly patients compared with younger patients (Figure 1C and D). Since we observed that elderly patients had more frequently a right-sided primary tumor, we additionally investigated the survival outcomes according to age in the subgroup of patients with left-sided and PRESSING negative status, i.e. with 'EGFR-dependent' tumors. Similarly to what was observed in the entire population, no significant differences between elderly and younger patients were identified (Supplementary Figure S1A and B, available at https://doi.org/10.1016/j.esmoop.2021.100246). To investigate the contribution of the post-progression treatments to OS according to age, we analyzed the number of subsequent lines of systemic therapy and the post-progression agents received according to age. No difference in terms of the number of subsequent lines received was observed in elderly patients compared with younger patients (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100246), whereas elderly patients less frequently received investigational agents in the post-progression setting ($P = 0.035$) (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100246).

No significant difference in terms of overall response rate (ORR) or clinical benefit rate was observed according to age (Table 1).

Efficacy analysis according to gender

When looking at gender, no difference in terms of PFS and OS was observed for male patients (median PFS: 11.1 months, 95% CI 9.5-13.6 months; median OS: 28.1 months, 95% CI 23.8-34.0 months) compared with female patients (median PFS: 10.4 months, 95% CI 8.3-13.2 months; median OS: 27.8 months, 95% CI 24.8-38.9 months; HR for PFS: 1.03, 95% CI 0.76-1.41; $P = 0.834$; HR for OS: 0.99, 95% CI 0.71-1.38; $P = 0.944$) (Figure 2A and B). The effect of the treatment arm on the survival outcomes was similar in male and female patients (Figure 2C and D). No significant differences in terms of ORR or clinical benefit rate were observed according to gender (Table 1).

Safety analysis according to age

In the safety analysis dataset of 226 patients, a total of 167 (74%) and 59 (26%) patients were included in the <70- and ≥70-year age subgroups, respectively. Considering the overall occurrence of treatment-related AEs, during induction and/or maintenance treatment phases, no statistically significant differences were reported in terms of occurrence of overall or specific AEs, of both any grade and grade 3/4 AEs between the two subpopulations (Table 2). In the overall per-protocol population of patients entering the maintenance phase, accounting for 125 and 39 patients <70 and ≥70 years of age, respectively, no significant differences were shown neither for overall any grade and grade 3/4 AEs nor for all the singular AEs assessed (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2021.100246). In the analysis divided per treatment arm, both in arm A (panitumumab plus 5-FU/LV) and arm B (panitumumab), no statistically significant differences were obtained for overall and specific AEs according to age (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2021.100246). Regarding dose intensity, no differences with statistical significance were reported between patients <70 and ≥70 years of age in terms of dose delays and dose reductions overall and during maintenance phase, specifically for what concerns panitumumab and 5-FU/LV (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2021.100246).

Safety analysis according to gender

In the safety analysis dataset, a total of 150 (66%) and 76 (34%) patients were male and female, respectively. Considering the overall occurrence of treatment-related AEs, during induction and/or maintenance treatment phases, no statistically significant differences were reported in terms of occurrence of overall or specific any grade AEs in male and female patients, whereas a significantly increased rate of overall grade 3/4 AEs was shown in female patients (male versus female 65% versus 83%, $P = 0.008$). For the incidence of specific AEs, a statistically significant higher rate of grade 3/4 thrombocytopenia (male versus female 1% versus 7%, $P = 0.017$), any grade and grade 3/4 neutropenia (male versus female 29% versus 63%, $P < 0.0001$ and 15% versus 47%, $P < 0.0001$) and any grade conjunctivitis (male versus female 15% versus 28%, $P = 0.033$) was reported in female patients. On the other hand, a statistically significant increased incidence of any grade skin rash (male versus

