Physicians' preferences for later-line treatment of metastatic colorectal cancer in Germany and the UK

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Background and objective

- At initial diagnosis of colorectal cancer (CRC), approximately 15–30% of patients present with metastatic colorectal cancer (mCRC; also known as stage IV CRC). Additionally, 20–50% of patients diagnosed with stage I–III CRC eventually develop mCRC[1]
- Third-line or later (3L+) treatments for mCRC, such as trifluridine-tipiracil +/- bevacizumab, regorafenib, and fruquintinib, extend survival by approximately 2–3 months.[2–5] However, 3L+ treatments have different side effect profiles; some have a greater incidence of hematologic events such as neutropenia, whereas others have higher rates of hand-foot syndrome or hypertension[2–6]
- When determining the best treatment options for patients with mCRC, extending survival must be balanced with managing treatment risks and preserving quality of life[7]
- This survey aimed to explore the influence of treatment attributes (characteristics) on physicians' preferences for 3L+ mCRC treatments in Germany and the United Kingdom (UK)

Methods

- Oncologists and gastroenterologists (hereafter "physicians") in Germany and the UK who self-reported having treated ≥10 patients with mCRC in the past year were recruited through established physician panels. They completed an online survey after providing informed consent
- The survey included multidimensional thresholding exercises consisting of two attribute ranking exercises and 13–15 paired treatment comparison tasks, followed by sociodemographic and medical practice-related questions
- The treatment attributes in the multidimensional thresholding exercises (**Table 1**) were developed based on a targeted review of scientific literature and clinical data, patient engagement, and pilot interviews with patients and physicians
- In the attribute ranking exercise, physicians ranked the eight attributes in terms of their importance for improvement. The ranking ranged from first place (indicating the most important attribute to improve) to eighth place (indicating the least important attribute to improve). The attribute ranking was conditional on the specific levels of improvement for each attribute characterised by the level ranges outlined in **Table 1**. The range for the treatment regimen presented the most and least preferred options as determined by a separate regimen ranking exercise
- The thresholding exercise was constructed based on individual attribute rankings. Physicians chose their preferred treatment through a series of paired comparison tasks (**Figure 2**)
- Physicians' preferences were examined through the ranking of attributes by importance and the trade-offs they would make between two attributes
- Data from the ranking and multidimensional thresholding exercises were analysed using a Dirichlet regression model. Marginal rates of substitution were calculated to quantify physicians' willingness to accept treatment-related risks in exchange for treatment benefits

Table 1: Treatment attributes and level ranges

Treatment attributes	Level ranges*
Time alive after starting treatment (OS)	4–12 months
Chance of no cancer progression at 3 months (3-month PFS)	10–75%
Risk of severe hand-foot syndrome (grade ≥3)	0–20%
Risk of diarrhea (all grades)	5–50%
Risk of severe neutropenia (grade ≥3)	0–55%
Risk of mild-to-moderate hypertension (grade <3)	0–65%
Risk of fatigue (all grades)	10–65%
Treatment regimen	• Two oral pills taken once daily • Three oral pills taken twice daily • Three oral pills taken twice daily + intravenous infusion every 2 weeks

*Informed by clinical trial data including active treatment, placebo, and best supportive care.
OS, overall survival; PFS, progression-free survival.

Question

What treatment attributes influence physicians' preferences for 3L+ mCRC treatments?

Survey design

Description of the treatment attributes with their level ranges → Regimen ranking exercise; Attribute ranking exercise → Thresholding exercise with a series of paired treatment comparison tasks → Demographic and medical practice questions

Key results

Figure 1: Minimum additional OS required for physicians to accept changes in other treatment attributes

Attribute change	Germany (n=81)	UK (n=75)
3 pills BID → 3 pills BID + IV Q2W	0.6	1.8
2 pills QD → 3 pills BID + IV Q2W	1.1	2.5
2 pills QD → 3 pills BID	0.4	0.7
3-month PFS (10% decrease)	0.6	0.7
All-grade fatigue (10% increase)	0.3	0.7
Grade ≥3 hand-foot syndrome (10% increase)	1.1	1.3
Grade <3 hypertension (10% increase)	0.2	0.3
Grade ≥3 neutropenia (10% increase)	0.5	0.6
All-grade diarrhea (10% increase)	0.5	0.6

Mean months of OS

BID, twice daily; IV, intravenous; Q2W, every 2 weeks; QD, once daily.

