Fruquintinib (Fruzaqla®) as monotherapy for the treatment of metastatic colorectal cancer (mCRC)

General information [1]

Drug description

The active substance of Fruzaqla® is fruquintinib, an antineoplastic agent and vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor. Fruzaqla® is a selective inhibitor of the tyrosine kinases VEGFR-1, 2 and 3, whose antitumor effects result from the suppression of tumour angiogenesis.

Indication

Fruquintinib (Fruzaqla®) as monotherapy is indicated for the treatment of adult patients with mCRC who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine-tipiracil or regorafenib.

Incidence [2]

In Austria, in 2022, a total of 4,467 persons were newly diagnosed with cancer of the colon and rectum. The age-standardised incidence rate was 57.4/100,000 in men and 39.1/100,000 in women.

Current treatment [3]

The Onkopedia recommendation for the treatment of stage IV colon cancer with primarily non-resectable metastases is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [1]	FDA [4]
Approval status for this indication: On April 25 2024, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Fruzaqla®. Fruzaqla will be available as 1 and 5 mg hard capsules. The full indication is: ❖ Fruzaqla® as monotherapy is indicated for the treatment of adult patients with mCRC who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine-tipiracil or regorafenib. **Other indications**: none	**Approval status for this indication**: On November 8 2023, the FDA approved fruquintinib (Fruzaqla®) for adult patients with metastatic colorectal cancer (mCRC) who received prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type and medically appropriate, an anti-EGFR therapy. ✓ Priority review **Other indications**: none

Manufacturer

Fruzaqla® is manufactured by Takeda Pharmaceuticals.

Costs

Currently, there is no cost information available.

Warnings and precautions[1] [5]

❖ **Hypertension**

[1] Since there is currently no EMA EPAR available, chapter "Warnings and precautions" refers to the FDA label information.

- Control blood pressure prior to treatment and monitor during treatment. Manage with anti-hypertensive medications and adjustment of the dose of Fruzaqla®, if necessary. Withhold, dose reduce, or permanently discontinue based on the severity of hypertension.

❖ **Haemorrhagic events**
- Closely monitor patients who are at risk for bleeding. Withhold, reduce dose, or permanently discontinue Fruzaqla® based on severity and persistence of haemorrhage.

❖ **Infections**
- Monitor for infection during treatment and withhold Fruzaqla® during active infections. Do not start Fruzaqla® in patients with active infections.

❖ **Gastrointestinal perforation**
- Periodically monitor for gastrointestinal perforation. Permanently discontinue Fruzaqla® in patients who develop gastrointestinal perforation or fistula.

❖ **Hepatotoxicity**
- Monitor liver laboratory tests prior to the start of Fruzaqla® and periodically during treatment. Withhold, reduce the dose, or permanently discontinue based on severity.

❖ **Proteinuria**
- Monitor urine protein.
- Discontinue Fruzaqla® for nephrotic syndrome.

❖ **Palmar-plantar erythrodysesthesia**
- Withhold Fruzaqla® based on severity.

❖ **Posterior reversible encephalopathy syndrome**
- Immediately discontinue Fruzaqla® if posterior reversible encephalopathy syndrome is suspected and confirmed via MRI.

❖ **Impaired wound healing**
- Withhold Fruzaqla® for 2 weeks before major surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Fruzaqla® after resolution of wound healing complications has not been established.

❖ **Arterial thromboembolic events**
- Initiation of Fruzaqla® in patients with a recent history of thromboembolic events should be carefully considered. Discontinue Fruzaqla® in patients who develop arterial thromboembolism.

❖ **Allergic reactions to FD&C Yellow No. 5 (Tartrazine) and No. 6 (Sunset Yellow FCF)**
- Contains FD&C Yellow No. 5 (tartrazine) and No. 6 (sunset yellow FCF) as colour additives, which may cause allergic reactions (including bronchial asthma) in certain susceptible patients.

❖ **Embryo-foetal toxicity**
- Can cause foetal harm. Advise patients of reproductive potential of the potential risk to the foetus and to use effective contraception.