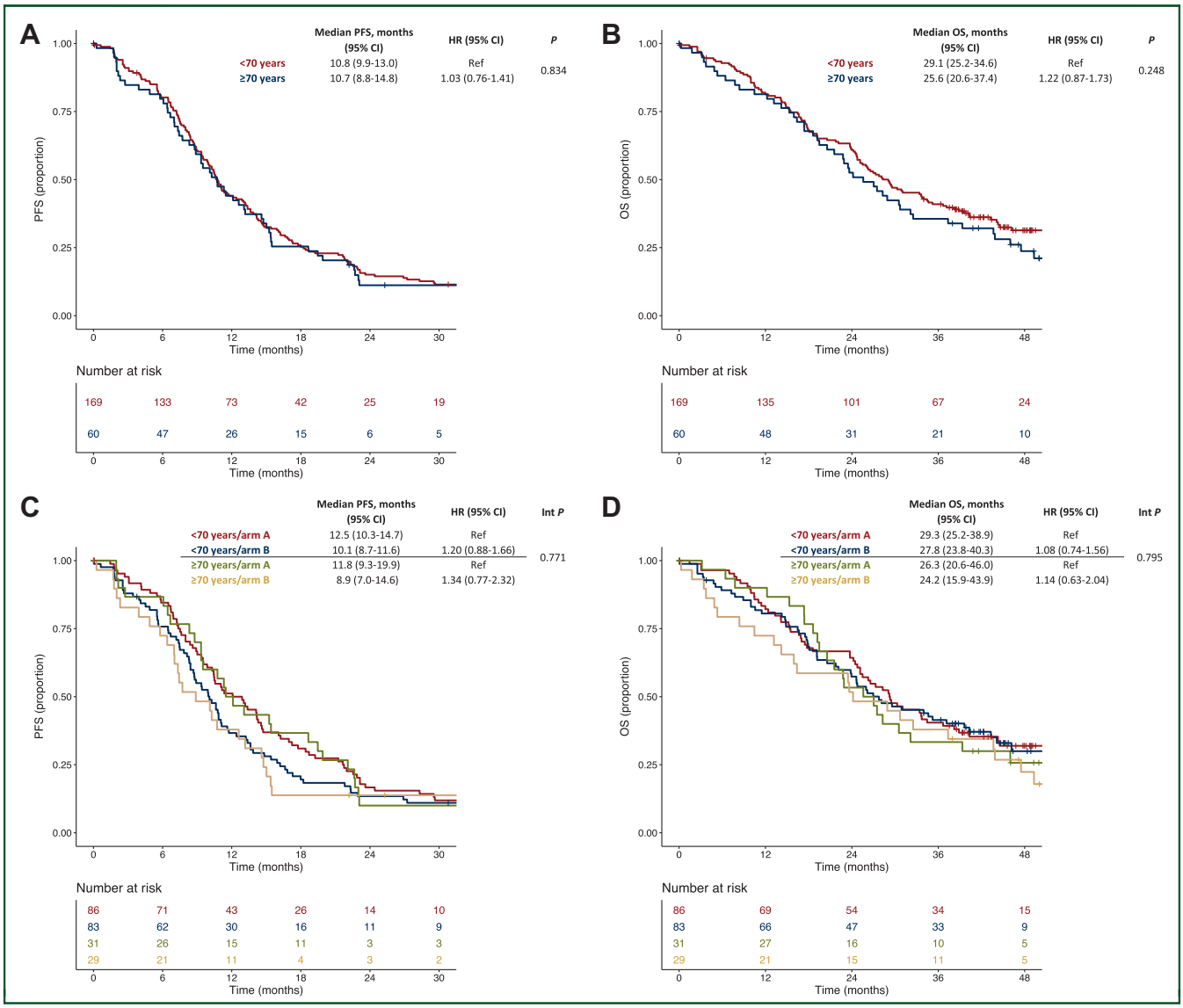

Figure 1. Survival analysis according to age.
This figure depicts the Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) in patients stratified according to age (<70 and ≥70 years) in panels A and B and in patients stratified according to age and treatment arm (<70 years arm A, <70 years arm B, ≥70 years arm A and ≥70 years arm B) in panels C and D, respectively.
CI, confidence interval; HR, hazard ratio.

Table 1. Radiological best response according to age and gender

RECIST response	Age <70 years (n = 150)	Age ≥70 years (n = 55)	P value	Female (n = 65)	Male (n = 140)	P value
	n (%)	n (%)		n (%)	n (%)	
Best response			0.092			0.531
PD	7 (4.7)	7 (12.7)		5 (7.7)	9 (6.4)	
SD	32 (21.3)	6 (10.9)		11 (16.9)	27 (19.3)	
PR	103 (68.7)	38 (69.1)		43 (66.2)	98 (70.0)	
CR	8 (5.3)	4 (7.3)		6 (9.2)	6 (4.3)	
Overall response			0.730			0.866
No	39 (26.0)	13 (23.6)		16 (24.6)	36 (25.7)	
Yes	111 (74.0)	42 (76.4)		49 (75.4)	104 (74.3)	
Clinical benefit			0.059			0.769
No	7 (4.7)	7 (12.7)		5 (7.7)	9 (6.4)	
Yes	143 (95.3)	48 (87.3)		60 (92.3)	131 (93.6)	

