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THE HEART OF MEDICAL EDUCATION

INTERPRETING REAL-WORLD EVIDENCE IN LATER LINE mCRC

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APRIL 2024

mCRC, metastatic colorectal cancer

DEVELOPED BY GI CONNECT

This programme is developed by GI CONNECT, an international group of experts in the field of gastrointestinal oncology.

Acknowledgement and disclosures

This GI CONNECT programme is supported through an independent educational grant from Bayer. The programme is therefore independent, the content is not influenced by the supporter and is under the sole responsibility of the experts.

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Expert disclosures:

- **Prof. Tanios Bekaii-Saab** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies:
  - Research Funding (to institution): Agios, Arys, Arcus, Atreca, Boston Biomedical, Bayer, Eisai, Celgene, Lilly, Ipsen, Clovis, Seattle Genetics, Genentech, Novartis, Mirati, Merus, Abgenomics, Incyte, Pfizer, BMS. Consulting (to institution): Servier, Ipsen, Arcus, Pfizer, Seattle Genetics, Bayer, Genentech, Incyte, Eisai, Merus, Merck KGaA and Merck. Consulting (to self): Stemline, AbbVie, Blueprint Medicines , Boehringer Ingelheim, Janssen, Daiichi Sankyo, Natera, TreosBio, Celularity, Caladrius Biosciences, Exact Science, Sobi, Beigene, Kanaph, AstraZeneca, Deciphera, Zai Labs, Exelixis, MJH Life Sciences, Aptitude Health, Illumina, Foundation Medicine and Sanofi. Glaxo SmithKline , Xilio. IDMC/DSMB: The Valley Hospital, Fibrogen, Suzhou Kintor, AstraZeneca, Exelixis, Merck/Eisai, PanCan and 1Globe. Scientific Advisory Board: Imugene, Immuneering, Xilis, Replimune, Artiva and Sun Biopharma. Royalties: Uptodate. Inventions/Patents: WO/2018/183488: HUMAN PD1 PEPTIDE VACCINES AND USES THEREOF – Licensed to Imugene, WO/2019/055687: METHODS AND COMPOSITIONS FOR THE TREATMENT OF CANCER CACHEXIA – Licensed to Recursion

- **Prof. Shubham Pant** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies:
  - Consulting or advisory Role: Zymeworks, Ipsen, Novartis, Janssen, AskGene Pharma, BPGBio, Jazz, AstraZeneca, Boehringer Ingelheim, USWorldmeds, Nihon Medi-Physics Co, Ltd, Alligator Bioscience, Theriva Biosciences. Research funding (funding to institution): Mirati Therapeutics, Lilly, Xencor, Novartis, Bristol-Myers Squibb, Astellas, Framewave, 4D Pharma, Boehringer Ingelheim, NGM Pharmaceuticals, Janssen, Arcus, Elicio, Biontech, Ipsen, Zymeworks, Pfizer, ImmunoMET, Immuneering, Amal Therapeutics.

THIS PROGRAMME HAS BEEN DEVELOPED BY THE FOLLOWING EXPERTS

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EDUCATIONAL OBJECTIVES

- Understand how real-world evidence can complement data obtained from randomised controlled trials
- Know the benefits and limitations of real-world evidence
- Review recent RWE data for mCRC and understand its implications for clinical practice

mCRC, metastatic colorectal cancer; RWE, real-world evidence

CLINICAL TAKEAWAYS

- Randomised clinical trials are the gold standard to determine causal effect and help guide clinical practice, but do not represent patients in routine clinical practice
- Real-world evidence can augment traditional clinical data by providing useful efficacy and safety information of treatments in patients representative of those in clinical practice
- However, we need to be mindful of the limitations and potential biases that might arise from real-world data collection and analysis methods

UTILITY OF REAL-WORLD EVIDENCE

WHAT IS RWD AND RWE?

Real-world data (RWD)

Data relating to patient health status and/or the delivery of health care routine collected from electronic health records (EHRs), claims databases, registries, PROs and devices, etc.

Data that are collected outside of a clinical trial.