Physicians would require a minimum additional OS benefit to accept a 10% increase in treatment-related risks or to switch to a treatment with a less desirable regimen. For example:

- To accept treatment with a 10% increased risk of grade ≥3 hand-foot syndrome, physicians in Germany required a 1.1-month increase in OS and physicians in the UK required a 1.3-month increase in OS
- To accept a treatment regimen that includes three oral pills twice daily and an intravenous infusion every 2 weeks instead of a treatment regimen requiring only two oral pills once daily, physicians in Germany required a 1.1-month increase in OS and physicians in the UK required a 2.5-month increase in OS

Key takeaways

- **Changes in OS, 3-month PFS, and the risk of grade ≥3 neutropenia influenced physicians' preferences for 3L+ treatments**
- **Physicians were willing to make trade-offs to balance OS with avoiding treatment-related risks or more burdensome treatment regimens**

Methods

Figure 2: Example multidimensional thresholding choice task

	Treatment A	Treatment B
Chance of no cancer progression at 3 months (3-month PFS)	10 out of 100 patients (10%) live at least 3 months with no cancer progression	32 out of 100 patients (32%) live at least 3 months with no cancer progression
Risk of severe neutropenia	0 out of 100 patients (0%) experience severe neutropenia	55 out of 100 patients (55%) experience severe neutropenia
Which treatment would you choose?	○	○

This example illustrates a choice task where a 3-month PFS was ranked higher than the risk of grade ≥3 (severe) neutropenia. PFS, progression-free survival.

Results

- In total, 156 physicians (Germany: n=81; UK: n=75) completed the survey (**Figure 3**)

Figure 3: Physician characteristics

	Germany (n=81)	UK (n=75)
Sex	16.0% female; 80.2% male; Prefer not to answer: 3.7%	17.3% female; 80.0% male; Prefer not to answer: 2.7%
Specialty	86.4% medical oncologist, 3.7% radiation oncologist, 22.2% gastroenterologist*	82.7% medical oncologist, 16.0% radiation oncologist, 20.0% gastroenterologist*
Number of patients with mCRC treated in the past year	10–19: 12.3%; 20 or more: 87.7%	10–19: 9.3%; 20 or more: 90.7%
Number of patients with mCRC receiving 3L+ treatments treated in the past year	1–19: 60.5%; 20 or more: 39.5%	1–19: 53.3%; 20 or more: 46.7%

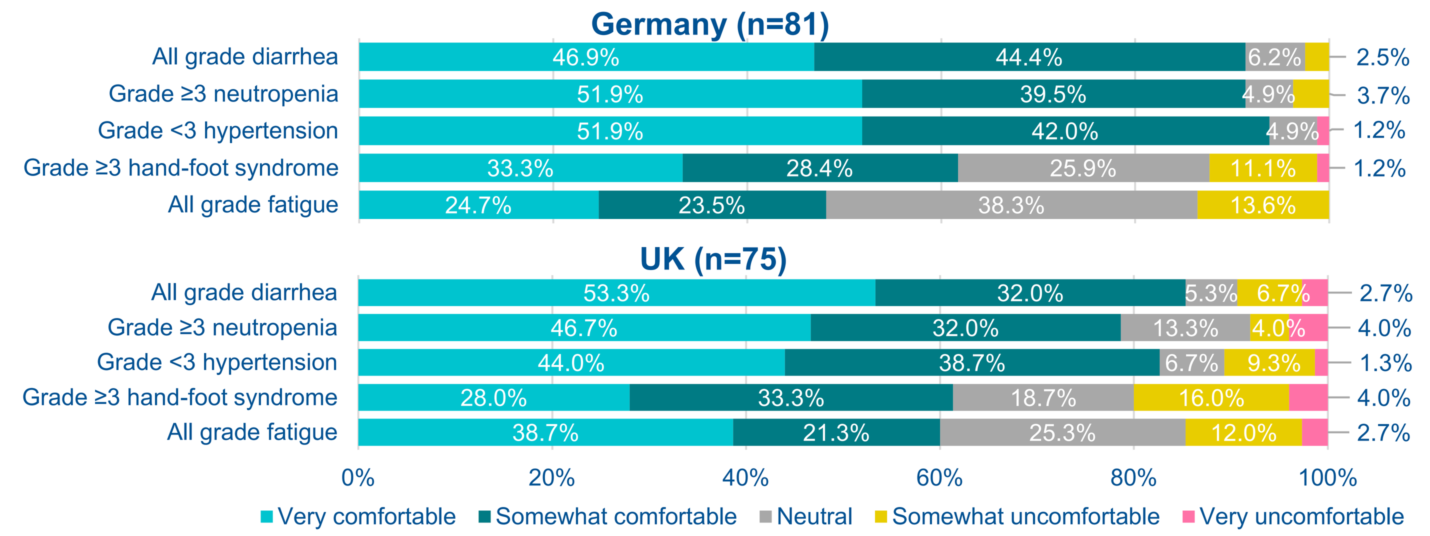
*Multiple responses were allowed for medical specialty. 3L+, third-line or later; mCRC, metastatic colorectal cancer.