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

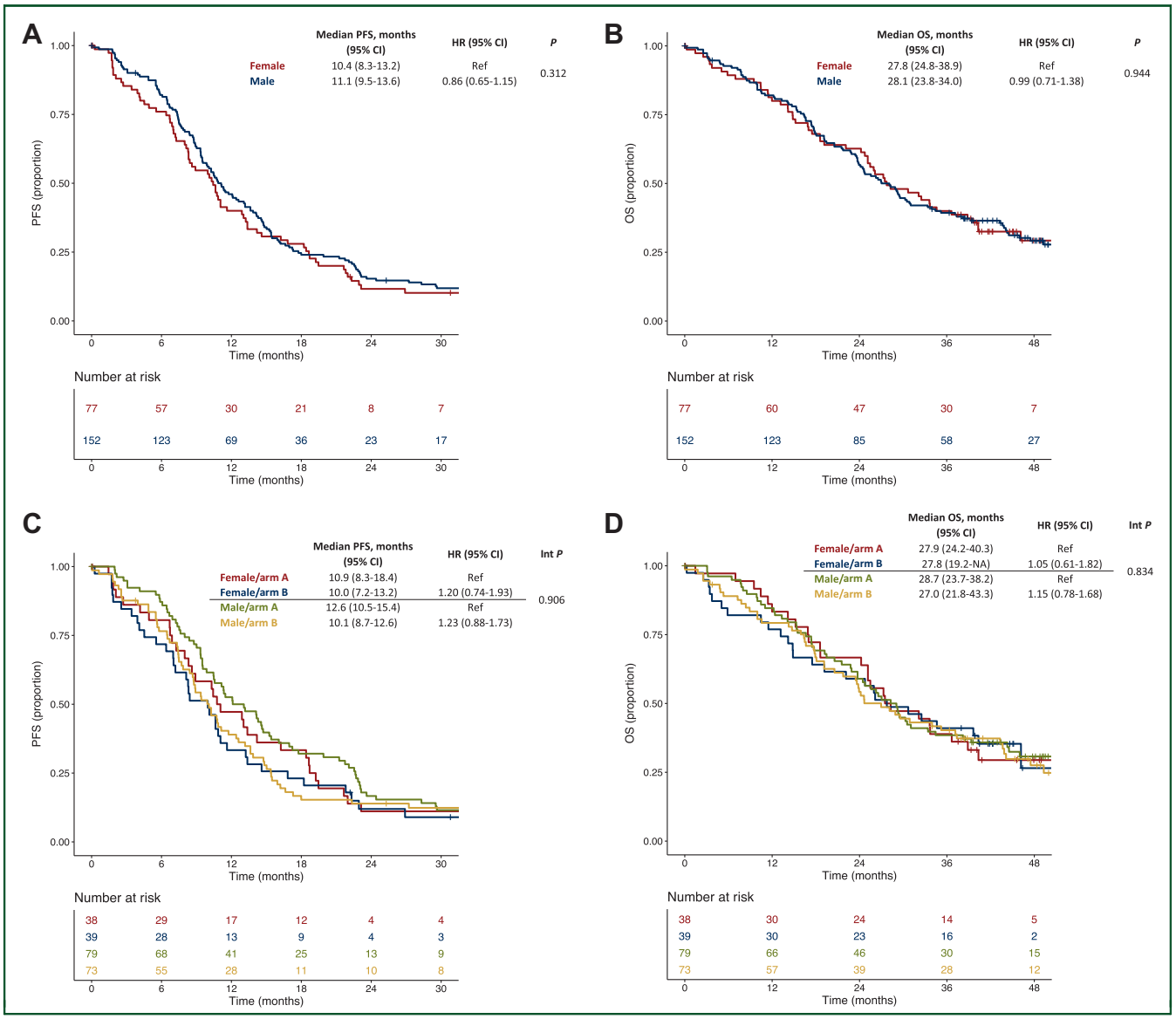

Figure 2. Survival analysis according to gender.
This figure depicts the Kaplan—Meier curves for progression-free survival (PFS) and overall survival (OS) in patients stratified according to gender (female and male) in panels A and B and in patients stratified according to gender and treatment arm (female arm A, female arm B, male arm A and male arm B) in panels C and D, respectively.
CI, confidence interval; HR, hazard ratio.

