THE PROSPECTIVE, NATIONAL RESEARCH PLATFORM AZURITE

CURRENT ROUTINE CARE OF METASTATIC COLORECTAL CANCER IN GERMANY

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Funding
AZURITE is designed, managed and analysed by iOMEDICO and receives continuous financial support from continous financial support from Merck Sharp & Dome LLC, MSD Sharp&Dohme GmbH, Onkovis GmbH and Pierre Fabre Pharma GmbH. None of the funders had any role in study design, data collection and analysis, interpretation of results, decision to publish, or preparation of this analysis.

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Acknowledgement
The AZURITE Registry group thanks all participating patients, physicians and study teams.
Project idea, design, management and analysis: iOMEDICO.

Conflicts of Interest
M. Michl: Advisory Role or Expert Testimony and Honoraria: Roche, MSD, Amgen, Merck, BMS, SIRTex | **S. Stintzing:** Employment or Leadership Position: Charité – Universitaetsmedizin Berlin; Advisory Role or Expert Testimony: AMGEN, AstraZeneca, Bayer, BMS, ESAI, Lilly, Merck KGaA, MSD, Pierre-Fabre, Roche, Sanofi, Servier, Taiho, Takeda; Honoraria: AMGEN, AstraZeneca, Bayer, BMS, ESAI, LEO Pharma, Lilly, Merck KGaA, MSD, Pierre-Fabre, Roche, Sanofi, Servier, Taiho, Takeda; Financing of Scientific Research: Merck KGaA, Pierre-Fabre, Servier, Roche

DGHO Jahrestagung 2022
7. - 10. Oktober, Wien
Postennummer: P1001

INTRODUCTION

Since 2006, the Tumor Registry Colorectal Cancer (TKK) represents an important source for clinical research in Germany. Prospective patient data on treatments and outcomes were documented for 6872 colorectal cancer patients, thereof 4845 patients with metastatic disease (mCRC) (Marschner et al. 2015, Marschner et al. 2019). Since 2021, AZURITE continues this successful work focusing on current changes in treatment patterns, clinical and patient-reported-outcomes (PROs) after the approval of novel treatment options, such as the immune checkpoint inhibitors pembrolizumab and nivolumab for patients with MSI-H/dMMR tumors or the kinase inhibitor encorafenib for patients with BRAF V600E mutation. Furthermore, a decentralized biobank for future translational research is established.

CONCLUSIONS

The registry platform AZURITE shows that testing for biomarkers relevant for recently approved treatments, such as BRAF V600E mutation or MSI-H/dMMR has been quickly implemented in routine care in Germany. Whereas testing for RAS and BRAF mutation is well established and routinely performed prior to first-line treatment in mCRC patients, testing for MSI/MMR is only done in approximately 60%/30% of patients, respectively. Future analyses will show treatment sequences including the integration of novel treatment regimens and whether biomarker-guided therapies improve survival and QoL in a real-world setting.

METHODS

AZURITE (NCT04867525) is a prospective observational open multicenter clinical registry platform. Therapies and outcomes of additional 500 mCRC patients treated in more than 100 sites (comprehensive cancer centers, clinics and office-based gastroenterologists and oncologists) are documented. Enrolment is at start of first palliative treatment and follow-up continues until death or up to a maximum of 3 years. There is no treatment specification. In detail, data on sociodemographic status, tumor characteristics, biomarker testing in routine clinical practice, (sequential) systemic treatments and their effectiveness, physician-reported factors influencing treatment decision, and additional treatment modalities (e.g., surgery, radiotherapy) are documented in an electronic data capture system with implemented checks for completeness and plausibility. Data are monitored by remote data management and on-site. A decentralized biobank serves for future translational research. Longitudinal PRO evaluation regardless of treatment line aims to display PROs in clinical practice.

Between May 12th, 2021 and March 31st, 2022, a total of 507 patients with advanced mCRC were recruited into AZURITE. At database cut for this interim analysis data of 441 patients were evaluable. Here, data on biomarker testing rates are presented for those 441 patients and first data on patient characteristics and systemic first-line treatment are presented for 386 patients who could be assigned to the four specific biomarker-defined subgroups: RAS/BRAF wildtype, RAS mutated, BRAF V600E mutated, MSI-H/dMMR.

RESULTS

At start of first-line treatment, 93% of the 441 AZURITE patients with mCRC were tested for at least one biomarker (KRAS, NRAS, BRAF or MSI/MMR). KRAS (88%) and BRAF (83%) were tested the most followed by testing for NRAS (74%) and MSI (64%) (**figure 1**). 47% of all patients (corresponding to 54% of all patients tested) had a KRAS/NRAS mutated tumor, 10% (12% of all patients tested) had a BRAF V600E mutated tumor and 5% (7% of all patients tested) had an MSI-H/dMMR tumor. Results for each biomarker are displayed in **figure 1**.

Median age for patients recruited into AZURITE was 66 years at start of first-line treatment, 34% of patients were female. 39% of patients had an ECOG performance status of 0. In 74% of patients the tumor was already metastasized at diagnosis (stage IV). Metastases were mostly localized in the liver (69%), the lung (30%) and the peritoneum (22%). Patient and tumor characteristics for the specific biomarker-defined subgroups are displayed in **table 1**.

