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Patterns of Use, Safety, and Effectiveness of Targeted Therapies in First-Line Treatment of Metastatic Colorectal Cancer According to Age: The STROMBOLI Cohort Study

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Abstract

Elderly patients are excluded from clinical trials, yet they can be treated in clinical practice. This large cohort of metastatic colorectal cancer patients treated in first-line with targeted therapies reinforces their benefit in elderly patients. Safety and effectiveness of targeted therapies are similar between elderly and younger metastatic colorectal cancer patients.

Background: Metastatic colorectal cancer (mCRC) is increasingly treated using targeted therapies. Their real-life evaluation is insufficient, especially in elderly and frail patients. The aim was to describe use, safety, and effectiveness of targeted therapies in first-line mCRC treatment according to age. **Patients and Methods:** Two field cohorts of patients initiating bevacizumab or cetuximab for first-line mCRC were pooled. Patients characteristics, use, and safety were compared between younger and elderly patients (<75 vs. ≥75 years). Two-year overall survival (OS) and progression-free survival (PFS) were estimated in both age groups using the Kaplan–Meier method adjusted on factors associated with death or progression identified with Cox multivariate modeling. **Results:** Eight hundred patients (n = 411, 51.4% bevacizumab) were included: 498 (62.3%) male, median age 64 years, 118 (14.8%) Eastern Cooperative Oncology Group performance status (ECOG-PS) ≥2. Elderly patients (n = 126, 15.8%) were more often treated with 5-fluorouracil alone than younger. Severe adverse events were equivalent across age groups. ECOG-PS ≥1, abnormal hemoglobin, and abnormal alkaline phosphatases were associated with a higher risk of death; OS adjusted on these factors was similar between elderly and younger patients. ECOG-PS ≥1, lung metastases, abnormal hemoglobin, and abnormal creatinine clearance were associated with a higher risk of progression or death; PFS adjusted on these factors was similar across groups. **Conclusion:** Despite treatment adaptations, elderly patients could benefit from targeted therapies as younger without safety warning.

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Keywords: Aged, Colorectal neoplasm, Frail elderly, Molecular targeted therapy, Neoplasm metastasis

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Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide. It is more frequent among the elderly; nearly one-third of incident cases are diagnosed in patients aged 75 years or older.[1] At diagnosis, 20% of patients have metastases, and approximately 40% will at one point have metastatic CRC (mCRC).[2,3] Since 2005, targeted therapies have become available and recommended for the treatment of mCRC, in combination with chemotherapy.[4,5] Bevacizumab, an antibody targeting vascular endothelial growth factor and cetuximab, an antibody targeting epidermal growth factor receptor are the most frequently used in first-line treatment.[4,5]

Clinical trials of targeted therapies in mCRC suffer from an under-representation of elderly patients and only provide information on middle-aged healthy subjects fit to undergo treatment with anticancer medications.[6] In routine clinical practice, targeted therapies might be prescribed to patients who would be excluded from clinical trials because of advanced age or other frailty parameters (eg, comorbidities). As a consequence, observational studies are necessary to fill this gap in evaluation.

The aim of the STROMBOLI (Sujets âgés et TRaitements innovants en Oncologie: cétuxiMab et Bévacizumab dans le cancer cOlorectal métastatique en vIe réelle) study was to describe the use, safety, and effectiveness of targeted therapies used in first-line mCRC treatment in a real-life setting according to age.

Patients and Methods

Study Design and Population

The STROMBOLI cohort corresponds to the pooled population of 2 existing observational cohorts: ETNA (Etude de Terrain sur les traitements iNnovants en cancérologie: un anti-angiogénique, l'Avastin) and EREBUS (Evaluation des thérapies ciblées chez des patients traités en première ligne métastatique pour un cancer colorectal: le cétuximab en situation réelle de soins). Details on the ETNA and EREBUS studies have been reported elsewhere.[7,8] Briefly, ETNA was an observational cohort study conducted in 28 public and private clinical centers of Southwest France. All patients who initiated bevacizumab treatment between January 2006 and December 2007 were identified using nominative dispensations from hospital pharmacies. Patients treated for first-line mCRC with inoperable metastases were included and followed for 2 years after initiation of first-line therapy. EREBUS was an observational cohort study conducted in 65 public and private clinical centers of France. All patients who initiated cetuximab treatment between January 2009 and December 2010 were identified using the same process as for the ETNA cohort. Patients treated for first-line mCRC with inoperable metastases and KRAS (Kirsten RAt Sarcoma viral oncogene homolog) wild type status were included and followed for 2 years after initiation of first-line therapy.

Before inclusion in the ETNA and EREBUS cohorts, patients were informed of the study objectives and data collection, and could indicate their wish not to participate. The STROMBOLI study protocol was approved by the French data protection agencies. In accordance with French regulations for observational studies applicable at the time of the study conception, ethics committee approval was not required.

Available Data

Data extracted from patient medical records at baseline and during follow-up of both cohorts were pooled. Baseline characteristics included demographic data, history of CRC (primary tumor and metastatic disease), significant medical history, as well as clinical and biological exams before initiation of first-line therapy. During the 2 years of follow-up, patterns of bevacizumab or cetuximab use in first-line therapy were collected including doses, timing of administration, combined chemotherapy, as well as adverse events occurring at each treatment cycle, treatment response, and subsequent treatment lines (with or without targeted therapy).

