Initial panitumumab and Oxaliplatin Plus Fluorouracil, Leucovorin, and Oxaliplatin or Plus Fluorouracil and Leucovorin in Elderly Patients With RAS and BRAF Wild-Type Metastatic Colorectal Cancer: The PANDA Trial by the GONO Foundation

Sara Lonardi, MD[1] ; Cosimo Rasola, MD[1] ; Riccardo Lobefaro, MD[2] ; Daniele Rossini, MD[3,4]; Vincenzo Formica, MD, PhD[5] ; Mario Scartozzi, MD, PhD[6]; Giovanni Luca Frassineti, MD[7]; Giorgia Boscolo, MD[8]; Saverio Cinieri, MD[9]; Samantha Di Donato, MD, PhD[10]; Nicoletta Pella, MD[11]; Francesca Bergamo, MD[1] ; Alessandra Raimondi, MD[2]; Ermenegildo Arnoldi, MD[12]; Lorenzo Antonuzzo, MD, PhD[13,14]; Cristina Granetto, MD[15]; Fable Zustovich, MD[16]; Monica Ronzoni, MD[17]; Silvana Leo, MD[18]; Federica Morano, MD[2] ; Fotios Loupakis, MD, PhD[1]; Federica Buggin, BSc[1]; Vittorina Zagonel, MD[1]; Matteo Fassan, MD, PhD[19,20] ; Chiara Cremolini, MD, PhD[4] ; Luca Boni, MD[21] ; and Filippo Pietrantonio, MD[2] ; on behalf of the GONO Foundation Investigators

PURPOSE To verify whether both doublet chemotherapy with a modified schedule of fluorouracil, leucovorin, and oxaliplatin (mFOLFOX) and monochemotherapy with fluorouracil plus leucovorin (5-FU 1 LV) achieve satisfactory efficacy when both regimens are combined with panitumumab (PAN) as initial treatment of elderly patients with RAS/BRAF wild-type metastatic colorectal cancer (mCRC).

PATIENTS AND METHODS PANDA (ClinicalTrials.gov identifier NCT02904031) was an open-label, randomized phase II noncomparative trial in previously untreated patients age 70 years and older with unresectable RAS/BRAF wild-type mCRC. Patients were randomly assigned 1:1 to mFOLFOX 1 PAN (arm A) or 5-FU 1 LV 1 PAN (arm B) for up to 12 cycles, followed by PAN maintenance. The primary end point was progression-free survival (PFS). In each arm, assuming a null hypothesis of median PFS time £6 months and target PFS ≥9.65, 90 patients per arm were needed to achieve 90% power and 5% type I error (one-sided Brookmeyer-Crowley test).

RESULTS Between July 2016 and April 2019, 91 patients were randomly assigned to arm A and 92 to arm B. At a median follow-up of 50.0 months (IQR, 45.6-56.4), median PFS was 9.6 and 9.0 months for arm A and B, respectively (P < .001 in each arm). Overall response rate was 69% and 52%, whereas median overall survival was 23.5 and 22.0 months in arm A and B, respectively. The overall rate of grade >2 chemotherapy-related adverse events was 60% and 37%, respectively. Baseline G8 and Chemotherapy Risk Assessment Scale for High-Age Patients scores were prognostic, but they were not associated with efficacy and safety of the two arms.

CONCLUSION Both mFOLFOX and 5-FU 1 LV 1 PAN are reasonable options as initial therapy of elderly patients with RAS/BRAF wild-type mCRC. 5-FU 1 LV 1 PAN is associated with a better safety profile.

INTRODUCTION

As a result of the aging population, the percentage of elderly patients with metastatic colorectal cancer (mCRC) is expected to constantly increase over years. The probability of developing CRC is <1% in the population younger than 70 years, but it reaches about 3% in people 70 years or older.[1] In a meta-analysis of 20,023 patients enrolled in 24 phase III trials and receiving first-line therapies for mCRC, the oldest group of patients had a 42% increased risk of death.[2] Limited evidenced-based data are available to support the treatment decision making in older patients. The clinical definition of elderly (≥70 years) is still debated and physicians should carry out a comprehensive evaluation of the biological age, performance status (PS), comorbidities, polypharmacy, family and social network, and cost-effectiveness of available options to make their treatment choices.[3] Pretreatment geriatric screening tools have been evaluated in elderly

patients to better stratify their prognosis and predict treatment-related toxicity. Among these, the G8 questionnaire covers multiple domains and the cutoff of 14 shows good accuracy in identifying more vulnerable patients.[4-6] Additionally, the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score aims at defining an objective risk estimation of treatment-related toxicities in elderly patients with cancer.[7,8]

Elderly patients with mCRC remain under-represented in trials and the available data mostly derive from retrospective or noncontrolled studies and post hoc analyses of randomized clinical trials (RCTs).[9-12] Pivotal trials conducted in elderly populations showed a narrow therapeutic index of oxaliplatin- or irinotecan-based doublets, thus questioning therole ofupfront combination chemotherapyinfrail or very old patients.[13-15] As suggested by the major guidelines, fluoropyrimidine monotherapy or reduced doses of doublet regimens may be used in clinical practice after geriatric assessment.[16,17]

Regarding the efficacy and safety of bevacizumab or anti-epidermal growth factor receptor (EGFR) agents added to doublets, post hoc analyses of RCTs did not show a major impact of older age in terms of progression-free survival (PFS), overall survival (OS), and grade 3-4 adverse events (AEs).[18-20] Nonetheless, elderly patients eligible for those clinical trials were a highly selected and small subgroup, with consequent lack of evidence on more frail and aged patients.

To fill this gap, the phase III AVEX trial established bevacizumab plus capecitabine as a valuable upfront option for patients with mCRC noneligible for combination chemotherapy.[21]

On the other hand, doublets plus anti-EGFR monoclonal antibodies are the preferred first-line treatment options for fit patients with RAS/BRAF wild-type, left-sided mCRC.[16] However, the prospective trials conducted with panitumumab (PAN) or cetuximab in elderly patients had a nonrandomized design, small sample size, and absent or limited molecular selection. Moreover, no solid data about the efficacy of the combination of anti-EGFR agents with fluoropyrimidine monotherapy are available.

Drawing from these considerations, we designed the randomized phase II PANDA trial to explore the safety and efficacy of PAN added to infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or 5-FU 1 LV as initial therapy of elderly patients with RAS/BRAF wild-type mCRC.