Data science

Real-world evidence (RWE)

Clinical evidence about the usage and potential benefits or risks of a medical product derive from analysis of RWD

Analysis of real-world data, leads to real-world evidence

PRO, patient reported outcomes; RWD, real-world data; RWE, real-world evidence

NICE real-world evidence framework summary. Accessed 01-Apr-24; Saesen R, et al. Eur J Cancer 2023;186:52-61; Khosla S, et al. F1000Res. 2018;7:111; Castelo-Branco L, et al. Ann Oncol. 2023;34:1097-1112

THERE ARE MULTIPLE SOURCES OF REAL-WORLD DATA

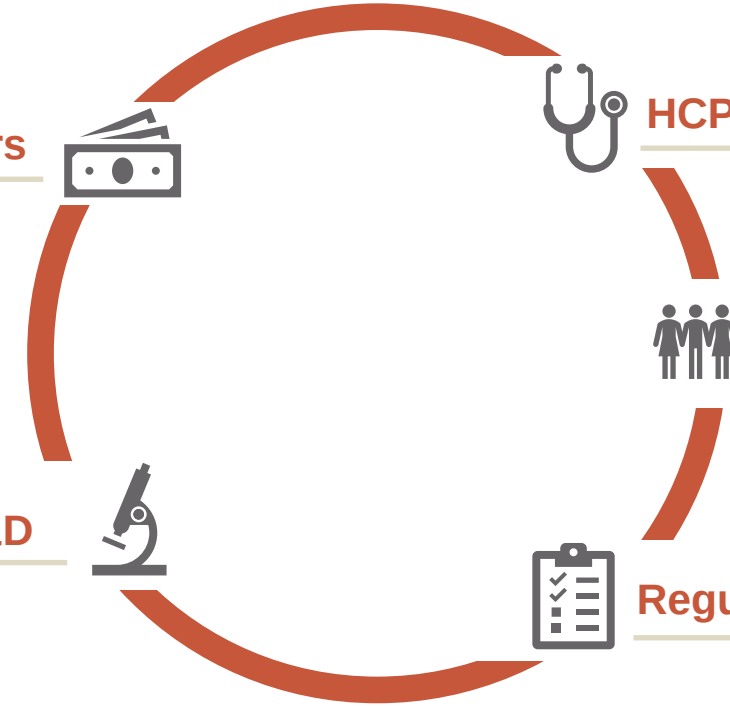
Adapted from: CHCUK[1]

EHR, electronic health record

1. China – Key Considerations in Using Real-World Evidence to Support Drug Development. https://www.chcuk.co.uk/china-key-considerations-in-using-real-world-evidence-to-support-drug-development/. Accessed 15-Apr-2024; 2. NICE real-world evidence framework summary. Accessed 15-Apr-24; 3. Saesen R, et al. Eur J Cancer. 2023;186:52-61; 4. Khosla S, et al. F1000Res. 2018;7:111; 5. Castelo-Branco L, et al. Ann Oncol. 2023;34:1097-1112; 6. Moss B, et al. Future Oncol. 2023;19:1811-1823

HOW CAN RWD AND RWE BE USED?

More **effective reimbursement** based on the value of medicines



Optimisation of **patient management** (e.g., tailoring treatments in subpopulations)

Access to most appropriate treatment based on evidence generated from both clinical trials and the real world

Supplemental/confirmatory understanding of the **potential impact and outcomes** of treatment (**efficacy and safety**)

Generating new targets that direct R&D towards areas of unmet need

HCP, healthcare professional; R&D, research and development; RWD, real-world data; RWE, real-world evidence

Khosla S, et al. F1000Res. 2018;7:111

CLINICAL TRIALS VERSUS REAL-WORLD EVIDENCE

RCT

"Gold standard" for determining cause-effect relationship of treatment and outcome[1]

Prospective[1]

Interventional (fixed treatment protocol)[2]

Randomised to minimise bias[2]

Control and experimental arms[2]

Homogenous/highly selected study group – not representative of patients in routine practice[1]

RWE

Can provide insights into patient populations underrepresented in RCTs[3]

Prospective or retrospective[2]

Observational (flexible regimen)[2]

Not usually randomised[4]

May or may not have a control arm[2]

Heterogenous/real-world study group[4]

RCT, randomised clinical trial; RWE, real-world evidence

1. Tang M, et al. Curr Oncol. 2023;30:1844-1859; 2. Moss B, et al. Future Oncol. 2023;19:1811-1823; 3. European Medicines Agency and Heads of Medicines Agencies. https://www.ema.europa.eu/en/documents/report/european-union-medicines-agencies-network-strategy-2025-protecting-public-health-time-rapid-change_en.pdf. Accessed 15-Apr-2024; 4. Di Maio M, et al. Oncologist. 2020;25:e746-e752

HOW RWE MIGHT INFLUENCE HCP DECISION-MAKING

Optimise patient management in clinical practice: Real-life use of drugs, impact of any associated comorbidities, help identify patient subgroups that may be more likely to benefit

Pharmacovigilance: Characterise rare or long-term toxicities

Access to most appropriate treatment: Based on evidence generated from RCTs and RWE