Study characteristics [6-8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
FRESCO-2 NCT04322539	691 (2:1)	fruquintinib (5 mg capsule) orally once daily on days 1–21 in 28-day cycles	matched placebo orally once daily on days 1–21 in 28-day cycles	OS	11.3 months vs. 11.2 months	international, randomised, double-blind, placebo-controlled, phase 3 study	VEGF	HUTCHMED	FRESCO-2 trial [7]

Inclusion criteria[2]	Exclusion criteria	Patient characteristics at baseline (n=461 vs. n=230)
❖ ≥18 years with histologically and/or cytologically documented metastatic colorectal adenocarcinoma. RAS, BRAF, and microsatellite instability	❖ ANC <1.5×10^9/L, platelet count <100×10^9/L, or haemoglobin <9.0 g/dL. ❖ Serum total bilirubin >1.5 × the ULN. Subjects with previously documented Gilbert syndrome and bilirubin <2 X ULN are eligible.	❖ Median age: 64 (56–70) vs. 64 (56–69) ❖ ≥65: 46% vs. 48 ❖ Female sex: 47% vs. 39% ❖ Race:

[2] For detailed in- and exclusion criteria, please see trial protocol.

(MSI)/MMR status must be documented, according to country level guidelines. ❖ Patients must have progressed on or been intolerant to treatment with either trifluridine/tipiracil (TAS-102) or regorafenib. Subjects must also have been previously treated with: • standard approved therapies: fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, • an anti-VEGF biological therapy, and, • if RAS wild-type, an anti-EGFR therapy. ❖ Subjects with microsatellite-high (MSI-H) or mismatch repair deficient (dMMR) tumors must have been treated with immune checkpoint inhibitors if approved and available in the subject's country unless the subject is ineligible for treatment with a checkpoint inhibitor; ❖ Subjects who received oxaliplatin in the adjuvant setting and developed metastatic disease during or within 6 months of completing adjuvant therapy are considered eligible without receiving oxaliplatin in the metastatic setting. Subjects who developed metastatic diseasemore than 6 months after completion of oxaliplatin-containing adjuvant treatment must be treated with oxaliplatin-based therapy in the metastatic setting to be eligible. ❖ Body weight ≥40kg ❖ ECOG PS of 0 to 1 ❖ Have measurable disease according to RECIST v1.1, assessed locally. ❖ Expected survival >12 weeks.	❖ ALT or AST >2.5 × ULN in subjects without hepatic metastases; ALT or AST >5 × ULN in subjects with hepatic metastases. ❖ Serum creatinine >1.5 × ULN or creatinine clearance <60 mL/min. ❖ Urine dipstick or urinalysis with protein ≥2+ or 24-hour urine protein ≥1.0 g/24-h. Subjects with 1+ proteinuria must undergo a 24-hour urine collection to assess urine protein level. ❖ Uncontrolled hypertension, defined as: systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg despite optimal medical management. ❖ INR >1.5 x ULN or activated partial thromboplastin time >1.5 × ULN, unless the subject is currently receiving or intended to receive anticoagulants for prophylactic purposes. ❖ History of, or active gastric/duodenal ulcer or ulcerative colitis, active haemorrhage of an unresected gastrointestinal tumour, history of perforation or fistulas; or any other condition that could, in the investigator's judgment, result in gastrointestinal haemorrhage or perforation; within the 6 months prior to screening. ❖ History or presence of haemorrhage from any other site within 2 months prior to screening. ❖ History of a thromboembolic event, including deep vein thrombosis, pulmonary embolism, or arterial embolism within 6 months prior to screening. ❖ Stroke and/or transient ischaemic attack within 12 months prior to screening. ❖ Clinically significant cardiovascular disease, including but not limited to acute myocardial infarction or coronary artery bypass surgery within 6 months prior to enrollment, severe or unstable angina pectoris, NYHA Class III/IV congestive heart failure, ventricular arrhythmias requiring treatment, or left ventricular ejection fraction <50% by ECG; ❖ Corrected QT interval using the Fridericia method >480 msec or any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in a first-degree relative. ❖ Concomitant medications with a known risk of causing QT prolongation and/or torsades de pointes. ❖ Systemic anti-neoplastic therapies or any investigational therapy within 4 weeks prior to the first dose of study drug, including chemotherapy, radical radiotherapy, hormonotherapy, biotherapy and immunotherapy. ❖ Systemic small molecule targeted therapies within 5 half-lives or 4 weeks (whichever is shorter) prior to the first dose of study drug. ❖ Palliative radiotherapy for bone metastasis/lesion within 2 weeks prior to the initiation of study drug. ❖ Brachytherapy within 60 days prior to the first dose of study drug. ❖ Use of strong inducers or inhibitors of CYP3A4 within 2 weeks (or 5 half-lives, whichever is longer) before the first dose of study drug.	• White 367 (80%) 192 (83%) • Asian 43 (9%) 18 (8%) • Black or African American 13 (3%) 7 (3%) • Other 38 (8%) 13 (6%) ❖ Ethnicity: • Hispanic or Latino: 4% vs. 6% • Not Hispanic or Latino: 88% vs. 88% • Not reported or unknown: 8% vs. 6% ❖ Region: • North America: 18% vs. 18% • Europe: 71% vs. 72% • Japan: 9% vs. 7% • Australia: 2% vs. 3% ❖ ECOG performance status score: • 0: 43% vs. 44% • 1: 57% vs. 56% ❖ Primary site at first diagnosis: • Colon left: 42% vs. 40% • Colon right: 21% vs. 23% • Colon left and right: 1% vs. 1% • Colon unknown: 5% vs. 6% • Rectum: 31% vs. 30% ❖ Liver metastases • Yes: 74% vs. 68% • No: 26% vs. 32% ❖ Duration of metastatic disease, months: • ≤18: 8 vs. 6% • >18: 92% vs. 94% ❖ RAS status: • Wild type: 37% vs. 37% • Mutant: 63% vs. 63% ❖ BRAF V600E mutation: • No: 87% vs. 86% • Yes: 2% vs. 4% • Other or unknown: 11% vs. 10% ❖ Microsatellite or mismatch repair status: • MSS or pMMR: 93% vs. 93% • MSI-H or dMMR: 1% vs. 2% • Unknown: 6% vs. 5%