female 91% versus 72%, $P = 0.0007$) and any grade hypomagnesemia (male versus female 43% versus 28%, $P = 0.029$) and a non-significant trend for higher occurrence of any grade panitumumab-related AEs (male versus female 93% versus 84%, $P = 0.062$) were shown in male patients (Table 3). In the overall per-protocol population of patients starting the maintenance phase, accounting for 112 and 52 male and female patients, respectively, no significant differences were shown for overall or specific AEs, of both any grade and grade 3/4, except for an increased rate of any grade conjunctivitis in female patients (male versus female 7% versus 27%, $P = 0.001$) (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2021.100246), and a consistent result was obtained in the analysis divided per treatment arm (Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2021.100246).

Regarding dose intensity, no differences with statistical significance were reported between male and female patients in terms of dose delays and dose reductions overall and during maintenance phase, specifically for what concerns panitumumab and 5-FU/LV (Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2021.100246).

Quality-of-life analysis according to age and gender

Out of the 229 patients enrolled and randomized in the trial, a total of 210 patients completed the QLQ-C30 questionnaire at baseline and were considered for the PRO analyses: 156/169 (92.3%) among patients aged <70 years, 54/60 (90.0%) among patients aged ≥70 years, 137/152 (90.1%) among males and 73/77 (94.8%) among females. Compliance progressively decreased at the following

Table 2. Association between overall toxicity (induction + maintenance) and age

	Any grade AEs *n* (%)			Grade 3/4 AEs *n* (%)		
	<70 years *n* = 167	≥70 years *n* = 59	*P* value	<70 years *n* = 167	≥70 years *n* = 59	*P* value
Overall	165 (99)	57 (97)	0.280	120 (72)	41 (69)	0.740
Stomatitis/oral mucositis	73 (44)	25 (42)	0.880	14 (8)	5 (8)	1.000
Nausea	59 (35)	18 (31)	0.523	3 (2)	2 (3)	0.608
Vomiting	30 (18)	10 (17)	1.000	2 (1)	1 (2)	1.000
Diarrhea	86 (51)	32 (54)	0.763	21 (13)	9 (15)	0.656
Hand–foot syndrome	37 (22)	10 (17)	0.459	4 (2)	1 (2)	1.000
Peripheral neuropathy	65 (39)	19 (32)	0.434	6 (4)	1 (2)	0.680
Anemia	30 (18)	8 (14)	0.545	4 (2)	0	0.575
Thrombocytopenia	40 (24)	10 (17)	0.362	5 (3)	1 (2)	1.000
Neutropenia	72 (43)	20 (34)	0.281	46 (28)	11 (19)	0.223
Fatigue	72 (43)	27 (46)	0.761	6 (4)	5 (8)	0.160
Panitumumab-related AE	150 (90)	53 (90)	1.000	64 (38)	23 (39)	1.000
Skin rash	142 (85)	49 (83)	0.682	44 (26)	16 (27)	1.000
Paronychia	29 (17)	8 (14)	0.547	3 (2)	4 (7)	0.078
Hypomagnesemia	59 (35)	27 (46)	0.164	4 (2)	1 (2)	1.000
Conjunctivitis	33 (20)	11 (19)	1.000	2 (1)	1 (2)	1.000

AE, adverse event.

timepoints. There were no significant differences between age groups, or between gender groups, in baseline scores for global QoL, functional scales and symptoms. In detail, mean score (standard deviation) for global QoL at baseline was 66.29 (20.22) for patients aged <70 years versus 66.36 (19.69) for patients aged ≥70 years ($P = 0.952$); 65.33 (18.91) for males versus 68.15 (22.02) for females ($P = 0.238$). The only baseline significant difference was in the emotional functioning, favoring patients aged ≥70 years; further details are shown in Supplementary Tables S10 and S11, available at https://doi.org/10.1016/j.esmoop.2021.100246. During the treatment, at the pre-defined timepoints of 8, 16, 24, 32 and 40 weeks and at disease progression, no significant differences in terms of mean changes versus baseline of global QoL were found between the two age groups (Supplementary Figure S2A, available at https://doi.org/10.1016/j.esmoop.2021.100246) and between males and females (Supplementary Figure S2B, available at https://doi.org/10.1016/j.esmoop.2021.100246).