Adherence: RWE could show that an oral formulation is associated with a higher proportion of days covered than an injectable

Long-term efficacy: RWE can show that effects of one treatment do not last as long as another

HCP, healthcare professional; RCT, randomised controlled trial; RWE, real-world evidence

Khosla S, et al. F1000Res. 2018;7:111; Essentials of Real World Evidence, Medical Affairs Professional Society 2020, available from: https://medicalaffairs.org/essentials-real-world-evidence/

CONSIDERATIONS AND CHALLENGES OF RWE

LIMITATIONS

- There are several limitations associated with the use of real-world data that need to be considered[1,2,4]
  - **Variability** in data from multiple sources can increase the heterogeneity of the results[1,4]
  - Susceptibility to **confounding** bias due to lack of randomisation[2,4,5]
  - **Bias** due to variability in the quality of the data and in the handling of missing data[3-5]

MITIGATING SOLUTIONS

- Transparency in reporting methodology and data source(s)[2-4]
- Use best methodologic standards, including strategies for handling missing values and adjusting for confounding factors (e.g., propensity score matching)[3,4]
- Follow best practice guidelines in planning and reporting[2]

RWE, real-world evidence

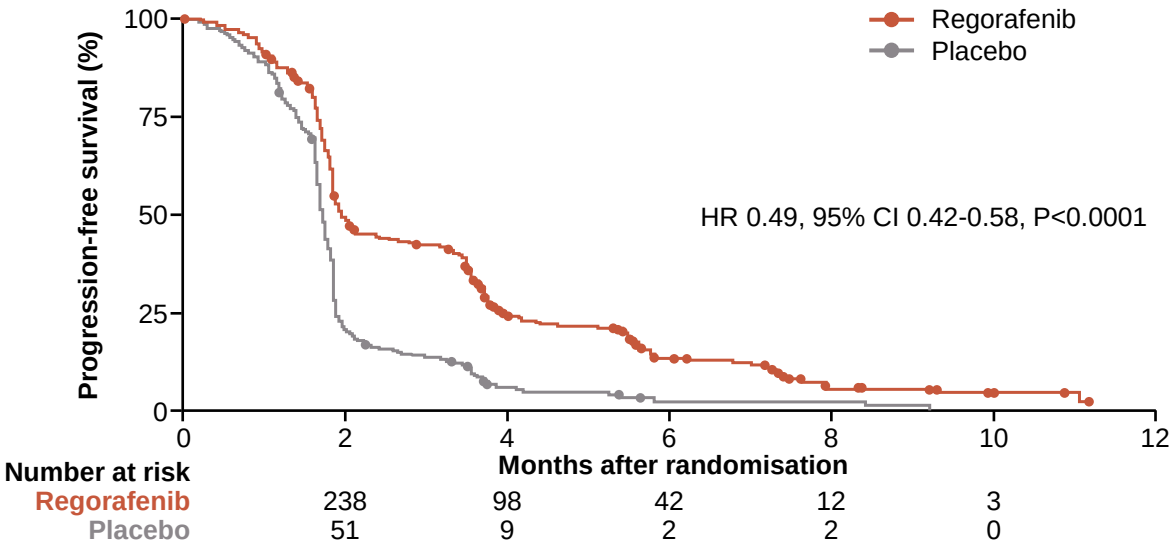
1. Saesen R, et al. Eur J Cancer. 2023;186:52-61; 2. Khosla S, et al. F1000Res. 2018;7:111; 3. Castelo-Branco L, et al. Ann Oncol. 2023;34:1097-1112; 4. Cave A, et al. Clin Pharmacol Ther. 2019;106:36-39; 5. Tang M, et al. Curr Oncol. 2023;30:1844-1859