❖ For female subjects of childbearing potential and male subjects with partners of childbearing potential, agreement to use a highly effective form(s) of contraception, that results in a low failure rate (<1% per year) when used consistently and correctly, starting during the screening period, continuing throughout the entire study period, and for 90 days after taking the last dose of study drug. ❖ Subjects with BRAF-mutant tumors must have been treated with a BRAF inhibitor if approved and available in the subject's country unless the subject is ineligible for treatment with a BRAF inhibitor.	❖ Surgery or invasive procedure within 60 days prior to the first dose of study drug or unhealed surgical incision. ❖ Any unresolved toxicities from a previous antitumor treatment greater than NCI-CTCAE v5.0 grade 1. ❖ Known HIV infection; ❖ Known history of active viral hepatitis. For subjects with evidence of chronic HBV infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Subjects with HCV infection who are currently on treatment are eligible if they have an undetectable HCV viral load. ❖ Clinically uncontrolled active infection requiring IV antibiotics. ❖ Tumor invasion of a large vascular structure. ❖ Women who are pregnant or lactating. ❖ Brain metastases and/or spinal cord compression untreated with surgery and/or radiotherapy, and without clinical imaging evidence of stable disease for 14 days or longer; subjects requiring steroids within 4 weeks prior to start of study treatment are excluded. ❖ Other malignancy, except for non-melanoma skin cancer, in situ cervical cancer or bladder cancer (Tis and T1) that have been adequately treated during the 5 years prior to screening. ❖ Inability to take medication orally, dysphagia or an active gastric ulcer resulting from previous surgery or a severe gastrointestinal disease, or any other condition that investigators believe may affect absorption of the investigational product. ❖ Other disease, metabolic disorder, physical examination anomaly, abnormal laboratory result, or any other condition that investigators suspect may prohibit use of the investigational product, affect interpretation of study results, or put the subject at undue risk of harm based on the investigator's assessment. ❖ Known hypersensitivity to fruquintinib or any of its (or placebo) inactive ingredients including the azo dyes Tartrazine - FD&C Yellow 5 and Sunset yellow FCF - FD&C Yellow 6. ❖ Subjects who have received prior fruquintinib. ❖ Live vaccine ≤28 days before the first dose of study drug(s).	❖ Number of previous treatment lines in metastatic disease: • Median: 4 (3–6) vs. 4 (3–6) • ≤3: 27% vs. 28% • >3: 73% vs. 72% ❖ Previous therapies: • VEGF inhibitor: 97% vs. 96% • EGFR inhibitor: 39% vs. 38% • Immune checkpoint inhibitor: 5% vs. 5% • BRAF inhibitor: 2% vs. 3% ❖ Previous trifluridine–tipiracil or regorafenib • Trifluridine–tipiracil: 52% vs. 53% • Regorafenib: 9% vs. 8% • Both: 39% vs. 40%