PATIENTS AND METHODS

Patients

PANDA (ClinicalTrials.gov identifier: NCT02904031) was an open-label, multicenter, phase II randomized trial specifically dedicated to elderly patients with unresectable RAS/BRAF wild-type mCRC. Main eligibility criteria were age 70-75 years with an Eastern Cooperative Oncology Group (ECOG) PS ≤2, OR older than 75 years with an ECOG PS of ≤1; histologically confirmed metastatic and unresectable adenocarcinoma of the colon or rectum; measurable disease according to RECIST v1.1; no previous systemic chemotherapy for metastatic disease (previous adjuvant fluoropyrimidines were allowed if at least 6 months had elapsed between the end of treatment and disease relapse); central confirmation of RAS and BRAF wild-type status; and adequate organ function. Patients who had received previous oxaliplatin-based chemotherapy or anti-EGFR agents were excluded. A full list of eligibility criteria is listed in the Protocol (online only).

The trial was conducted in compliance with the Declaration of Helsinki. The protocol was approved by the ethics committees of all participating centers and all patients provided written informed consent before any study procedure.

The molecular prescreening was centrally performed at Veneto Institute of Oncology IRCCS, Padua, and included the mutational analysis of KRAS/NRAS codons 12, 13, 59, 61, 117, and 146 and BRAF codon 600 by MALDI-TOF MassArray (Sequenom).

Study Procedures

Eligible patients were randomly assigned (1:1) to receive PAN with either modified FOLFOX (arm A) or modified 5-FU 1 LV (arm B). Randomization was stratified according to age (≤75 v >75 years), ECOG PS (0-1 v 2), and G8 score (≤14 v >14). In arm A, PAN was given intravenously once every two weeks at 6 mg/kg and followed by oxaliplatin 85 mg/m^2, L-leucovorin 200 mg/m^2, and 5-FU 2,400 mg/m^2 as a 48-hour continuous infusion. In arm B, PAN at 6 mg/kg was followed by L-leucovorin 200 mg/m^2 and 5-FU 2,400 mg/m^2 as a 48-hour continuous infusion once every two weeks. In both arms, treatment was administered for a maximum of 12 cycles, followed in case of disease control by single-agent PAN as maintenance therapy. Study treatment was continued until disease progression, unacceptable toxicity, informed consent withdrawal, or patient/medical decision (Data Supplement [Fig S1], online only).

Thorax-abdomen computerized tomography scans were performed at baseline and every 8 weeks until disease progression and disease re-assessments according to RECIST v1.1 were centrally reviewed. Multidisciplinary team evaluation was recommended every 2 months in potentially resectable patients. After secondary resection of metastases, postoperative therapy with PAN plus the same randomly allocated regimen was recommended, up to a total of 12 perioperative cycles.

Safety assessments were done at each visit and included recording of the incidence, nature, and severity of AEs, changes in vital signs, and laboratory abnormalities, graded as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

The geriatric assessment was performed locally with the G8 and CRASH questionnaires at baseline and G8 at progression. A detailed description of these tools is available in the Protocol and the Data Supplement (Methods).

Study End Points

The primary end point of the trial was PFS, defined as the interval between random assignment and progressive disease or death due to any cause, whichever occurred first. Secondary end points were objective response rate, defined as the percentage of patients achieving a complete response (CR) or partial response (PR) according to RECIST v1.1 during the induction and the maintenance phases of treatment; R0 resections; OS, defined as the time from random assignment to death due to any cause or censored at the last follow up for alive patients; safety profile; and AEs according to NCI CTCAE v4.0.

Statistical Analysis

PANDA was designed as a phase II non comparative go/no-go or pick-the-winner trial. Assuming a median PFS time ≥9.65 months with both experimental regimens, corresponding to a 6-month PFS probability ≥65%, against a null hypothesis of a median PFS time ≤6 months corresponding to a 6-month PFS probability ≤50%, a sample size of 90 patients for each arm was necessary to refuse the null hypothesis with a power of 90% for a one-sided Brookmeyer-Crowley test with a type I error rate of 5%. The primary analysis of PFS was performed in the modified intention-to-treat population including all randomly assigned patients who received at least one cycle. Survival curves were calculated according to the Kaplan-Meier method, and the reverse Kaplan-Meier method was used to calculate the median period of follow-up. The median times to event and corresponding 2-sided 90% CIs were calculated. Post hoc, unplanned comparisons between the two arms for survival measures were performed according to the log-rank test, and hazard ratios (HRs) with 95% Cis were estimated with the Cox proportional hazard model. For these analyses, arm A has been taken as the reference group, as modified schedule of fluorouracil, leucovorin, and oxaliplatin (mFOLFOX) is the standard on-label chemotherapy backbone for PAN combinations. The chi-square test and the OR with 95% CIs were used to compare the ORR and disease control rate (ie, percentage of patients achieving CR, PR, or stable disease) between treatment groups.

Statistical analyses were done by means of SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients' Characteristics

The CONSORT diagram of the study is depicted in Figure 1. Between July 21, 2016, and April 23, 2019, 394 patients were screened at 53 of 63 active Italian centers. Among them, 180 (46%) patients were ineligible because of the detection of RAS/BRAF mutations and 29 for other reasons. Thus, 185 were randomly assigned to PAN 1 either mFOLFOX (arm A) or 5-FU 1 LV (arm B). As one patient per arm withdrew consent before the treatment start, the modified intention-to-treat population included 91 patients in arm A and 92 in arm B. Conversely, the safety population included 92 patients treated with PAN 1 mFOLFOX and 91 treated with PAN 1 5-FU 1 LV, since one patient in arm B received PAN 1 mFOLFOX.

FIG 1. CONSORT diagram showing flow of patients through the PANDA trial. 5-FU 1 LV, fluorouracil plus leucovorin; AE, adverse event; mFOLFOX, modified schedule of fluorouracil, leucovorin, and oxaliplatin; mITT, modified intention-to-treat; mut, mutated; PS, performance status.

Table 1 shows the main patients' baseline characteristics in the two treatment arms. Median age was 77 years in both arms, whereas ECOG PS was 0 in 50% and 46% of patients in arm A and B, respectively. Liver-limited disease was reported in 25% of patients in both arms and primary tumor sidedness was left-sided in 77% and 79% in arm A and B, respectively. G8 score was >14 in 32% and 30%, respectively, and CRASH score was low, medium-low, medium-high, or high in 12%, 36%, 43%, and 7% of cases in arm A and in 17%, 38%, 44%, and 0% of cases in arm B, respectively.