DISCUSSION

The topic of the optimal therapeutic management of elderly patients with mCRC gained increasing importance given the continuous rise of the average age of the population. Specifically, the safety and efficacy outcome of elderly patients fit enough to receive combination chemotherapy plus biological agents is an issue of growing interest.[16-18]

In this subgroup analysis of the Valentino study, no significant differences for efficacy in terms of PFS, OS, clinical

Table 3. Association between overall toxicity (induction + maintenance) and gender

	Any grade AEs *n* (%)			Grade 3/4 AEs *n* (%)		
	Male *n* = 150	Female *n* = 76	*P* value	Male *n* = 150	Female *n* = 76	*P* value
Overall	148 (99)	74 (97)	0.604	98 (65)	63 (83)	**0.008**
Stomatitis/oral mucositis	66 (44)	32 (42)	0.887	14 (9)	5 (7)	0.615
Nausea	47 (31)	30 (39)	0.237	5 (3)	0	0.170
Vomiting	23 (15)	17 (22)	0.201	2 (1)	1 (1)	1.000
Diarrhea	80 (53)	38 (50)	0.674	17 (11)	13 (17)	0.299
Hand–foot syndrome	27 (18)	20 (26)	0.166	3 (2)	2 (3)	1.000
Peripheral neuropathy	57 (38)	27 (36)	0.772	4 (3)	3 (4)	0.692
Anemia	23 (15)	15 (20)	0.453	3 (2)	1 (1)	1.000
Thrombocytopenia	36 (24)	14 (18)	0.398	1 (1)	5 (7)	**0.017**
Neutropenia	44 (29)	48 (63)	**<0.0001**	22 (15)	36 (47)	**<0.0001**
Fatigue	69 (46)	30 (39)	0.396	7 (5)	4 (5)	1.000
Panitumumab-related AE	139 (93)	64 (84)	0.062	61 (41)	26 (34)	0.387
Skin rash	136 (91)	55 (72)	**0.0007**	44 (29)	16 (21)	0.205
Paronychia	27 (18)	10 (13)	0.447	2 (1)	1 (1)	1.000
Hypomagnesemia	65 (43)	21 (28)	**0.029**	4 (3)	1 (1)	0.666
Conjunctivitis	23 (15)	21 (28)	**0.033**	1 (1)	2 (3)	0.262

Statistically significant values are indicated in bold.
AE, adverse event.

benefit and response rate were observed between patients aged <70 or ≥70 years and the effect of the maintenance treatment arm on the survival outcomes was similar in the two age subgroups. Moreover, the safety profile of both induction and maintenance treatment, as well as the impact on QoL, was similar in elderly and younger patients, with no clinically meaningful or statistically significant differences. Finally, no significant differences in dose intensity, in terms of dose delays or reductions, were reported, as well as no differences for post-progression treatments between the two age groups. Nevertheless, we acknowledge the possible impact of the imbalances in two putative prognostic factors between the subpopulations, even though with potentially opposite prognostic effect, since elderly patients had received more frequently a primary tumor resection and had more often a right-sided primary tumor.

These results are in line with the available literature data. Specifically, in the pivotal first-line CRYSTAL and PRIME trials, the efficacy and safety of doublets plus cetuximab or panitumumab were similar in trial-eligible patients with *RAS* wild-type disease and age ≥65 years versus younger patients.[7,8,19,20] In the CRYSTAL study, only 26 patients had age ≥70 years, thus subgroup analyses were not conducted by using this age cut-off, whereas in the PRIME study patients aged ≥75 years ($n = 34$) had apparently satisfactory outcomes, although the potential increase of toxicity with age and comorbidities could not be ruled out.[7,8] Finally, in the pooled analysis of CRYSTAL and OPUS trials including 320 and 78 patients aged <70 and ≥70 years,[20] the molecular selection adopted *KRAS* exon 2 wild-type status alone. Therefore, the shorter duration of treatment in new *RAS*- or *BRAF*-mutated patients may have conditioned a reduced risk of toxicity.