Efficacy (I vs. C)	**Safety** (I vs. C, n=456 vs. n=230)
Data cutoff June 24 2022; median follow-up 11.3 vs. 11.2 months **Median OS**: 7.4 months (95% CI, 6.7–8.2) vs. 4.8 months (4.0–5.8); absolute difference 2.6 months; HR 0.66, 95% CI 0.55–0.80; p<0.0001 **Patients who were still alive at 9 months:** 41% (95% CI 36–46) vs. 28% (22–34) **Patients who had disease progression or died**: 85% vs. 93% **Median PFS**: 3.7 months (95% CI 3.5–3.8) vs. 1.8 months (1.8–1.9); absolute difference 1.9 months; HR 0.32, 95% CI 0.27–0.39; p<0.0001 **Objective response rate**: 2% (0.6–3.1) vs. 0% (0.0–1.6); p=0.059	**AEs grade ≥3**: 63% vs. 50% **Serious AEs grade ≥3**: 36% vs. 37% **AEs leading to death**: 11% vs. 20% **Treatment-related death[3]:** n=1 vs. n=1 **Discontinuation of treatment due to AEs**: 20% vs. 21%

[3] One in each group; intestinal perforation in the fruquintinib group and cardiac arrest in the placebo group.

Median duration of response: 10.7 months (95% CI 3.9–not estimable) vs. 0 (not applicable) Disease control rate: 56% vs. 16% (37 of 230); adjusted difference 39%, 95% CI 32.8–46.0; p<0.0001	

Patient-reported outcomes (abstract data) [9]

- EORTC QLQ-C30 and EQ-5D-5L were assessed at baseline and on Day (D) 1 of each Cycle (C) until treatment discontinuation, and ECOG PS was evaluated at baseline, D1 of each C and D21 of C1 to C3.
- LSM change from baseline to post-baseline visits, and the difference between F and P in QLQ-C30 scale scores (e.g. GHS/QoL) and EQ-5D-5L scale scores (e.g. VAS) were calculated using mixed model repeated measures approach. For each scale, the appropriate minimally important difference (MID) thresholds were determined to evaluate the improvement or deterioration.
- Time to deterioration (TTD), defined as worsening from baseline in scale-specific MID or death, was analysed using the Kaplan-Meier method, adjusted log-rank test, and stratified Cox PH model.
- QLQ-C30 and EQ-5D-5L analyses were conducted on the ITT population, and ECOG PS was on the safety population.
- More than 79% of patients on both arms had a baseline and ≥1 post-baseline assessment for QLQ-C30, EQ-5D-5L, and ECOG PS.
- GHS/QoL was similar between fruquintinib group patients and placebo group patients at baseline; the LSM differences between I and C were 1.7 (95% CI: -1.7, 5.0) for C2 and 1.6 (95% CI: -3.2, 6.4) for C3.
- At C4, <30 placebo group patients were available. The % of patients who remained stable (MID-6.38 to <8.43) or improved (≥8.43) was numerically higher for I vs. C (C2: 61.5% vs 57.1%; C3: 56.4% vs. 50.9%).
- Median TTD was 2.1 months in the fruquintinib group and 1.8 months in the placebo group (HR=0.9; 95% CI: 0.7-1.0; p=0.098).
- EQ-5D VAS was similar between I and C at baseline; the LSM differences between I and C were 0.6 (95% CI: -2.3, 3.5) for C2 and 1.4 (95% CI: -2.8, 5.6) for C3. The % of patients who remained stable (MID -7 to <7) or improved (≥7) was similar for I and C (C2: 64.6% vs. 58.3%; C3: 64.2% vs. 64.8%). Median TTD was 2.6 months in I and 1.9 months in C (HR=0.8; 95% CI: 0.6-0.9; p=0.001). The % of patients with ≥1-point increase from baseline in ECOG PS was 52.1% in the fruquintinib group vs. 54.0% in the placebo group.