Treatment Exposure and Safety Results

During the induction phase, the median number of treatment cycles was 11 (range, 1-15) in arm A and 12 cycles (range, 1-16) in arm B. Details about treatment exposure are described in the Data Supplement (Table S1). Forty of 92 (44%) and 91 (44%) patients in both arms started maintenance therapy and they received a median of 10 (range, 1-30) versus 5 (range, 2-45) PAN cycles in arm A and B, respectively. Reasons for treatment discontinuation during induction or maintenance phase are detailed in the Data Supplement (Table S2).

The treatment-related AEs are summarized in Table 2. Grade 3-4 AEs occurring to more than 5% of the patients in arm A and B, respectively, were skin rash (25% and 24%), diarrhea (16% and 1%), stomatitis (10% and 4%), neutropenia (10% and 1%), and fatigue (8% and 4%). As expected, PAN-related AEs (skin rash, hypomagnesemia, paronychia, and conjunctivitis) were comparable between the two arms, whereas the incidence of neurotoxicity was higher in arm A versus B (47% v 3%). No treatment-related deaths occurred.

Efficacy and Activity Outcomes

At the data cutoff date of December 15, 2022, with a median follow-up time of 50.0 months (IQR, 45.6-56.4), 171 (93%) PFS events were recorded, encompassing 155 disease progressions and 16 deaths as the first event: 86 (95%) of 91 patients in arm A and 85 (92%) of 92 patients in arm B; 154 (84%) patients died: 76 (84%) in arm A and 78 (85%) in arm B. The median PFS was 9.6 months (90% CI, 8.8 to 10.9) in the PAN 1 mFOLFOX arm and 9.0 months (90% CI, 7.7 to 9.9) in the PAN 1 5-FU 1 LV arm ($P < .001$ according to the Brookmeyer-Crowley test in each arm against the null hypothesis of a median PFS time ≤6 months corresponding to a 6-month PFS probability ≤50%; Fig 2A). The unplanned comparison between arms revealed no significant PFS difference (HR, 1.08; 95% CI, 0.80 to 1.46; P 5 .611).

As detailed in Table 3, overall response rate (ORR) was 69%(95% CI, 59 to78) in arm A and 52% (95% CI, 42 to 63) in

TABLE 1. Baseline Characteristics of the Modified Intent-to-Treat Population

Characteristic	mFOLFOX 1 PAN (n 5 91)	5-FU 1 LV 1 PAN (n 5 92)
Age, years		
Median	77.0	77.0
Range	70.0-86.0	70.0-86.0
IQR	73.0-79.0	74.0-79.0
Age, years, No. (%)		
≤75	37 (40.7)	35 (38.0)
>75	54 (59.3)	57 (62.0)
Sex, No. (%)		
Female	31 (34.1)	36 (39.1)
Male	60 (65.9)	56 (60.9)
ECOG performance status, No. (%)		
0	45 (49.5)	42 (45.7)
1-2	46 (50.5)	50 (54.3)
Primary tumor side, No. (%)		
Right colon	21 (23.1)	19 (20.7)
Left colon	42 (46.2)	41 (44.6)
Rectum	28 (30.8)	32 (34.8)
Primary tumor resected, No. (%)		
Yes	56 (61.5)	62 (67.4)
No	35 (38.5)	30 (32.6)
Previous adjuvant chemotherapy, No. (%)		
No adjuvant chemotherapy	76 (83.5)	79 (85.9)
Capecitabine	10 (11.0)	10 (10.9)
FOLFOX	1 (1.1)	0 (0.0)
CapeOx	4 (4.4)	3 (3.3)
Time to metastases, No. (%)		
Synchronous	67 (73.6)	65 (70.7)
Metachronous	24 (26.4)	27 (29.3)
No. of metastatic sites, (%)		
Single	39 (42.9)	38 (41.3)
Multiple	52 (57.1)	54 (58.7)
Liver-only disease, No. (%)		
Yes	23 (25.3)	23 (25.0)
No	68 (74.7)	69 (75.0)
G8 screening score, No. (%)		
≤14	62 (68.1)	64 (69.6)
>14	29 (31.9)	28 (30.4)
CRASH score risk categories, No. (%)		
Low	11 (12.1)	16 (17.4)
Medium-low	33 (36.3)	35 (38.0)
Medium-high	39 (42.9)	40 (43.5)
High	6 (6.6)	0 (0.0)
NA	2 (2.2)	1 (1.1)

NOTE. Percentages may not total to 100 because of rounding.
Abbreviations: 5-FU 1 LV, fluorouracil plus leucovorin; CapeOx, capecitabine plus oxaliplatin; CRASH, Chemotherapy Risk Assessment Scale for High-Age Patients; ECOG, Eastern Cooperative Oncology Group; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; mFOLFOX, modified schedule of fluorouracil, leucovorin, and oxaliplatin; NA, not available; PAN, panitumumab; PS, performance status.

TABLE 2. AEs in the Full Safety Population According to Treatment Arms

	mFOLFOX 1 PAN (n 5 92), No. (%)		5-FU 1 LV 1 PAN (n 5 91), No. (%)	
Adverse Event	G1-2	G3-4	G1-2	G3-4
Anemia	38 (41.3)	1 (1.1)	28 (30.8)	1 (1.1)
Neutropenia	23 (25.0)	9 (9.8)	0 (0.0)	1 (1.1)
Highest grade of hematologic toxicity	48 (52.2)	12 (13.0)	34 (37.4)	2 (2.2)
Anorexia	31 (33.7)	1 (1.1)	12 (13.2)	1 (1.1)
Vomiting	6 (6.5)	3 (3.3)	8 (8.8)	1 (1.1)
Stomatitis	32 (34.8)	9 (9.8)	28 (30.8)	4 (4.4)
Palmar-plantar erythrodysesthesia	22 (23.9)	3 (3.3)	25 (27.5)	1 (1.1)
Hypomagnesemia	36 (39.1)	3 (3.3)	21 (23.1)	7 (7.7)
Conjunctivitis	23 (25.0)	0 (0.0)	21 (23.1)	1 (1.1)
Highest grade of toxicity	36 (39.1)	55 (59.8)	54 (59.3)	34 (37.4)

Abbreviations: 5-FU 1 LV, fluorouracil plus leucovorin; AEs, adverse events; mFOLFOX, modified schedule of fluorouracil, leucovorin, and oxaliplatin; PAN, panitumumab.

arm B (OR, 0.51; 95% CI, 0.19 to 1.33; P 5 .0182), with a disease control rate of 92% in arm A and 86% in arm B (P 5 .163). The proportion of patients undergoing R0 resection of metastases was superimposable between the two arms (8% v 9%; OR, 1.14; 95% CI, 0.40 to 3.29; P 5 .805).