The preliminary results of the PANDA study, designed as a randomized non-comparative trial, showed that both panitumumab plus FOLFOX and panitumumab plus 5-FU/LV achieve satisfactory outcomes in patients aged 70-75 years with performance status (PS) >0, or >75 years. Considering that doublet chemotherapy increased the toxicity burden, monochemotherapy plus anti-EGFRs was suggested as a reasonable first-line option in elderly *RAS* wild-type mCRC patients.[21] Nevertheless, it should be noted that combination chemotherapy achieves a higher response rate and a deeper tumor shrinkage, thus representing the optimal choice in fit elderly patients with high tumor burden and disease-related symptoms or if the treatment goal is downsizing to reach secondary resection. Finally, focusing on the selected subgroup of patients aged 70-75 years and fit enough for an intensified and highly active regimen, the pooled analysis of the TRIBE and TRIBE2 trials showed that the FOLFOXIRI triplet plus bevacizumab induced a significantly higher burden of chemotherapy-related toxicity, potentially severely impairing the QoL of this elderly population.[22] Since no significant differences in terms of rate of any grade and grade 3/4 AEs and QoL were reported in our study, doublets plus an anti-EGFR should be regarded as the preferred modern regimen in patients aged 70-75 years with *RAS* and *BRAF* wild-type, left-sided mCRC. This is supported by a recent propensity score-based analysis that showed that, in this clinically and molecularly selected population, no significant differences in terms of PFS, OS, response rate and disease control were observed between FOLFOX plus panitumumab and FOLFOXIRI plus bevacizumab, besides an increased AE rate with the triplet.[23]

Based on all these considerations, in frail elderly patients, the therapeutic algorithm should be carefully balanced and adapted to avoid unacceptable toxicity, besides reaching an adequate tumor control. On the other hand, elderly patients in good clinical conditions and potentially eligible for a clinical trial may reach superimposable outcomes to those of younger patients; therefore, the risk of under-treatment should be minimized thanks to a careful and comprehensive clinical evaluation beyond chronological age, encompassing PS, functional status, comorbidities and a multidimensional geriatric assessment including even mental health and social status, thus optimizing the therapeutic management.[24]

Another topic of growing interest is the differential outcome in terms of efficacy and safety of cancer treatments according to gender-specific peculiarities. Recent studies reported a potential effect of gender on cancer risk and survival, besides impacting the response to antineoplastic therapies, since drug metabolism in terms of pharmacokinetics and pharmacodynamics is deeply influenced by gender for genetics and hormone levels.[10,25] When focusing on CRC patients, the available data did not show significant differences in terms of efficacy of chemotherapy in women and men, providing similar survival and response rates.[9,12,22] Nevertheless, an excess of toxicity has been shown in female versus male patients, with evidence of significantly increased frequency of any grade and severe chemotherapy-related AEs, specifically to fluoropyrimidines (mainly 5-FU), possibly because of different dihydropyrimidine dehydrogenase activity.[9,12,22,26-28] Consistently, in this subgroup analysis of the Valentino study, no statistically significant differences in activity outcomes, in terms of PFS, OS, response rate and clinical benefit, were found in male and female patients, with a similar effect of the maintenance treatment arm in the two subpopulations. On the other hand, for what concerns safety, although no significant differences were reported in dose intensity between male and female patients, we showed a significantly higher rate of overall grade 3/4 AEs and of grade 3/4 thrombocytopenia, any grade and grade 3/4 neutropenia and any grade conjunctivitis in female patients. Moving to the differential safety profile of anti-EGFR agents in men and women, we reported a significantly higher incidence of any grade skin rash and any grade hypomagnesemia and a non-significant trend for higher any grade panitumumab-related AEs in male patients, even though no significant differences were observed for overall and singular anti-EGFR-related grade 3/4 AEs. These results should be interpreted in light of the literature-based evidence on higher rate of grade 3 skin rash observed in molecularly unselected CRC male patients,[29,30] not confirmed in this subset, but potentially suggesting that men may be susceptible to a broader spectrum of the anti-EGFR-related toxicities beyond skin

rash. The potential reasons underlying this differential toxicity profile could be found in the hormonal milieu, since androgens and estrogens display a remarkable interaction with EGFR; thus, the differences in the hormone profile in men and women may justify the increased skin toxicity in men, even though more solid evidence is warranted.[31] These data may be useful in order to carefully identify patients who may benefit from a pre-emptive prophylaxis with oral tetracyclines and topical products for anti-EGFR-induced skin rash.[32] In fact, the prophylactic or reactive treatment with tetracyclines for EGFR inhibitor-induced skin toxicity is currently in clinical practice, though non-conclusive results are available.[30] In the previously reported post hoc analysis of the Valentino study, we did not report any significant or clinically meaningful difference in the reduction of panitumumab-related toxicity or on treatment intensity for the administration of a pre-emptive antibiotic prophylaxis for skin toxicity in the overall study population.[32] Nevertheless, further data could be obtained to estimate the potential predicted risk for increased or severe skin toxicity, including gender, allowing to perform a better patient selection for the supportive care measures, that may positively impact treatment-related toxicity and patients' QoL, thus optimizing the therapeutic management, especially in the first-line setting.