For 138 patients a RAS/BRAF wildtype tumor was documented. Of 99 patients with left-sided RAS-wildtype mCRC 69% of patients received chemotherapy in combination with an EGFR-inhibitor, 11% received an VEGF-inhibitor as part of their first-line treatment. Of 34 patients with right-sided RAS-wildtype mCRC, 32% of patients received chemotherapy combined with an EGFR-inhibitor, 47% received a VEGF-inhibitor in first-line (**figure 2**). Details on regimens are displayed in **figure 3**.

Of 207 patients with RAS-mutated tumors, 59% received chemotherapy + VEGF-inhibitor, 41% received chemotherapy without VEGF-inhibitor as first-line treatment (**figure 2 and 4).**

19 out of 41 patients with BRAF V600E mutation were treated upfront with chemotherapy + VEGF-inhibitor (**figure 2 and 5**). Of note, 9 out of 43 patients had a BRAF mutated and an additional MSI-H/dMMR mCRC. Data on second-line therapies are not yet mature.

Of 22 patients with MSI-H/dMMR tumors, 8 patients received the checkpoint inhibitor pembrolizumab as first-line treatment, the others were treated with chemotherapy (**figure 4 and 6**).

Table 1

Characteristic	KRAS/BRAF WT left-sided	KRAS/BRAF WT right-sided	RAS mutation	BRAF V600E mutation	MSI-H/dMMR
Number of patients (n [%])	99 [100.0]	34 [100.0]	207 [100.0]	41 [100.0]	22 [100.0]
Sex, female (n [%])	18 [18.2]	17 [50.0]	72 [34.8]	23 [56.0]	10 [45.5]
Age (median [quartiles])	64 [57-71]	69 [60-76]	67 [59-74]	71 [65-77]	68 [63-72]
ECOG Performance Status (n [%])					
ECOG 0	40 [40.4]	15 [44.1]	78 [37.7]	15 [36.6]	7 [31.8]
ECOG ≥1	50 [50.4]	17 [50.0]	103 [49.7]	23 [56.1]	12 [54.5]
Unknown/missing	9 [9.1]	2 [5.9]	26 [12.6]	3 [7.3]	3 [13.6]
Comorbidities at inclusion (n [%])					
At least one comorbidity	82 [82.8]	28 [82.4]	160 [77.3]	36 [87.8]	17 [77.3]
Metastasis at diagnosis (n [%])					
Yes (synchronous, M1)	70 [70.7]	27 [79.4]	155 [74.9]	29 [70.7]	15 [68.2]
No (metachronous, M0)	89 [23.2]	7 [20.6]	42 [20.2]	10 [24.4]	5 [22.7]
MX/Unknown/missing	6 [6.1]	0 [0.0]	10 [4.8]	2 [4.9]	2 [9.1]
Metastasis at start of first-line (n [%])[a]					
Liver	72 [72.7]	21 [61.8]	145 [70.0]	24 [58.5]	13 [59.1]
Lung	25 [25.3]	7 [20.6]	75 [36.2]	9 [22.0]	4 [18.2]
Peritoneum	18 [18.2]	12 [35.3]	43 [20.8]	12 [29.3]	3 [13.6]

Table 1 Patient and tumor characteristics.

A patient can be assigned to more than one subgroup. ECOG: Eastern Cooperative Oncology Group. [a] Most frequent metastasis sites at start of palliative 1st-line therapy.

Figure 1

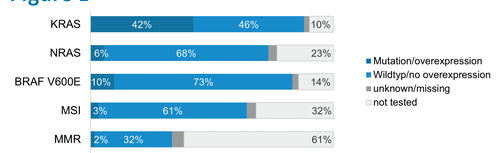

Figure 1 Biomarker testing rate and test results (n=441)

Figure 2

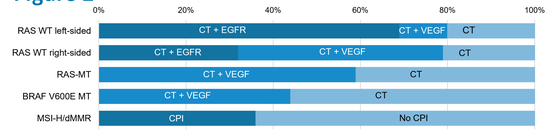

Figure 2 First-line treatment strategies according to different subgroups.

CT: chemotherapy | EGFR: EGFR-inhibitor (cetuximab, panitumumab); VEGF: VEGF-inhibitor (bevacizumab, aflibercept, ramucirumab) | CPI: checkpoint-inhibitor (pembrolizumab)

Figure 3

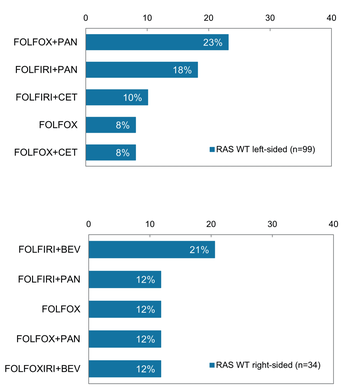

Figure 3 Most frequent first-line therapies | RAS wildtype tumor

Figure 4

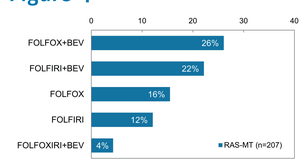

Figure 4 Most frequent first-line therapies | RAS mutated tumor

Figure 5

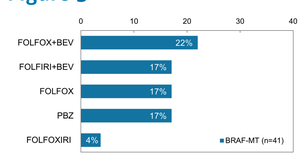

Figure 5 Most frequent first-line therapies | BRAF mutated tumor

Figure 6

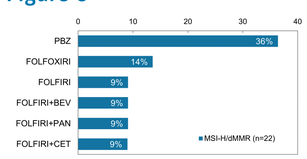

Figure 6 Most frequent first-line therapies | MSI-H/dMMR tumor