Median OS was 23.5 months (95% CI, 18.9 to 28.7) in arm A and 22.0 months (95% CI, 16.9 to 29.5) in arm B (HR, 1.00; 95% CI, 0.73 to 1.38; P 5 .986; Fig 2B).

In the study population, 56 (61.5%) patients in arm A and 55 (59.8%) in arm B received at least one subsequent systemic treatment, while 45.1% and 40.2%, respectively, received at least two subsequent chemotherapy lines (median number of chemotherapy lines after disease progression, 2; range, 0-6 in both arms; IQR, 1-3.5 and 1-3.0 in arm A and B, respectively).

Regarding the subgroup analyses, there was no interaction between treatment arm and stratification factors, or most key baseline characteristics in terms of PFS (Fig 3) or ORR (Data Supplement [Fig S2]). Statistically significant interactions between treatment and number of metastatic sites or liver-limited disease were reported in terms of PFS, favoring PAN 1 mFOLFOX in patients with multiple sites or non–liver-limited disease. Regarding OS, only age subgroups (70-75 v >75 years) were associated with a differential treatment effect (P for interaction 5 .026), with better outcome with PAN 1 mFOLFOX in the younger subgroup (N 5 72) and with PAN 1 5-FU 1 LV in the older one (N 5 111; Data Supplement [Fig S3]). Interestingly, no interaction effect between treatment arm and primary tumor sidedness was evident, but patients with right-sided tumors treated with PAN 1 5-FU 1 LV had extremely poor PFS versus PAN 1 mFOLFOX (median PFS, 4.0 and 8.8 months). This difference did not translate into a clear OS difference (Data Supplement [Fig S4]).

Microsatellite instability (MSI) status was available in 158 patients, with 5 (2.7%) MSI-high (MSI-H) samples. Since the study was conducted in the preimmunotherapy era, patients with MSI-H status had significantly worse PFS and OS compared with MSS (Data Supplement [Fig S5]).

Association of Age, G8, and CRASH Scores With Safety and Outcomes

Of note, as shown in Data Supplement (Fig S6), no difference in overall grade >2 AEs with PAN 1 mFOLFOX and PAN 1 5-FU 1 LV was found according to the age subgroup (P for interaction 5 .830), G8 score at baseline (P for interaction 5 .341), or CRASH score categories (P for interaction 5 .220).

The overall trial population was analyzed regardless of treatment arm: age subgroup analysis (70-75 v >75 years) didnot demonstrate a significant association with PFS andOS (Data Supplement [Figs S7A and S7B]); patients

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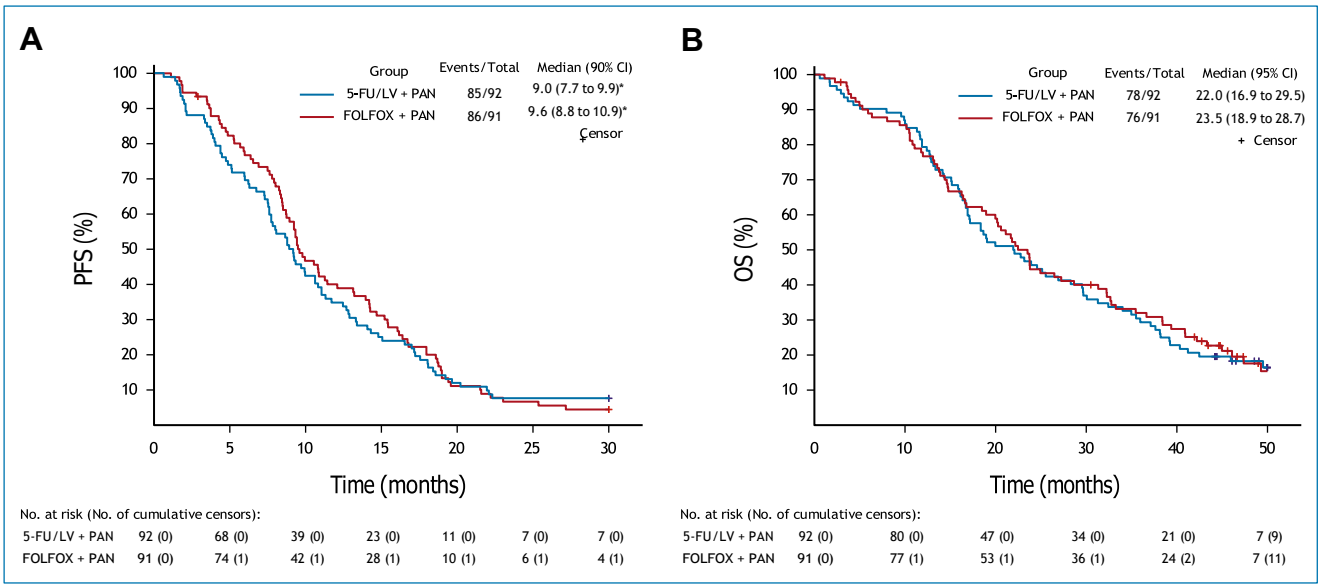

FIG 2. Kaplan-Meier curves of (A) PFS and (B) OS according to the treatment arm in the modified intention-to-treat population. The 1 symbol indicates patients censored at the time of data cutoff and analysis (December 15, 2022). *$P \leq .001$ Brookmeyer-Crowley test. 5-FU 1 LV, fluorouracil plus leucovorin; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; OS, overall survival; PAN, panitumumab; PFS, progression-free survival.