Adverse events documented in the medical files were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.[9] Treatment response evaluation in current practice using computed tomography scan every 2 to 3 months was on the basis of the Response Evaluation Criteria in Solid Tumors.[9,10]

Statistical Analyses

Descriptive analyses were performed to compare baseline characteristics, and use and safety of targeted therapies between younger and elderly patients (<75 years vs. ≥75 years). Categorical variables were compared across groups using Pearson χ^2 test, or Fisher exact χ^2 test where appropriate. Continuous variables were compared across groups using Student t test.

Survival analyses included 2 steps. First, factors associated with death or progression were identified as follows. The list of all potential poor prognosis factors available was established in agreement with 2 clinicians (for details, see Supplemental Tables 1-3 in the online version). Cox proportional hazards modeling was used to identify the factors independently associated with death or progression providing hazard ratios with 95% confidence intervals (CIs). The baseline was the initiation of the first-line therapy and the follow-up was censored at death or progression, loss to follow-up, or the end of the study period, whichever came first. For variables with >10% of missing data, a multiple imputation using Markov Chain Monte Carlo was performed.[11] All variables associated with a $P < .25$ in univariate analyses were included in an initial multivariate model, and the less significantly associated variables successively removed to keep only those associated with a $P < .05$. However, to minimize confounding, age and sex were systematically kept in the model.

Second, overall survival (OS) and progression-free survival (PFS) were estimated in both age groups using the Kaplan–Meier method. OS was defined as the interval between start of first-line therapy and death from any cause and PFS as the interval between start of first-line therapy and first disease progression or death. To avoid channeling, these survival analyses were adjusted on factors identified as associated with death or progression in multivariate Cox proportional hazards modeling. Median OS and PFS estimates along with their 95% CIs were reported, as well as 2-year OS and PFS rates (with 95% CI). OS or PFS were compared across groups using the log rank test. All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Cary, NC).

Table 1 Baseline Demographic and Clinical Characteristics According to Age in the STROMBOLI Study (n = 800)

Characteristic	Patients Aged <75 Years (n = 674)	Patients Aged ≥75 Years (n = 126)	*P*
Median Age (IQR), Years	62.0 (57.0-68.0)	77.0 (76.0-80.0)	**<.0001**
Male Sex	414 (61.4)	84 (66.7)	.27
ECOG-PS			**.005**
0	270 (40.1)	31 (24.6)	
1	264 (39.2)	57 (45.2)	
≥2	93 (13.8)	25 (19.8)	
Missing data	47 (7.0)	13 (10.3)	
BMI[a]			**.007**
Normal	608 (90.2)	103 (81.7)	
Denutrition	45 (6.7)	17 (13.5)	
Missing data	21 (3.1)	6 (4.8)	
Synchronous Metastases	487 (72.3)	82 (65.1)	.10
Metastasis Localization[b]			
Liver	501 (74.3)	94 (74.6)	.95
Lung	200 (29.7)	37 (29.4)	.94
Peritoneum	147 (21.8)	24 (19.0)	.49
Lymph node	147 (21.8)	21 (16.7)	.19
Other	97 (14.4)	14 (11.1)	.33
Number of Metastatic Sites			.12
1	367 (54.5)	73 (57.9)	
2	214 (31.8)	44 (34.9)	
≥3	93 (13.8)	9 (7.1)	
Medical History			
Cardiovascular disorders	285 (42.3)	76 (60.3)	**.0002**
Nervous disorders	64 (9.5)	7 (5.6)	.15
Renal disorders	32 (4.7)	13 (10.3)	**.01**
Abnormal Hemoglobin	324 (48.1)	73 (57.9)	**.04**
Abnormal Creatinine Clearance	81 (12.0)	49 (38.9)	**<.0001**

Data are presented as n (%) except where otherwise noted.
Data in bold correspond to significant value.
Abbreviations: BMI = body mass index; ECOG-PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; STROMBOLI = Sujets âgés et TRaitements innovants en Oncologie: cétuxiMab et Bévacizumab dans le cancer cOlorectal métastatique en vle réelle.
[a]Denutrition defined as: BMI <18.5 if age ≤70 years and BMI <21 if age >70 years.
[b]More than 1 site possible.

Results

Study Population Characteristics

A total of 800 patients were included in the STROMBOLI cohort, 411 (51.4%) were treated with bevacizumab and 389 (48.6%) with cetuximab. The median age was 64.0 years (interquartile range, 58.0-72.0); 126 patients (15.8%) were ≥75 years old, 498 (62.3%) were male, and 585 (73.1%) had a primary tumor in the colon. The Eastern Cooperative Oncology Group performance status (ECOG-PS) was ≥2 for 118 patients (14.8%) and 361 (45.1%) had at least 1 cardiovascular disorder. Most patients (n = 588, 73.5%) received an irinotecan-based chemotherapy regimen in combination with targeted therapy and more than one-third (n = 285, 35.6%) had at least 1 dose reduction of targeted therapy. Definitive discontinuation of first-line therapy was observed in 673 (84.1%) patients, nearly two-thirds because of progressive disease (n = 511, 63.9%) and 66 (8.3%) because of poor tolerability. The incidence of Grade 3/4 adverse events was 52.0% (n = 416), most frequently asthenia (n = 84, 10.5%), diarrhea (n = 74, 9.3%), and neutropenia (n = 71, 8.9%).