In conclusion, the upfront choice of an anti-EGFR-based doublet chemotherapy followed by a maintenance strategy represents a valuable option in *RAS* wild-type mCRC irrespective of gender and age. A comprehensive clinical evaluation of patients, encompassing the functional assessment and the comorbidity profile besides chronological age, together with the potential predicted risk of treatment-related toxicity, should be always carried out before the start of a first-line treatment in order to guide the therapeutic choice maximizing the risk—benefit profile.

ACKNOWLEDGEMENTS

We thank all the patients who agreed to take part in the trial. We also thank the investigators and the study teams who participated.

FUNDING

This was an academic study. A research grant and drug supply during panitumumab-based maintenance treatment was provided by Amgen (no grant number).

DISCLOSURE

FP has received honoraria for speaker activities and participation in advisory boards from Sanofi, Amgen, Bayer, Merck-Serono, Lilly, Roche and 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 and Bristol-Myers Squibb. AZ has received honoraria for speaker bureau from Amgen, Merck, Servier and Bayer. SC has received honoraria for participation in advisory boards from Merck. MDB has received honoraria for speaker activities and participation in advisory boards from Amgen, Roche, Lilly, Servier, Incyte and Celgene. FM has received honoraria for speaker activities from Servier. The remaining authors have declared no conflicts of interest.

REFERENCES

1. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27(8):1386-1422.
2. Aranda E, Garcia-Alfonso P, Benavides M, et al. First-line mFOLFOX plus cetuximab followed by mFOLFOX plus cetuximab or single-agent cetuximab as maintenance therapy in patients with metastatic colorectal cancer: phase II randomised MACRO2 TTD study. *Eur J Cancer*. 2018;101:263-272.
3. Munemoto Y, Nakamura M, Takahashi M, et al. SAPPHIRE: a randomised phase II study of planned discontinuation or continuous treatment of oxaliplatin after six cycles of modified FOLFOX6 plus panitumumab in patients with colorectal cancer. *Eur J Cancer*. 2019;119:158-167.
4. Pfeiffer P, Sorbye H, Qvortrup C, et al. Maintenance therapy with cetuximab every second week in the first-line treatment of metastatic colorectal cancer: the NORDIC-7.5 study by the nordic colorectal cancer biomodulation group. *Clin Colorectal Cancer*. 2015;14(3):170-176.
5. Wasan H, Meade AM, Adams R, et al. Intermittent chemotherapy plus either intermittent or continuous cetuximab for first-line treatment of patients with KRAS wild-type advanced colorectal cancer (COIN-B): a randomised phase 2 trial. *Lancet Oncol*. 2014;15(6):631-639.
6. Simkens LH, van Tinteren H, May A, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. *Lancet*. 2015;385(9980):1843-1852.
7. Van Cutsem E, Kohne C-H, Folprecht G, Guenther S, Beier F, Papamichael D. Efficacy and safety of first-line cetuximab + FOLFIRI in older and younger patients (pts) with RAS wild-type (wt) metastatic colorectal cancer (mCRC) in the CRYSTAL study. *J Clin Oncol*. 2016;34(suppl 4):647.
8. Douillard J, Siena S, Peeters M, Koukakis R, Terwey J, Tabernero J. Impact of baseline age on efficacy and safety of first-line panitumumab (pmab) + FOLFOX4 vs FOLFOX4 treatment. *Ann Oncol*. 2014;25(suppl 4):iv167-iv209.
9. Abdel-Rahman O. Impact of sex on chemotherapy toxicity and efficacy among patients with metastatic colorectal cancer: pooled analysis of 5 randomized trials. *Clin Colorectal Cancer*. 2019;18(2):110-115.e2.
10. Singh S, Parulekar W, Murray N, et al. Influence of sex on toxicity and treatment outcome in small-cell lung cancer. *J Clin Oncol*. 2005;23(4):850-856.
11. Wang J, Huang Y. Pharmacogenomics of sex difference in chemotherapeutic toxicity. *Curr Drug Discov Technol*. 2007;4(1):59-68.
12. Wagner AD, Rakez M, Chibaudel B, et al. Sex differences in efficacy and toxicity of first-line treatment of metastatic colorectal cancer (CRC): an analysis of 18,339 patients in the ARCAD database. *J Clin Oncol*. 2020;38(suppl 15):4029.
13. 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;5:1268-1275.
14. 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(33):3099-3110.
15. Raimondi A, Di Maio M, Morano F, et al. Health-related quality of life in patients with RAS wild-type metastatic colorectal cancer treated with panitumumab-based first-line treatment strategy: a pre-specified secondary analysis of the Valentino study. *Eur J Cancer*. 2020;135:230-239.