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2A	≤12 months	OS: +2.6 months	0.66 (0.55–0.80)	HR≤0.65 AND gain ≥2.0-<3months	3	-	-	-	3
Adapted	NC	2A	≤12 months	OS: +2.6 months	0.66 (0.55–0.80)	HR>0.65 AND gain ≥1.5-<2.0	2	+13.0% AEs grade ≥3	-	-1[4]	1

Risk of bias (RCT) [11]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	yes low risk	yes low risk	unclear[5] unclear risk	yes[6] high risk	unclear risk

Ongoing trials [12]

NCT number/trial name	Description	Estimated study completion date

No ongoing phase 3 trials were identified. However, the efficacy and safety of fruquintinib is evaluated in numerous phase 2 trials.

Available assessments

- In January 2023, NIHR published a Health Technology Briefing „Fruquintinib for treating refractory metastatic colorectal cancer" [13].
- No assessments were identified via NICE, CDA-AMC, ICER and G-BA.

[4] Toxicity adjustment.

[5] Final analysis data is not yet available.

[6] The funder of the study and steering committee members designed the study. The funder also contributed to data collection, data analysis, data interpretation, and manuscript review and approval. The funder provided financial support for medical writing assistance.

Other aspects and conclusions

- In April 2024, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for Fruzaqla®, indicated for the treatment of adult patients with mCRC who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine-tipiracil or regorafenib. In November 2023, the **FDA approved** Fruzaqla® for adult patients with mCRC who received prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type and medically appropriate, an anti-EGFR therapy.
- **FRESCO-2 (NCT04322539)** is an international, randomised, double-blind, placebo-controlled, **phase 3 trial** aiming to evaluate the efficacy and safety of fruquintinib in patients with heavily pretreated mCRC. Eligible patients were aged ≥18 years (≥20 years in Japan) with histologically or cytologically documented metastatic colorectal adenocarcinoma, who had received all standard treatments, including fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy, anti-VEGF therapy, and anti-EGFR therapy (if RAS wild type), and had disease progression on or been intolerant to trifluridine–tipiracil or regorafenib. Patients with an ECOG PS of 0-1 and measurable disease by RECIST v.1.1), were included.
- **The primary endpoint** was **OS**; median OS was 7.4 months (95% CI 6.7–8.2) in the fruquintinib group vs. 4.8 months (4.0–5.8) in the placebo group (**HR 0.66,** 95% CI 0.55–0.80; **p<0.0001**).
- For **patient-reported outcomes**, currently, only abstract data is available showing that TTD is improved for patients receiving fruquintinib.
- Since the final analysis data was lacking, the **risk of bias was considered unclear**. However, it is increased by the involvement of the funder in study design, data collection, data analysis and data interpretation.
- The **original and adapted ESMO-MCBS** were applied, resulting in a **final adjusted magnitude of clinical benefit of 3 and 1**, respectively.
- **No ongoing phase 3 trials** for fruquintinib in mCRC patients were identified via ClinicalTrials.gov.
- Final analysis data from the FRESCO-2 trial and further robust phase 3 data are required to determine the role of fruquintinib in the assessed patient population.

First published: 06/2024

Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, C=comparator, C=cycle, CDA-AMC=Canada's Drug Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, D=day, dMMR=deficient mismatch repair, ECG=echocardiogram, ECOG PS=ECOG Eastern Cooperative Oncology Group performance status, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, EQ-5D-5L= EuroQol Group 5-Dimension 5-Level questionnaire, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GHS=global health score, HBV=hepatitis B virus, HIV=human immunodeficiency virus, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, INR=international Normalized Ratio, Int.=intention, ITT=Intent-to-treat, LSM=least-squares mean, mCRC=metastatic colorectal cancer, MG=median gain, MID=minimally important difference, MRI=Magnetic resonance imaging, MSI-H=high levels of microsatellite instability, n=number of patients, NCI-CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Event, NICE=National Institute for Health Care Excellence, NYHA=New York Heart Association, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, pMMR=proficient mismatch repair, QoL=quality of life, RECIST=Response Evaluation Criteria In Solid Tumors, SAE=serious adverse event, ST=standard treatment, TTD=time to deterioration, ULN=upper limit of normal, VAS=visual analogue scale, VEGF=vascular endothelial growth factor, VEGFR=vascular endothelial growth factor receptor