Descriptive Analyses Stratified According to Age

Denutrition and ECOG-PS ≥1 were significantly more frequent in elderly patients compared with younger patients (65.0% vs. 53.0%, $P = 0.005$ and 13.5% vs. 6.7%, $P = .007$, respectively). Among medical histories, cardiac and renal disorders were significantly more frequent in elderly patients (60.3% vs. 42.3%, $P = .0002$ and 10.3% vs. 4.7%, $P = .01$, respectively) as well as anemia (57.9% vs. 48.1%, $P = .04$; Table 1).

Regarding treatment patterns, elderly patients were more often treated with 5-fluorouracil alone in combination with bevacizumab or cetuximab (6.4% vs. 0.5%; $P = .0003$). There was no difference in the delay between the chemotherapy and targeted therapy initiation between age groups but elderly patients had less frequently dose reductions compared with younger patients (28.6% vs. 38.4%;

Table 2 Description of Targeted Therapy Usage Patterns in First-Line Therapy at 2 Years of Follow-Up in the STROMBOLI Study (n = 800)

Characteristic, *n (%)*	Patients Aged <75 Years (n = 674)	Patients Aged ≥75 Years (n = 126)	*P*
First-Line Chemotherapy Used With Targeted Therapy			.0003
Irinotecan-based regimen	486 (72.1)	92 (73.0)	
Oxaliplatin-based regimen	171 (25.4)	25 (19.8)	
Irinotecan and oxaliplatin-based regimen	10 (1.5)	0 (0.0)	
5-Fluorouracil alone	4 (0.5)	8 (6.4)	
No chemotherapy	3 (0.8)	1 (0.8)	
Initiation of the Targeted Therapy			.95
At the first cycle of treatment	414 (61.4)	77 (61.1)	
Delayed targeted therapy initiation	260 (38.6)	49 (38.9)	
Median delay (range), days	28 (14.0-41.5)	28 (18.0-43.0)	.55
At Least 1 Dose Reduction			**.01**
None	343 (50.9)	77 (61.1)	
At least 1	249 (38.4)	36 (28.6)	
Missing data	82 (12.2)	13 (10.3)	
Median Number of Cycles (IQR)	12 (7-16)	12 (5-18)	.85
Definitive Discontinuation of First-Line Therapy	564 (83.7)	109 (86.5)	.17
Main Reason for Definitive Discontinuation of First-Line Therapy[a]			.27
Progressive disease	432 (76.6)	79 (72.5)	
Poor tolerability	57 (10.1)	9 (8.3)	
Death	27 (4.8)	10 (9.2)	
Physician decision	27 (4.8)	4 (3.7)	
Other	15 (2.7)	6 (5.5)	
Missing data	6 (1.1)	1 (0.9)	
Premature Discontinuation of Targeted Therapy	88 (13.1)	11 (8.7)	.20
Main Reason for Definitive Discontinuation of Targeted Therapy[a]			.64
Poor tolerability	55 (62.5)	8 (72.7)	
Other	31 (35.2)	3 (27.3)	
Missing data	2 (2.3)	0 (0.0)	
At Least 1 Metastasectomy	166 (24.6)	20 (15.9)	**.03**
Initiation of a Second-Line Therapy[a]	428 (67.1)	70 (58.8)	.08
Same targeted therapy	119 (27.8)	24 (34.3)	
Change of targeted therapy	172 (40.2)	22 (31.4)	
Chemotherapy alone	136 (31.8)	23 (32.9)	
Radiotherapy alone	0 (0.0)	1 (1.4)	
Missing data	1 (0.1)	0 (0.0)	
At Least 1 Any Grade Adverse Event	662 (98.2)	123 (97.6)	.72
Blood and lymphatic system disorders	557 (82.6)	106 (84.1)	.68
Cardiovascular disorders	166 (24.6)	33 (26.2)	.71
Gastrointestinal disorders	543 (80.6)	102 (81.0)	.92
Nervous system disorders	252 (37.4)	30 (23.8)	**.003**
Skin and subcutaneous tissue disorders	371 (55.0)	55 (43.7)	**.02**
At Least 1 Grade 3 or 4 Adverse Event	349 (51.8)	67 (53.2)	.77
Blood and lymphatic system disorders	142 (21.1)	24 (19.1)	.61
Cardiovascular disorders	32 (4.8)	9 (7.1)	.26
Gastrointestinal disorders	117 (17.4)	23 (18.3)	.81
Nervous system disorders	30 (4.5)	2 (1.6)	.13
Skin and subcutaneous tissue disorders	57 (8.5)	12 (9.5)	.70

Data are presented as n (%) except where otherwise noted.
Data in bold correspond to significant value.
Abbreviations: IQR = interquartile range; STROMBOLI = Sujets âgés et TRaitements innovants en Oncologie: cétuxiMab et Bévacizumab dans le cancer cOlorectal métastatique en vle réelle.
[a]Among those concerned.