Results

Managing adverse events in the 3L+ setting

- Most physicians in Germany and the UK reported being 'somewhat' or 'very' comfortable managing diarrhea (all grades) (Germany: 91.4%; UK: 85.3%), grade ≥3 neutropenia (Germany: 91.4%; UK: 78.7%), and grade <3 hypertension (Germany: 93.8%; UK: 82.7%; **Figure 4**)
- Almost half of the physicians were 'somewhat' or 'very' comfortable managing grade ≥3 hand-foot syndrome (Germany: 61.7%; UK: 61.3%) and fatigue (all grades) (Germany: 48.1%; UK: 60.0%)

Figure 4: Physician-reported comfort in managing adverse events (3L+)

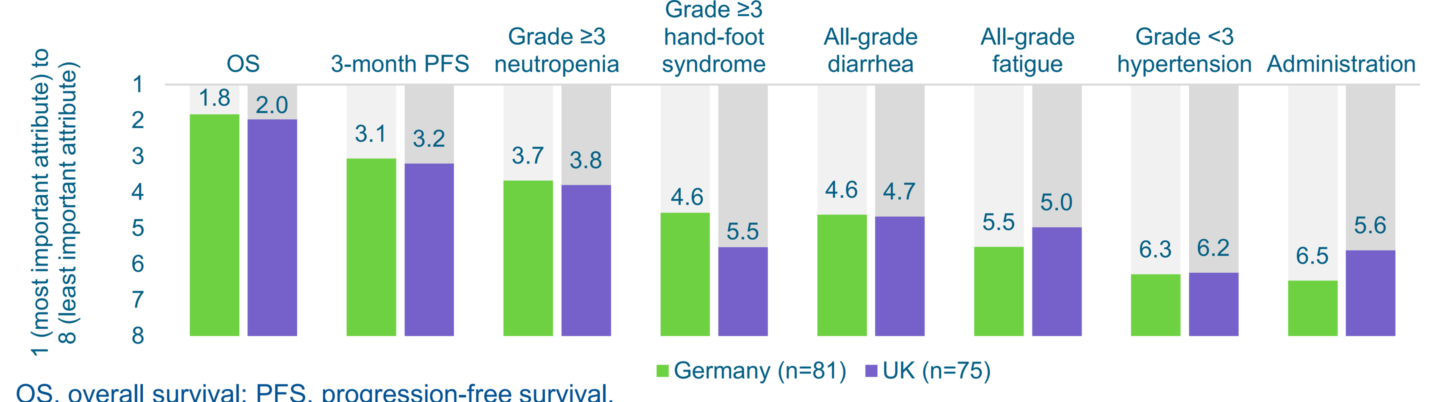


Totals may not sum to 100% due to rounding.

Attribute ranking

- OS, 3-month PFS, and risk of grade ≥3 neutropenia were the top-ranked attributes that physicians in both countries reported were most important for a 3L+ mCRC treatment to improve (**Figure 5**). Grade ≥3 hypertension and mode of administration were the lowest-ranked attributes in both countries
- On average, OS was most frequently ranked as the most important attribute to improve (Germany: 1.8; UK: 2.0). Grade ≥3 hand-foot syndrome was ranked lower by UK physicians (5.5) than German physicians (4.6). Mode of administration was ranked higher by UK physicians (5.6) than German physicians (6.5)

Figure 5: Average ranking scores of treatment attributes



OS, overall survival; PFS, progression-free survival.

Minimum additional OS required for chances in other treatment attributes

- Physicians would require a minimum additional OS benefit to accept a 10% increase in treatment-related risks or to switch to a treatment with a less desirable regimen **(Summary Panel; Figure 1)**

Conclusions

- Physicians treating patients with mCRC in Germany and the UK consider OS, PFS, and the risk of severe neutropenia as the most influential factors in treatment selection
- The findings indicate that physicians require survival gains to accept increased toxicity or more burdensome treatment regimens, such as those requiring intravenous administration
- Future studies should explore how these treatment attributes influence patients' preferences
- These insights highlight the importance of accounting for physicians' preferences when developing new treatments, to support alignment with clinical decision-making and real-world treatment considerations

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Disclosures

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