G8 score >14 at baseline experienced longer PFS (median PFS, 10.9 v 9.2 months; HR, 0.72 [95% CI, 0.52 to 1.00]; P 5 .049) and OS (median OS, 32.8 v 18.7 months; HR, 0.54 [95% CI, 0.37 to 0.77]; P < .001) than those with G8 score ≤14 (Data Supplement [Figs S7C and S7D]); patients with medium-high/high CRASH score had the worst outcomes, especially in terms of OS with a median value of 17.2 months (Data Supplement [Figs S7E and S7F]). No significant interaction effect between G8/CRASH scores and treatment arm was reported in terms of PFS, ORR, and OS (Fig 3; Data Supplement [Figs S2 and S3]).

DISCUSSION

Molecular profiling centered on microsatellite instability and RAS-BRAF mutational status is recommended to guide first-line treatment decisions in patients with mCRC. Doublet chemotherapy plus anti-EGFR agents is the preferred upfront option in patients with microsatellite stable, RAS/BRAF wild-type, left-sided mCRC.[16,22] When the intensity of chemotherapy is lightened to fluoropyrimidine monotherapy on the basis of patients' characteristics (poor PS, older age, and/or relevant comorbidities), the addition of bevacizumab is supported by phase III data as the strongest evidence-based practice regardless of molecular profiling.[21] However, the use of bevacizumab has absolute or relative contraindications, such as cardiovascular AEs that are significantly increased in elderly patients.[23]

Most importantly, anti-EGFR agents added to doublet chemotherapy provided an OS benefit compared with bevacizumab in patients selected by molecular profile and sidedness.[24,25]

On the basis of these considerations, there is a strong rationale to investigate the upfront use of anti–EGFR-based regimens in older patients. Some concerns had been historically raised because of the potential risk of impaired quality of life (QoL) and poor compliance because of relevant skin toxicity in the elderly population, and the overlapping toxicities of anti-EGFR agents and capecitabine, thus requiring infusional 5-FU as backbone. Small studies with low level of evidence underscored the feasibility and satisfactory outcomes of initial anti–EGFR-based therapy in older patients with mCRC.[26-30] Nevertheless, anti-EGFR monotherapy is recommended in patients judged unfit for chemotherapy including fluoropyrimidine monotherapy.[16,31]

The PANDA study is a unique trial specifically conducted in elderly patients fit enough to potentially receive first-line therapy with an anti-EGFR agent added to a chemotherapy backbone including a modified schedule of FOLFOX. Notably, the 5-FU bolus was omitted in both arms to improve chemotherapy tolerability without loss of efficacy.[32] The study met its primary end point and demonstrated promising PFS in both arms of PAN 1 either mFOLFOX or 5-FU 1 LV, with a post hoc evidence of similar PFS, OS, and DCR.

As expected, several chemotherapy-related toxicites were increased with PAN 1 mFOLFOX. Even if the subgoups analyses were not preplanned, there was no significnt interaction in terms of activity or efficacy of the two regmens in

TABLE 3. Antitumor Activity Outcomes in the Modified Intent-to-Treat Population

Activity Outcome	mFOLFOX 1 PAN (n 5 91)	5-FU 1 LV 1 PAN (n 5 92)	*P*
Best response, No. (%)			.0585[a]
CR	4 (4.4)	5 (5.4)	
PR	59 (64.8)	43 (46.7)	
SD	21 (23.1)	31 (33.7)	
Progressive disease	2 (2.2)	9 (9.8)	
Not evaluated	5 (5.5)	4 (4.3)	
Response rate, No. (%)			.0182[a]
CR 1 PR	63 (69.2)	48 (52.2)	
Other	28 (30.8)	44 (47.8)	
Events/N	63/91	48/92	.0189[b]
OR (95% CI)	Ref	0.48 (0.26 to 0.89)	
Disease control rate, No. (%)			
CR 1 PR 1 SD	84 (92.3)	79 (85.9)	.1628[a]
Other	7 (7.7)	13 (14.1)	
Events/N	84/91	79/92	.1687[b]
OR (95% CI)	Ref	0.51 (0.19 to 1.33)	
R0 surgery of metastases			.8047[b]
Events/N	7/91	8/92	
Event rate (95% CI)	0.08 (0.02 to 0.13)	0.09 (0.03 to 0.14)	
OR (95% CI)	Ref	1.14 (0.40 to 3.29)	

NOTE. Response to the treatment has been calculated according to RECIST criteria v 1.1.
Abbreviations: 5-FU 1 LV, fluorouracil plus leucovorin; CR, complete response; mFOLFOX, modified schedule of fluorouracil, leucovorin, and oxaliplatin; OR, odds ratio; PAN, panitumumab; PR, partial response; Ref, reference; SD, stable disease.
[a]Chi-square *P* value.
[b]Type-3 Wald *P* value.

the analyzed subgroups. The only exception was the significant interaction between age subgroups (70-75 v >75 years) and OS, with better outcome of mFOLFOX in younger patients versus 5-FU 1 LV in older ones. Although a careful risk/benefit assessment of PAN 1 mFOLFOX is clearly desirable in patients older than 75 years, these results from a subgroup analysis should be interpreted with caution; additionally, we could not identify any potential explanation such as increased toxicities or reduced compliance to mFOLFOX in older patients. Of note, we could not retrospectively investigate the predictive role of primary tumor sidedness for the efficacy of EGFR inhibition because of the study design with PAN-based therapy in both arms.[33] Consistently, the interaction between sidedness and treatment arm was nonsignificant. However, patients with right-sided tumors treated with PAN 1 5-FU 1 LV had extremely poor outcomes, especially in terms of PFS, thus confirming the negative prognostic role of sidedness and suggesting that alternative treatment options—such as bevacizumab added to reduced intensity and/or modified schedules of chemotherapy—may be preferred in this subgroup of elderly patients.

Putting the results of the PANDA trial in context, in the post hoc comparison between the two arms, the addition of oxaliplatin to PAN 1 5-FU 1 LV increased the ORR, but such a higher activity did not translate into PFS and OS benefit. The lack of correlation between activity and efficacy end points is especially important in elderly patients because of the narrower therapeutic index of chemotherapy. This finding is in line with the results of pivotal chemotherapy-only studies comparing monotherapy versus oxaliplatin- or irinotecan-based doublets[14,15] and the more recent phase III RESPECT trial of bevacizumab plus mFOLFOX7 or CapeOX versus bevacizumab 1 5-FU 1 l-LV or capecitabine.[34] Additionally, in the PANDA trial, the high efficacy of EGFR inhibition in properly selected patients with RAS-BRAF wild-type and mostly left-sided tumors may have limited the relative benefit from a more intense chemotherapy backbone, similarly to the TRIPLETE trial by GONO.[35] However, in specific clinical scenarios—such as elderly fit patients with high tumor burden and symptoms or potentially eligible for resection of metastases—mFOLFOX with an anti-EGFR agent may be a reasonable option after geriatric assessment and careful balance of the risks.