Table 3 Factors Associated With Death in the STROMBOLI Cohort According to Multivariable Cox Analyses

	Event Versus No Event, HR[a] (95% CI)	*P*
ECOG-PS		<.0001
0	1	
1	1.52 (1.18-1.96)	
≥2	2.92 (2.15-3.97)	
Hemoglobin		**.0044**
Normal	1	
Abnormal	1.39 (1.11-1.75)	
Alkaline Phosphatases		**.0005**
Normal	1	
Abnormal	1.55 (1.22-1.99)	

Data in bold correspond to significant value.
Abbreviations: ECOG-PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; STROMBOLI = Sujets âgés et TRaitements innovants en Oncologie: cétuximab et Bévacizumab dans le cancer cOlorectal métastatique en vle réelle.
[a]Adjusted for age and sex.

$P = .01$). There was no difference between elderly and younger patients regarding definitive discontinuation of first-line therapy (86.5% vs. 83.7%; $P = .17$); however, elderly patients seemed to have less frequently a second-line treatment (58.8% vs. 67.1%; $P = .08$).

Among any-grade adverse events, nervous system disorders and skin and subcutaneous tissue disorders were less frequent in elderly patients (37.4% vs. 23.8%, $P = .003$ and 55.0% vs. 43.7%, $P = .02$, respectively). In terms of Grade 3/4 adverse events, there was no significant difference between age groups (Table 2).

Survival Analyses

After 2 years of follow-up, 404 patients (50.5%) had died. After univariate Cox proportional hazards analyses (see Supplemental Table 1 in the online version), ECOG-PS, body mass index (BMI), primary tumor site, type of metastases, and all tested biological parameters were included in the multivariate model. After adjustment for age and sex, ECOG-PS ≥1, abnormal hemoglobin, and abnormal alkaline phosphatases were found to be associated with a higher risk of death in multivariate analyses (Table 3). There was no difference between elderly and younger patients in terms of OS (median 23.4 months [95% CI, 21.7; not reached (NR)] vs. 21.7 months [95% CI, 17.8; NR]; $P = .45$; Figure 1), using the Kaplan–Meier method adjusted for ECOG-PS, hemoglobin, and alkaline phosphatases.

After 2 years of follow-up, 712 (89.0%) had disease progression or had died. After univariate Cox proportional hazards analyses (see Supplemental Table 2 in the online version), ECOG-PS, BMI, number of metastatic sites, lung metastases, and all tested biological parameters except bilirubin were included in the multivariate model. After adjustment for age and sex, ECOG-PS ≥1, lung metastases, abnormal hemoglobin, and abnormal creatinine clearance were found to be associated with a higher risk of progression or death in multivariate analyses (Table 4). There was no difference between elderly and younger patients in terms of PFS (median 9.4 months [95% CI, 8.8-9.8] vs. 9.7 months [95% CI, 8.7-10.9]; $P = .59$; Figure 2). OS and PFS rates are reported in Supplemental Table 3 in the online version.

Discussion

The STROMBOLI study is one of the largest observational cohorts of patients treated with the 2 major targeted therapies available in first-line mCRC treatment. Its strength is to provide data on all useful aspects for post marketing evaluation (ie, use,

Figure 1 Overall Survival During the 2 Years After Inclusion Stratified According to Age (<75 Years vs. ≥75 Years; Adjusted Kaplan–Meier Curve)

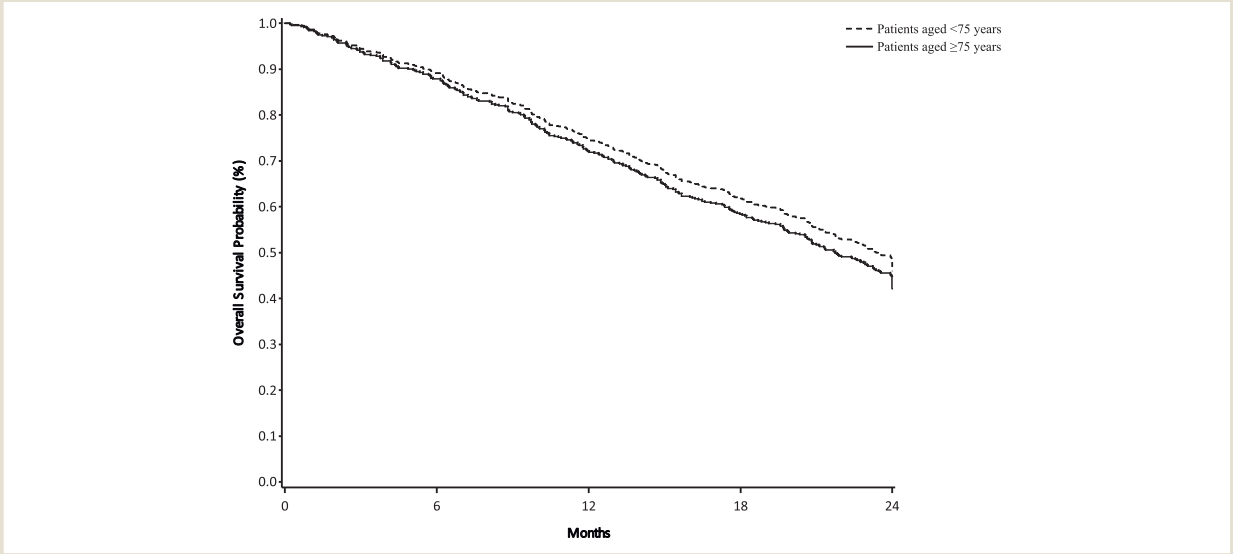


Table 4 Factors Associated With Progression or Death in the STROMBOLI Cohort According to Multivariable Cox Analyses