16. Asimakopoulou N, Souglakos J, Kentepozidis N, et al. Efficacy of panitumumab in older patients with metastatic colorectal cancer: a retrospective analysis using the database of the Hellenic Oncology Research Group (HORG). *J Geriatr Oncol*. 2019;10(1):143-148.
17. Rosati G, Aprile G, Cardellino GG, Avallone A. A review and assessment of currently available data of the EGFR antibodies in elderly patients with metastatic colorectal cancer. *J Geriatr Oncol*. 2016;7(2):134-141.
18. Tuca A, Gallego R, Ghanem I, Gil-Raga M, Feliu J. Chemotherapy and targeted agents in the treatment of elderly patients with metastatic colorectal cancer. *J Clin Med*. 2020;9(12):4015.
19. Martinelli E, Cardone C, Troiani T, et al. Clinical activity and tolerability of FOLFIRI and cetuximab in elderly patients with metastatic colorectal cancer in the CAPRI-GOIM first-line trial. *ESMO Open*. 2017;1(6):e000086.
20. Folprecht G, Kohne C, Bokemeyer C, et al. Cetuximab and 1st-line chemotherapy in elderly and younger patients with metastatic colorectal cancer (mCRC): a pooled analysis of the CRYSTAL and OPUS studies. *Ann Oncol*. 2010;21(suppl 8).
21. Lonardi S, Schirripa M, Buggin F, et al. First-line FOLFOX plus panitumumab versus 5FU plus panitumumab in RAS-BRAF wild-type metastatic colorectal cancer elderly patients: the PANDA study. *J Clin Oncol*. 2020;38(suppl 15):4002.
22. Marmorino F, Rossini D, Lonardi S, et al. Impact of age and gender on the safety and efficacy of chemotherapy plus bevacizumab in metastatic colorectal cancer: a pooled analysis of TRIBE and TRIBE2 studies. *Ann Oncol*. 2019;30(12):1969-1977.
23. Pietrantonio F, Fuca G, Rossini D, et al. FOLFOXIRI-bevacizumab or FOLFOX-panitumumab in patients with left-sided RAS/BRAF wild-type metastatic colorectal cancer: a propensity score-based analysis. *Oncologist*. 2021;26(4):302-309.
24. Wildiers H, Heeren P, Puts M, et al. International society of geriatric oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol*. 2014;32(24):2595-2603.
25. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet*. 2009;48(3):143-157.
26. Yamada Y, Koizumi W, Nishikawa K, et al. Sex differences in the safety of S-1 plus oxaliplatin and S-1 plus cisplatin for patients with metastatic gastric cancer. *Cancer Sci*. 2019;110(9):2875-2883.
27. Chansky K, Benedetti J, Macdonald JS. Differences in toxicity between men and women treated with 5-fluorouracil therapy for colorectal carcinoma. *Cancer*. 2005;103(6):1165-1171.
28. Sloan JA, Goldberg RM, Sargent DJ, et al. Women experience greater toxicity with fluorouracil-based chemotherapy for colorectal cancer. *J Clin Oncol*. 2002;20(6):1491-1498.
29. Jatoi A, Green EM, Rowland KM, Sargent DJ, Alberts SR. Clinical predictors of severe cetuximab-induced rash: observations from 933 patients enrolled in north central cancer treatment group study N0147. *Oncology*. 2009;77(2):120-123.
30. Lacouture ME, Anadkat MJ, Bensadoun RJ, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer*. 2011;19(8):1079-1095.
31. Migliaccio A, Castoria G, Di Domenico M, et al. Crosstalk between EGFR and extranuclear steroid receptors. *Ann N Y Acad Sci*. 2006;1089:194-200.
32. Raimondi A, Corallo S, Lonardi S, et al. Systemic doxycycline for preemptive treatment of anti-EGFR-related skin toxicity in patients with metastatic colorectal cancer receiving first-line panitumumab-based therapy: a post hoc analysis of the Valentino study. *Support Care Cancer*. 2021;29:3971-3980.