Regarding safety, anti–EGFR-related toxicities was similar in the two arms and in line with literature data in younger patients, thus reinforcing the few published data on the good safety profile of anti–EGFR-based regimens in elderly patients.[36] Indeed, PAN 1 mFOLFOX was associated with higher incidence of overall grade >2 AEs and specific chemotherapy-related toxicities, and this is another crucial

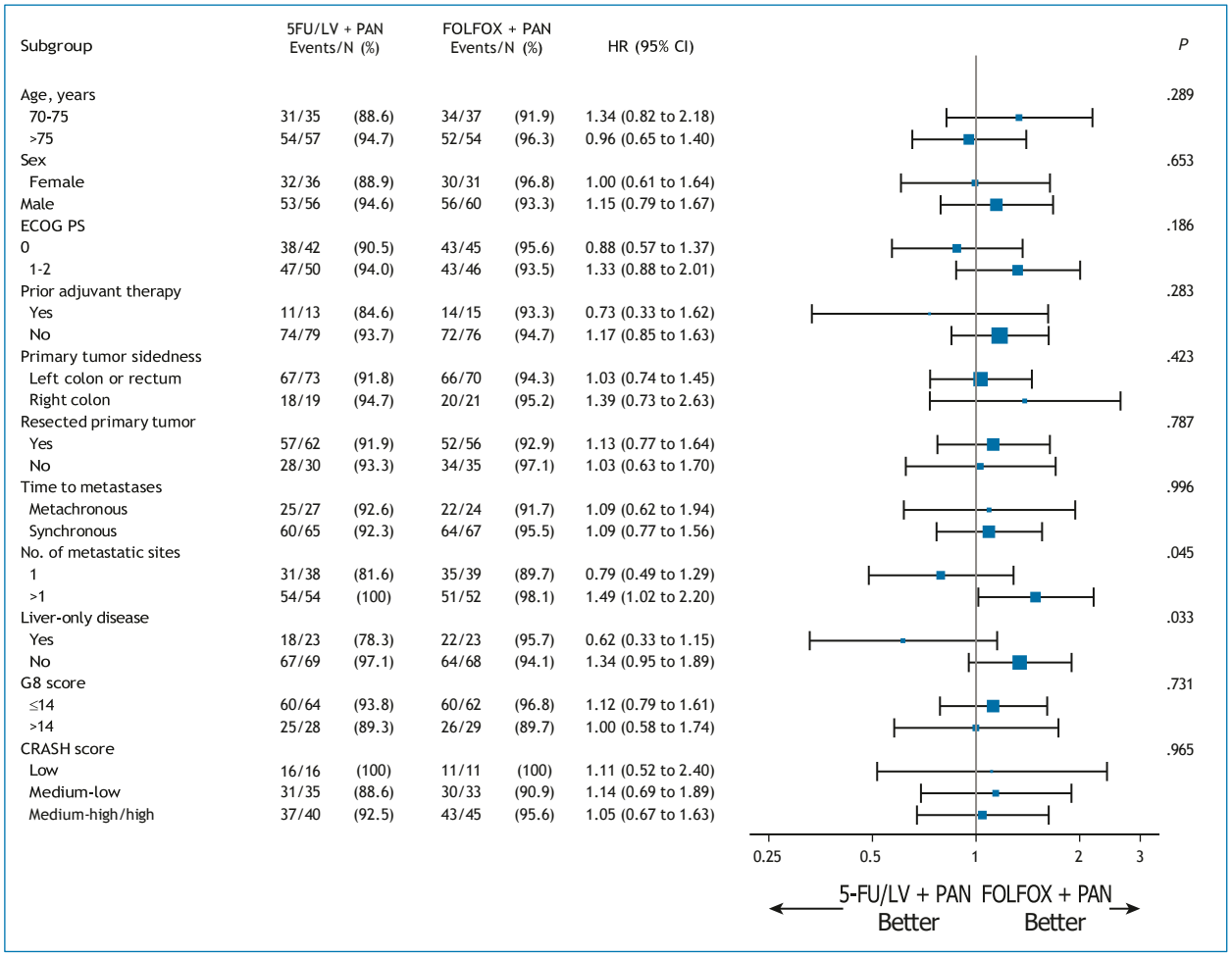

FIG 3. Subgroup analyses of PFS according to the two treatment arms. The boxes represent the HRs, with 95% CIs shown by the horizontal lines. The size of each box is proportional to the number of patients included in the corresponding subgroup. 5-FU 1 LV, fluorouracil plus leucovorin; CRASH, Chemotherapy Risk Assessment Scale for High-Age Patients; ECOG, Eastern Cooperative Oncology Group; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio; PAN, panitumumab; PS, performance status.

factor in weighting the benefit/risk ratio in favor of PAN 1 5-FU 1 LV monotherapy. Unfortunately, QoL data were not collected, thus not allowing to estimate the different impact of toxicities on QoL in each arm. However, one of the strengths of the PANDA trial is the prospective evaluation of G8 and CRASH scores.[37,38] Of note, PAN 1 mFOLFOX was associated with higher AEs regardless of the two baseline geriatric screening tools, whereas their prognostic impact may be related to a less aggressive management of frail patients.

Obviously, the results of this study are not fully transferable to a population of more frail elderly patients where, in the absence of contraindications to antiangiogenic agents, capecitabine 1 bevacizumab may still be a preferable treatment option, especially in right-sided primary tumors.

Our study has limitations. This study is characterized by a go/no go noncomparative design, where random assignment was needed to avoid unbalances in the baseline features but the statistical comparisons between the two arms were unplanned and conducted post hoc. However, a phase III trial would be hardly feasible in this patient population because of the clinical and molecular selection recommended for initial anti–EGFR-based therapy; the need to use a noninferiority design to formally validate PAN 1 5-FU 1 LV, thus requiring a very large sample size; and the risk of exposing frailer patients treated with PAN 1 mFOLFOX to excessive toxicity burden with a potentially quite modest PFS and OS gain.