	Event Versus No Event, HR[a] (95% CI)	*P*
ECOG-PS		<.0001
0	1	
1	1.19 (0.99-1.43)	
≥2	1.72 (1.34-2.20)	
Lung Metastases		**<.0001**
No	1	
Yes	1.43 (1.20-1.71)	
Hemoglobin		**.0212**
Normal	1	
Abnormal	1.22 (1.03-1.45)	
Creatinine Clearance		**.0493**
Normal	1	
Abnormal	1.24 (1.00-1.54)	

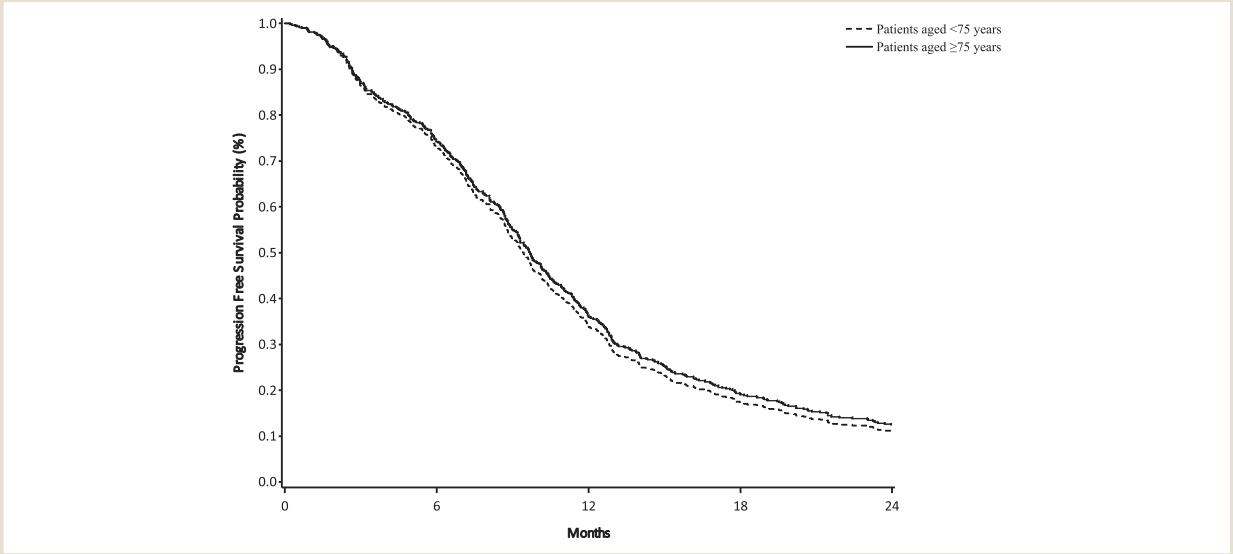
Data in bold correspond to significant value.
Abbreviations: ECOG-PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; STROMBOLI = Sujets âgés et TRaitements innovants en Oncologie: cétuximab et Bévacizumab dans le cancer cOlorectal métastatique en vle réelle.
[a]Adjusted for age and sex.

effectiveness, and safety) in 800 patients, especially patients who would have been excluded from clinical trials: patients with an ECOG-PS ≥2 (14.8%), with cardiovascular comorbidities (45.1%), or with biological abnormalities (low hemoglobin 49.6%, or low creatinine clearance 16.3%).

The main interest of this cohort analysis is the comparison performed between the younger and elderly patients. If age seems to be a factor driving the patterns of use (eg, 5-fluorouracil alone, second-line treatment), it was not associated with a different safety profile nor a lower effectiveness in terms of survival outcomes. In the BRITE (Bevacizumab Regimens Investigation of Treatment Effects) cohort, studying bevacizumab only, 4 age groups were compared: <65 years, 65 to 74 years, 75 to 79 years, and ≥80 years. If median PFS was similar across all age groups (ranging from 8.6 to 10.0 months), median OS was only different between patients aged ≥80 years and those aged <75 years (ranging from 16.8 to 24.6 months). Except for arterial thromboembolic events, which were more frequently reported in patients aged ≥75 years, the safety profile was equivalent across all age groups.[12,13] Finally, our results confirm that the use of targeted therapies in the elderly population is effective and safe in a real-life setting. However, even if the present cohort included 15% of patients aged ≥75 years, compared with approximately 8% in clinical trials, the median age was comparable with the median age of clinical trials (approximately 64 years).[6] This suggests that elderly patients treated with targeted therapies in clinical practice might be still selected according to good prognostic factors. This median age was consistent with that in other post marketing studies on targeted therapies in mCRC: an international pharmacovigilance study and other observational cohorts.[12,14,15] The next step would be to investigate determinants of treatment with targeted therapies in the whole elderly population with mCRC to assess if there is a real undertreatment of certain elderly patients.[16] Indeed, in an Australian cohort in a study of the use of chemotherapy and bevacizumab in patients aged ≥65 years, 3 factors were associated with no treatment with bevacizumab: age (≥75 years), type of center (public or private hospital), and Charlson comorbidity index (≥3); yet, not ECOG-PS ≥2.[17]