LATER-LINE CLINICAL TRIAL DATA FOR mCRC

mCRC, metastatic colorectal cancer

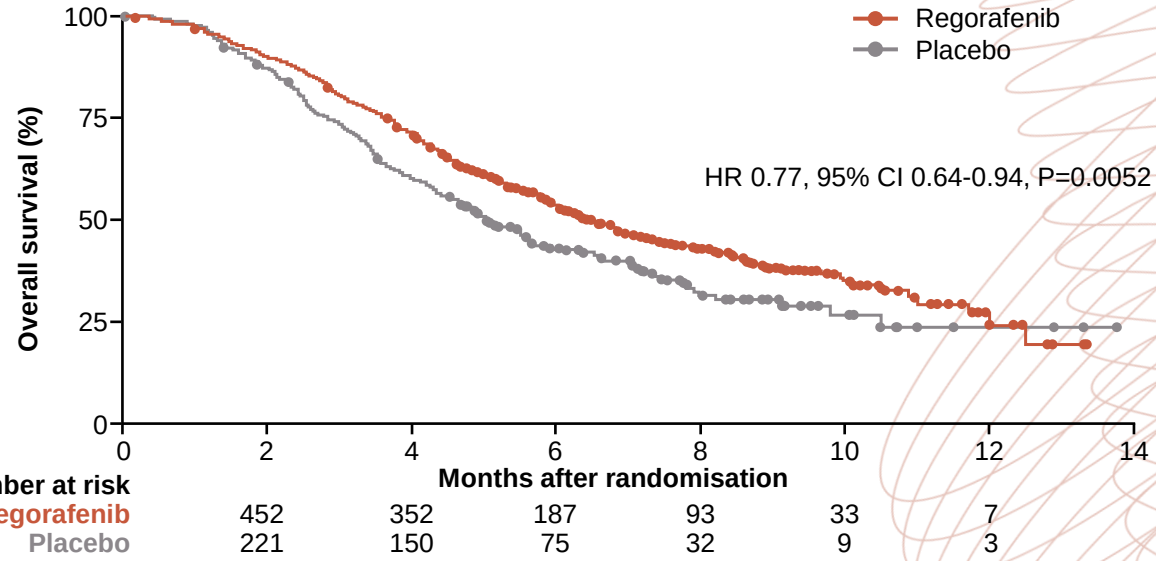
CORRECT STUDY: REGORAFENIB VS PLACEBO PROLONGED PFS AND OS IN REFRACTORY mCRC PATIENTS

PROGRESSION-FREE SURVIVAL



PFS: 1.9 mo vs. 1.7 mo (HR 0.49; p<0.0001)

OVERALL SURVIVAL



OS: 6.4 mo vs. 5.0 mo (HR 0.77; p= 0.0052)

Tumour response:

ORR: 1.0% vs. 0.4% (p=0.19)

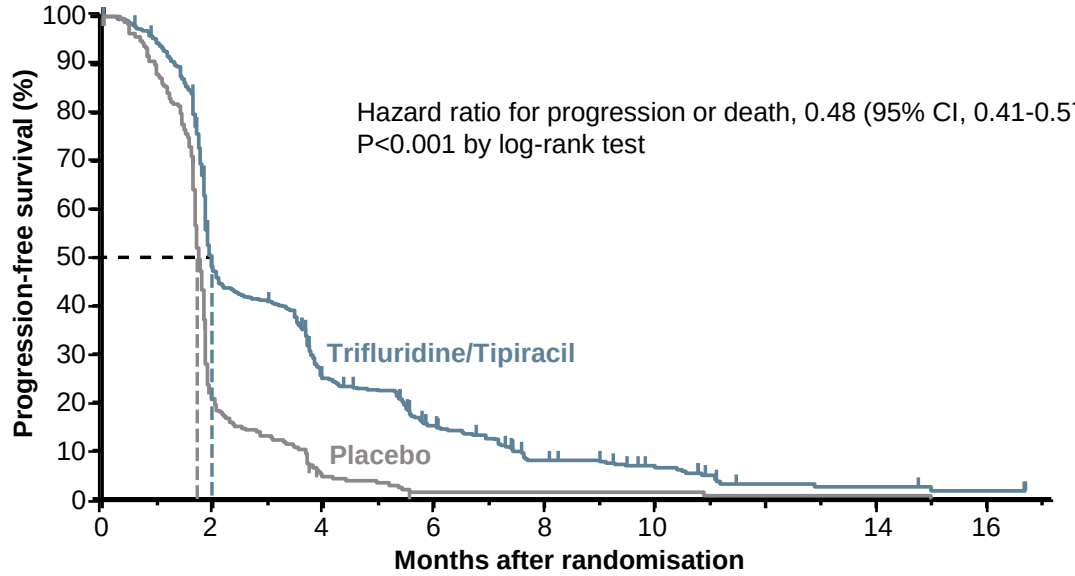
DCR: 41% vs. 15% (p<0.0001)

CI, confidence interval; DCR, disease control rate; HR, hazard ratio; mCRC, metastatic colorectal cancer; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression free survival