In conclusion, the PANDA trial showed that PAN added to 5-FU 1 LV monochemotherapy may be a reasonable initial treatment option in elderly patients with RAS/BRAF wild-type mCRC. Our data provide a better level of evidence to support the choices that physicians make in everyday clinical practice.

AFFILIATIONS

[1]Medical Oncology 1, Veneto Institute of Oncology IOV—IRCCS, Padova, Italy
[2]Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
[3]Unit of Medical Oncology 2, University Hospital of Pisa, Pisa, Italy
[4]Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy
[5]Medical Oncology Unit, Policlinico Tor Vergata, Roma, Italy
[6]Department of Medical Sciences and Public Health, Medical Oncology Unit, "Azienda Ospedaliero Universitaria" of Cagliari, University of Cagliari, Cagliari, Italy
[7]Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" (IRST), Meldola, Italy
[8]Medical Specialties Department, Oncology and Oncological Haematology, ULSS 3 Serenissima, Mirano, Italy
[9]Department of Medical Oncology, Hospital "Senatore Perrino", Brindisi, Italy
[10]Department of Medical Oncology, General Hospital, Prato, Italy
[11]Department of Oncology, ASUFC University Hospital, Udine, Italy
[12]Department of Oncology, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy
[13]Clinical Oncology Unit, Careggi University Hospital, Florence, Italy
[14]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
[15]Medical Oncology, ASL CN1, Cuneo, Italy
[16]Dipartimento di Oncologia Clinica, UOC Oncologia di Belluno, AULSS 1 Dolomiti, Ospedale S. Martino, Belluno, Italy
[17]Oncologia Medica, IRCCS Ospedale San Raffaele, Milano, Italy
[18]Medical Oncology Unit, Vito Fazzi Hospital, Lecce, Italy
[19]Department of Medicine (DIMED), Surgical Pathology & Cytopathology Unit, University of Padova, Padova, Italy
[20]Veneto Institute of Oncology IOV—IRCCS, Padova, Italy
[21]IRCCS Ospedale Policlinico San Martino, Genova, Italy

CORRESPONDING AUTHOR

Sara Lonardi, MD, Department of Oncology, Veneto Institute of Oncology IOV—IRCCS, Via Gattamelata 64, Padova 35128, Italy; Twitter: @sara_lonardi1; e-mail: sara.lonardi@iov.veneto.it.

EQUAL CONTRIBUTION

C.C., L.B., and F.P. contributed equally to this work.

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AUTHOR CONTRIBUTIONS

Conception and design: Sara Lonardi, Ermenegildo Arnoldi, Fotios Loupakis, Vittorina Zagonel, Luca Boni
Administrative support: Federica Buggin
Provision of study materials or patients: Vincenzo Formica, Mario Scartozzi, Saverio Cinieri, Samantha Di Donato, Francesca Bergamo, Ermenegildo Arnoldi, Lorenzo Antonuzzo, Fable Zustovich, Monica Ronzoni, Silvana Leo, Federica Morano, Fotios Loupakis, Federica Buggin, Vittorina Zagonel, Matteo Fassan, Filippo Pietrantonio
Collection and assembly of data: Sara Lonardi, Cosimo Rasola, Riccardo Lobefaro, Vincenzo Formica, Mario Scartozzi, Giorgia Boscolo, Saverio Cinieri, Samantha Di Donato, Nicoletta Pella, Francesca Bergamo, Lorenzo Antonuzzo, Cristina Granetto, Fable Zustovich, Monica Ronzoni, Silvana Leo, Federica Morano, Fotios Loupakis, Federica Buggin, Matteo Fassan, Chiara Cremolini, Luca Boni, Filippo Pietrantonio
Data analysis and interpretation: Sara Lonardi, Cosimo Rasola, Daniele Rossini, Mario Scartozzi, Giovanni Luca Frassineti, Saverio Cinieri, Alessandra Raimondi, Federica Morano, Fotios Loupakis, Vittorina Zagonel, Matteo Fassan, Chiara Cremolini, Luca Boni, Filippo Pietrantonio
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Initial Panitumumab Plus Fluorouracil, Leucovorin, and Oxaliplatin or Plus Fluorouracil and Leucovorin in Elderly Patients With RAS and BRAF Wild-Type Metastatic Colorectal Cancer: The PANDA Trial by the GONO Foundation

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Sara Lonardi
Consulting or Advisory Role: Amgen, Merck Serono, Lilly, Servier, AstraZeneca, Incyte, Daiichi Sankyo, Bristol Myers Squibb, MSD, Astellas Pharma
Speakers' Bureau: Roche, Lilly, Bristol Myers Squibb, Servier, Merck Serono, Pierre Fabre, GlaxoSmithKline, Amgen, MSD Oncology, Incyte
Research Funding: Amgen, Merck Serono, Bayer (Inst), Roche (Inst), Lilly (Inst), AstraZeneca (Inst), Bristol Myers Squibb (Inst)

Riccardo Lobefaro
Honoraria: Pfizer
Consulting or Advisory Role: Daiichi Sankyo/Astra Zeneca
Travel, Accommodations, Expenses: Lilly

Daniele Rossini
Speakers' Bureau: MSD Oncology, Amgen

Vincenzo Formica
Honoraria: Amgen, Servier, MSD, Pierre Fabre, Merck Serono

Mario Scartozzi
Consulting or Advisory Role: MSD, Merck, GlaxoSmithKline, Servier, Amgen, Bristol Myers Squibb/Sanofi, Rottapharm Biotech
Speakers' Bureau: MSD, Merck, Servier, GlaxoSmithKline, Bristol Myers Squibb/Sanofi, Amgen
Research Funding: Sanofi
Travel, Accommodations, Expenses: Merck, MSD, Servier

Samantha Di Donato
Consulting or Advisory Role: Amgen, Merck Serono, Servier, Bayer
Travel, Accommodations, Expenses: Bayer

Francesca Bergamo
Consulting or Advisory Role: Advanced Accelerator Applications/ Novartis, Servier
Speakers' Bureau: Lilly, MSD Oncology, Eisai, Bayer

Alessandra Raimondi
Speakers' Bureau: Elma Academy, Servier
Travel, Accommodations, Expenses: Amgen