Another interest of this cohort was to identify factors associated with death or progression in a large and homogeneous population of mCRC patients treated with targeted therapies in first-line therapy. In fact, age and comorbidities are frequently associated with the idea that these patients are vulnerable and cannot benefit from anticancer

Figure 2 Progression-Free Survival During the 2 Years After Inclusion Stratified According to Age (<75 Years vs. ≥75 Years; Adjusted Kaplan–Meier Curve)



medications. In the present study we did not find that older age was a risk factor of death or progression and among all other tested vulnerability factors that are often considered in rapid detection tools of frailty (eg, denutrition, comorbidities); none were found to be associated with a higher risk of death or progression, except that creatinine clearance was associated with progression or death.[18,19] This could be explained by the prescribing of lower doses of anticancer medications in patients with altered kidney function. Unfortunately, available data were not sufficiently accurate to confirm this hypothesis. All other criteria were rather related to the mCRC: ECOG-PS, lung metastases, abnormal hemoglobin (potential marker of bleeding), and abnormal alkaline phosphatases (potential marker of liver metastases). The prognostic score proposed by Köhne et al before the era of targeted therapies included 4 factors associated with early death: ECOG-PS, number of metastatic sites, abnormal alkaline phosphatases, and low white blood cell count.[20] More recently, Kabbinavar et al[21] showed that this score could be extended to patients treated with bevacizumab in association with a 5−fluorouracil-based regimen whereas Desot et al[22] reported that ECOG-PS and low white blood cell count could be sufficient to classify patients at risk of death in a study including patients treated with bevacizumab, cetuximab, or panitumumab. As in the present study, ECOG-PS is highlighted as a risk factor in most of evaluations. One explanation could be that this score explains some other frailty aspects (such as denutrition or comorbidities). Indeed, in a study that evaluated whether Comprehensive Geriatric Assessment (CGA) adds further information with respect to the ECOG-PS in elderly cancer patients, components of the CGA, especially Activities of Daily Living and Instrumental Activities of Daily Living and ECOG-PS were strongly correlated.[23] Even if ECOG-PS alone cannot be sufficient to detect patients who will not benefit from treatment, all of these data show that this is an important factor to take into account especially because it is systematically evaluated by the oncology community.

Conclusion

Elderly patients could benefit from treatment with targeted therapies without safety warning. However, further studies are needed to understand better treatment determinants in this population and more efficiently screen elderly patients who should be treated with targeted therapies.

Clinical Practice Points

- Bevacizumab or cetuximab used in combination with chemotherapy has shown improved survival outcomes in first-line mCRC treatment.
- In real-life settings, the use of bevacizumab or cetuximab in elderly mCRC patients resulted in outcomes close to those in younger patients. After adjustment, there was no difference between elderly and younger patients in terms of OS (median 23.4 months [95% CI, 21.7; NR] vs. 21.7 months [95% CI, 17.8; NR]; $P = .45$) and in terms of PFS (median 9.4 months [95% CI, 8.8-9.8] vs. 9.7 months [95% CI, 8.7-10.9]; $P = .59$).
- Older age was not a risk factor of death or progression. An ECOG-PS $\geq$1, lung metastases, abnormal hemoglobin, abnormal alkaline phosphatases, and abnormal creatinine clearance were risk factors of death or progression.
- Treatment using bevacizumab or cetuximab with chemotherapy as first-line therapy represents an option in the therapeutic strategy of mCRC in real-life practice for elderly patients.

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Supplemental Data

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Supplemental Table 1 Univariate Analyses of Overall Survival Cox Model