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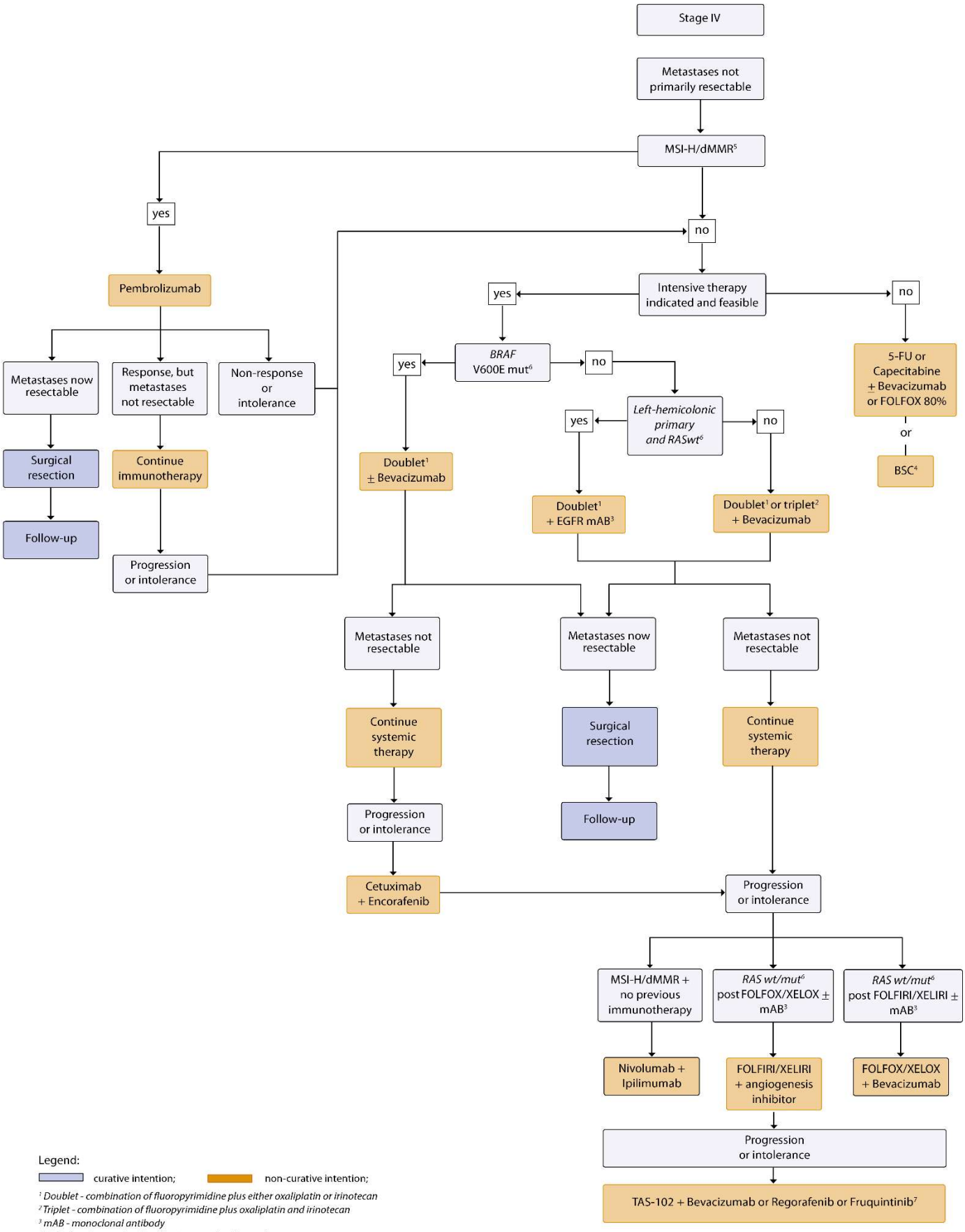
Appendix – Figure 1: Treatment structure in stage IV for primarily non-resectable metastases



Legend:

curative intention; non-curative intention;

[1] *Doublet - combination of fluoropyrimidine plus either oxaliplatin or irinotecan*
[2] *Triplet - combination of fluoropyrimidine plus oxaliplatin and irinotecan*
[3] *mAB - monoclonal antibody*
[4] *BSC - Best Supportive Care (best supportive therapy)*
[5] *MSI-H/dMMR - microsatellite instability-high/deficient DNA mismatch repair*
[6] *mut - mutated; wt - wild type (unmutated)*
[7] *Fruquintinib is not yet approved (February 2024)*