Lorenzo Antonuzzo
Honoraria: Amgen, Roche, AstraZeneca, Novartis

Federica Morano
Honoraria: Servier, Lilly, Pierre Fabre
Research Funding: Incyte (Inst)
Travel, Accommodations, Expenses: Daiichi Sankyo/Astra Zeneca

Fotios Loupakis
Employment: AstraZeneca

Vittorina Zagonel
Consulting or Advisory Role: Bristol Myers Squibb/Pfizer, Mundipharma
Speakers' Bureau: Bayer, Merck, Astellas Pharma
Research Funding: Bayer (Inst)
Travel, Accommodations, Expenses: Daiichi Sankyo/Lilly

Matteo Fassan
Consulting or Advisory Role: Astellas Pharma, GlaxoSmithKline, Roche, MSD Oncology, AstraZeneca, Pierre Fabre
Research Funding: Astellas Pharma, QED Therapeutics, Macrophage Pharma, Diaceutics

Chiara Cremolini
Honoraria: Roche, Amgen, Bayer, Servier, MSD, Merck, Pierre Fabre, Merck
Consulting or Advisory Role: Roche, Bayer, Amgen, MSD, Pierre Fabre, Nordic Bioscience
Speakers' Bureau: Servier, Merck, Pierre Fabre
Research Funding: Merck, Bayer, Roche, Servier

Luca Boni
Patents, Royalties, Other Intellectual Property: International Patent Number PCT/EP2012/065661

Filippo Pietrantonio
Honoraria: Servier, Bayer, AstraZeneca/MedImmune, Lilly, MSD Oncology, Amgen, Pierre Fabre, Bristol Myers Squibb, Merck Serono, Astellas Pharma
Consulting or Advisory Role: Amgen, Servier, MSD Oncology, Merck, Bayer, Merck Serono, Merck Serono
Research Funding: Bristol Myers Squibb (Inst), AstraZeneca (Inst), Incyte (Inst), Agenus (Inst)
Travel, Accommodations, Expenses: Pierre Fabre

No other potential conflicts of interest were reported.

APPENDIX. PANDA TRIAL: AUTHORSHIP CONSORTIUM FOR THE GONO FOUNDATION INVESTIGATORS

Principal Investigators of participating Oncology Units are listed in alphabetic order and with reference to their Center.

Ermenegildo Arnoldi, ASST Ospedale Papa Giovanni XXIII, Bergamo

Lorenzo Antonuzzo, Azienda Ospedaliero-Universitaria Careggi, Firenze

Giuseppe Aprile, Ospedale San Bortolo di Vicenza, Vicenza

Antonio Ardizzoia, Presidio Ospedaliero di Lecco—ASST Lecco, Lecco

Carlo Aschele, Ospedale Civile Sant'Andrea—Azienda Sanitaria Locale 5 Spezzino, La Spezia

Editta Baldini, Ospedale San Luca, Lucca

Alberto Ballestrero, Ospedale Policlinico San Martino IRCCS, Genova

Alessandro Bertolini, Azienda Ospedaliera della Valtellina e della Valchiavenna, Sondrio

Roberto Bordonaro, ARNAS Garibaldi—Presidio Ospedaliero Garibaldi Nesima, Catania

Giorgia Boscolo, Ospedale di Mirano—AULSS 3 Serenissima, Dolo

Angela Buonadonna, Centro di Riferimento Oncologic di Aviano, Aviano

Saverio Cinieri, Ospedale "A. Perrino"—ASL Brindisi, Brindisi

Matteo Clavarezza, Ente Ospedaliero "Ospedali Galliera," Genova

Domenico Corsi, Ospedale San Giovanni Calibita Fatebenefratelli Isola Tiberina, Roma

Enrico Cortesi, Policlinico Umberto I, Roma

Filippo De Braud, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano

Samantha Di Donato, Ospedale Santo Stefano, Prato

Alfredo Falcone, Azienda ospedaliero-universitaria pisana, Pisa

Adolfo Favaretto, Ospedale di Treviso—ULSS 2 Marca Trevigiana, Treviso

Vincenzo Formica, Policlinico Universitario di Roma "Tor Vergata", Roma

Luca Frassineti, Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori"—IRST IRCCS, Meldola

Antonio Frassoldati, Azienda Ospedaliero-Universitaria di Ferrara "Arcispedale Sant'Anna", Ferrara

Michela Frisinghelli, Ospedale Santa Chiara, Trento

Teresa Gamucci, Ospedale Sandro Pertini, Roma

Luca Gianni, IRCCS Ospedale San Raffaele, Milano

Filippo Giovanardi, Azienda USL di Reggio Emilia Ospedale di Guastalla, Reggio Emilia

Stefania Gori, IRCCS Ospedale Sacro Cuore Don Calabria, Negrar

Roberta Grande, Ospedale SS. Trinita`—ASL Frosinone, Frosinone

Cristina Granetto, Azienda Ospedaliera Santa Croce e Carle, Cuneo

Silvana Leo, Ospedale "Vito Fazzi," Lecce

Francesco Leone, Istituto di Candiolo IRCCS, Candiolo

Sara Lonardi, Istituto Oncologico Veneto IRCCS, Padova

Andrea Luciani, Presidio Ospedale San Paolo—ASST Santi Paolo e Carlo, Milano

Carlo Milandri, Ospedale San Giuseppe, Empoli

Nicoletta Pella, Ospedale Santa Maria della Misericordia, Udine

Andrea Sartore-Bianchi, ASST Grande Ospedale Metropolitano Niguarda, Milano

Mario Scartozzi, Presidio Ospedaliero "Duilio Casula"—AOU Cagliari, Cagliari

Nicola Silvestris, I.R.C.C.S. "Giovanni Paolo II", Bari

Emiliano Tamburini, Ospedale "Infermi", Rimini

Gianluca Tomasello, Ospedale di Cremona—ASST Cremona, Cremona

Giuseppe Tonini, Fondazione Policlinico Universitario Campus Bio-Medico, Roma

Gianpaolo Tortora, Ospedale Policlinico "G.B. Rossi" Borgo Roma—AOUI Verona, Verona

Claudio Vergani, Ospedale Citta` di Sesto San Giovanni—ASST Nord Milano, Sesto San Giovanni

Albrto Zaniboni, Fondazione Poliambulanza Istituto Ospedaliero, Brescia

Fable Zustovich, Ospedale San Martino di Belluno—ULSS 1 Dolomiti, Belluno