	Patient With Event (n = 404)	Patient Without Event (n = 396)	Total (n = 800)	Event Versus No Event, HR (95% CI)	*P*
Sex					.8894
Male	252 (62.4)	246 (62.1)	498 (62.3)	1	
Female	152 (37.6)	150 (37.9)	302 (37.8)	0.99 (0.81-1.21)	
Age					.5322
<65 years	207 (51.2)	196 (49.5)	403 (50.4)	1	
65-74 years	130 (32.2)	141 (35.6)	271 (33.9)	0.93 (0.74-1.15)	
≥75 years	67 (16.6)	59 (14.9)	126 (15.8)	1.09 (0.83-1.44)	
ECOG-PS					**<.0001**
Missing data	26 (6.4)	34 (8.6)	60 (7.5)		
0	116 (28.7)	185 (46.7)	301 (37.6)	1	
1	173 (42.8)	148 (37.4)	321 (40.1)	1.65 (1.30-2.08)	
≥ 2	89 (22.0)	29 (7.3)	118 (14.8)	3.33 (2.52-4.40)	
BMI[a]					**.0756**
Missing data	11 (2.7)	16 (4.0)	27 (3.4)		
Normal	355 (87.9)	356 (89.9)	711 (88.8)	1	
Denutrition	38 (9.4)	24 (6.1)	62 (7.8)	1.35 (0.97-1.89)	
Number of Comorbidities					.2798
0-1	148 (36.6)	127 (32.1)	275 (34.4)	1	
2-3	149 (36.9)	165 (41.7)	314 (39.3)	0.83 (0.66-1.04)	
≥4	107 (26.5)	104 (26.3)	211 (26.4)	0.93 (0.72-1.19)	
Primary Tumor Site					**.0870**
Colon	305 (75.5)	280 (70.7)	585 (73.1)	1	
Rectum	99 (24.5)	116 (29.3)	215 (26.9)	0.82 (0.65-1.03)	
Type of Metastases					**.0073**
Synchronous	305 (75.5)	264 (66.7)	569 (71.1)	1	
Metachronous	99 (24.5)	132 (33.3)	231 (28.9)	0.73 (0.59-0.92)	
Number of Metastatic Sites					.3702
1	207 (51.2)	233 (58.8)	440 (55.0)	1	
2	137 (33.9)	121 (30.6)	258 (32.3)	1.12 (0.90-1.38)	
≥3	60 (14.9)	42 (10.6)	102 (12.8)	1.22 (0.88-1.71)	
Liver Metastases					.6143
No	107 (26.5)	98 (24.7)	205 (25.6)	1	
Yes	297 (73.5)	298 (75.3)	595 (74.4)	0.95 (0.76-1.18)	
	Patients With Event (n = 605)	**Patients Without Event (n = 195)**			
Lung Metastases					.3478
No	289 (71.5)	274 (69.2)	563 (70.4)	1	
Yes	115 (28.5)	122 (30.8)	237 (29.6)	0.90 (0.73-1.12)	
Hemoglobin					**<.0001**
Missing data	35 (8.7)	30 (7.6)	65 (8.1)		
Normal	138 (34.2)	200 (50.5)	338 (42.3)	1	
Abnormal	231 (57.2)	166 (41.9)	397 (49.6)	1.69 (1.37-2.09)	
Creatinine Clearance (Between 10% and 50% of Missing Data; Multiple Imputations)					**.0293**
Missing data	56 (13.9)	71 (17.9)	127 (15.9)		
Normal	270 (66.8)	273 (68.9)		1	

Supplemental Table 1 Continued

	Patients With Event (n = 605)	Patients Without Event (n = 195)			
Abnormal	78 (19.3)	52 (13.1)	130 (16.3)	1.31 (1.03-1.68)	
Alkaline Phosphatases (Between 10% and 50% of Missing Data; Multiple Imputations)					**<.0001**
Missing data	109 (27.0)	117 (29.5)	226 (28.3)		
Normal	119 (29.5)	177 (44.7)	296 (37.0)	1	
Abnormal	176 (43.6)	102 (25.8)	278 (34.8)	1.85 (1.51-2.27)	
Bilirubin (Between 10% and 50% of Missing Data; Multiple Imputations)					**.0842**
Missing data	126 (31.2)	156 (39.4)	282 (35.3)		
Normal	240 (59.4)	221 (55.8)	461 (57.6)	1	
Abnormal	38 (9.4)	19 (4.8)	57 (7.1)	1.39 (0.95-2.03)	
Transaminases (Between 10% and 50% of Missing Data; Multiple Imputations)					**.0038**
Missing data	88 (25.8)	102 (25.8)	190 (23.8)		
Normal	185 (45.8)	211 (53.3)	396 (49.5)	1	
Abnormal	131 (32.4)	83 (21.0)	214 (26.8)	1.45 (1.13-1.85)	

Data are presented as n (%) except where otherwise noted.
Data in bold correspond to significant value.
Abbreviations: BMI = body mass index; ECOG-PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio.
[a]Denutrition defined as: BMI <18.5 if age ≤70 years and BMI <21 if age >70 years.

Supplemental Table 2 Univariate Analyses of Progression-Free Survival Cox Model

	Patients With Event (n = 712)	Patients Without Event (n = 88)	Total (n = 800)	Event Versus No Event, HR [95% CI]	*P*
Sex					.6125
Male	443 (62.2)	55 (62.5)	498 (62.3)	1	
Female	269 (37.8)	33 (37.5)	302 (37.8)	1.04 (0.89-1.21)	
Age					.4897
<65 years	346 (85.9)	57 (14.1)	403 (50.4)	1	
65-74 years	250 (92.3)	21 (7.8)	271 (33.9)	1.07 (0.91-1.26)	
≥75 years	116 (92.1)	10 (7.9)	126 (15.8)	1.12 (0.91-1.39)	
ECOG-PS					**<.0001**
Missing data	52 (7.3)	8 (9.1)	60 (7.5)		
0	261 (36.7)	40 (45.5)	301 (37.6)	1	
1	290 (40.7)	31 (35.2)	321 (40.1)	1.28 (1.09-1.52)	
≥2	109 (15.3)	9 (10.2)	118 (14.8)	1.84 (1.47-2.30)	
BMI[a]					**.1958**
Missing data	24 (3.4)	3 (3.4)	27 (3.4)		
Normal	631 (88.6)	80 (90.9)	711 (88.8)	1	
Denutrition	57 (8.0)	5 (5.7)	62 (7.8)	1.20 (0.91-1.57)	
Number of Comorbidities					.4093
0-1	248 (34.8)	27 (30.7)	275 (34.4)	1	
2-3	274 (38.5)	40 (45.5)	314 (39.3)	0.95 (0.80-1.13)	
≥4	190 (26.7)	21 (23.9)	211 (26.4)	1.08 (0.89-1.30)	
Primary Tumor Site					.5548
Colon	513 (72.1)	72 (81.8)	585 (73.1)	1	
Rectum	199 (27.9)	16 (18.2)	215 (26.9)	1.05 (0.89-1.24)	
Type of Metastases					.4432
Synchronous	508 (71.3)	61 (69.3)	569 (71.1)	1	
Metachronous	204 (28.7)	27 (30.7)	231 (28.9)	0.94 (0.80-1.10)	
Number of Metastatic Sites					**.0050**
1	379 (53.2)	61 (69.3)	440 (55.0)	1	
2	237 (33.3)	21 (23.9)	258 (32.3)	1.22 (1.04-1.43)	
≥3	96 (13.5)	6 (6.8)	102 (12.8)	1.42 (1.10-1.83)	
Liver Metastases					.8981
No	181 (25.4)	24 (27.3)	205 (25.6)	1	
Yes	531 (74.6)	64 (72.7)	595 (74.4)	0.99 (0.84-1.17)	
	Patients With Event (n = 605)	**Patients Without Event (n = 195)**			
Lung Metastases					**.0051**
No	487 (68.4)	76 (86.4)	563 (70.4)	1	
Yes	225 (31.6)	12 (13.6)	237 (29.6)	1.26 (1.07-1.47)	
Hemoglobin					**.0042**
Missing data	64 (9.0)	1 (1.1)	65 (8.1)		
Normal	294 (41.3)	44 (50.0)	338 (42.3)	1	
Abnormal	354 (49.7)	43 (48.9)	397 (49.6)	1.25 (1.07-1.46)	
Creatinine Clearance (Between 10% and 50% of Missing Data; Multiple Imputations)					**.0333**
Missing data	116 (16.3)	11 (12.5)	127 (15.9)		
Normal	475 (66.7)	68 (77.3)	543 (67.9)	1	
Abnormal	121 (17.0)	9 (10.2)	130 (16.3)	1.23 (1.02-1.49)	

Supplemental Table 2 Continued

	Patients With Event (n = 605)	Patients Without Event (n = 195)			
Alkaline Phosphatases (Between 10% and 50% of Missing Data; Multiple Imputations)					**.0138**
Missing data	207 (29.1)	19 (21.6)	226 (28.3)		
Normal	249 (35.0)	47 (53.4)	296 (37.0)	1	
Abnormal	256 (36.0)	22 (25.0)	278 (34.8)	1.23 (1.04-1.45)	
Bilirubin (Between 10% and 50% of Missing Data; Multiple Imputations)					.5555
Missing data	257 (36.1)	25 (28.4)	282 (35.3)		
Normal	403 (56.6)	58 (65.9)	461 (57.6)	1	
Abnormal	52 (7.3)	5 (5.7)	57 (7.1)	1.07 (0.85-1.36)	
Transaminases (Between 10% and 50% of Missing Data; Multiple Imputations)					**.0635**
Missing data	177 (24.9)	13 (14.8)	190 (23.8)		
Normal	337 (47.3)	59 (67.0)	396 (49.5)	1	
Abnormal	198 (27.8)	16 (18.2)	214 (26.8)	1.19 (0.99-1.43)	

Data are presented as n (%) except where otherwise noted.
Data in bold correspond to significant value.
Abbreviations: BMI = body mass index; ECOG-PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio.
[a]Denutrition defined as: BMI <18.5 if age ≤ 70 years and BMI <21 if age >70 years.

Supplemental Table 3 Overall Survival and PFS During the 24 Months After Inclusion (Adjusted Kaplan–Meier Probabilities)

	Total (n = 800)	Patients Aged <75 Years (n = 674)[a]	Patients Aged ≥75 Years (n = 126)[a]
1-Year OS Rate, % (95% CI)	75.3 (72.2-78.2)	74.7 (71.1-78.4)	72.1 (65.6-79.3)
2-Year OS Rate, % (95% CI)	48.2 (44.6-51.7)	48.6 (44.6-53.0)	44.8 (36.4-55.2)
1-Year PFS Rate, % (95% CI)	35.0 (31.7-38.3)	34.1 (30.4-38.2)	36.3 (29.3-45.0)
2-Year PFS Rate, % (95% CI)	10.5 (8.4-12.7)	11.0 (8.7-13.8)	12.5 (8.0-19.4)

Abbreviations: ECOG-PS = Eastern Cooperative Oncology Group performance status; OS = overall survival; PFS = progression-free survival.
[a]Overall survival rates were adjusted for age, sex, ECOG-PS, abnormal hemoglobin, and abnormal alkaline phosphatase, and PFS rates were adjusted for age, sex, ECOG-PS, lung metastases, abnormal hemoglobin, and abnormal creatinine.