Grothey A, et al. Lancet. 2013;381:303-12

RECOURSE STUDY: TRIFLURIDINE/TIPIRACIL PROLONGED PFS AND OS IN REFRACTORY mCRC PATIENTS

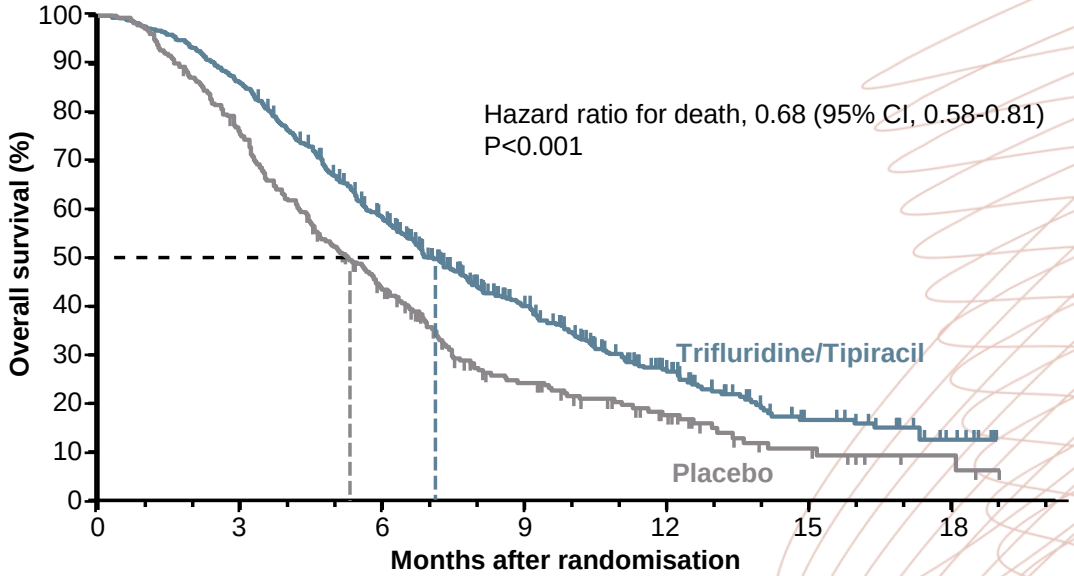
PROGRESSION-FREE SURVIVAL



Number at risk									
Trifluridine/Tipiracil	534	238	121	66	30	18	5	4	2
Placebo	266	51	10	2	2	2	1	1	0

PFS: 2.0 mo vs. 1.7 mo (HR 0.48; p<0.001)

OVERALL SURVIVAL



Number at risk							
Trifluridine/Tipiracil	534	459	294	137	64	23	7
Placebo	266	198	107	47	24	9	3

OS: 7.1 mo vs. 5.3 mo (HR 0.68; p<0.001)

<u>Tumour response:</u>

ORR: 1.6% vs. 0.4% (p=0.29)

DCR: 44% vs. 16% (p<0.001)

CI, confidence interval; DCR, disease control rate; HR, hazard ratio; mCRC, metastatic colorectal cancer; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression free survival

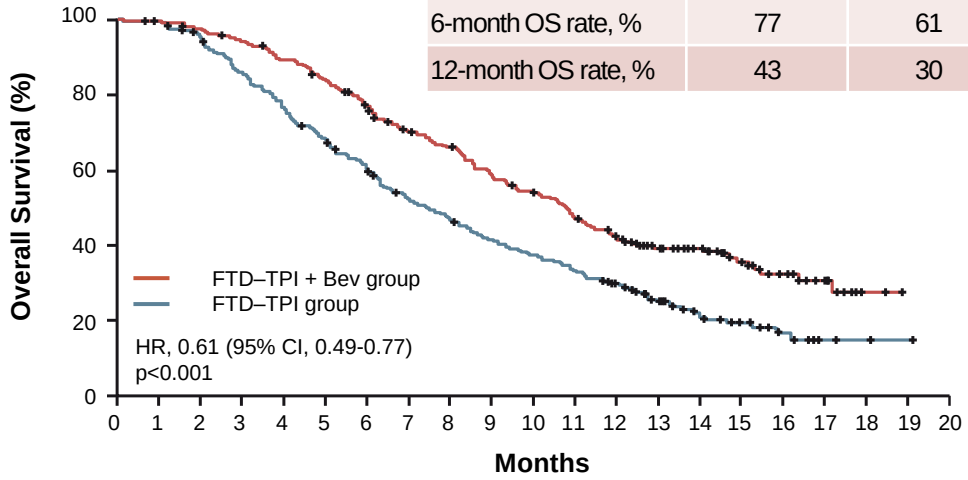
Mayer RJ, et al N Engl J Med. 2015;372:1909-19

SUNLIGHT: TRIFLURIDINE/TIPIRACIL PLUS BEVACIZUMAB IMPROVES OUTCOMES IN REFRACTORY mCRC

- Trifluridine/Tipiracil plus bevacizumab improved OS and PFS in refractory CRC patients

OVERALL SURVIVAL (PRIMARY ENDPOINT)

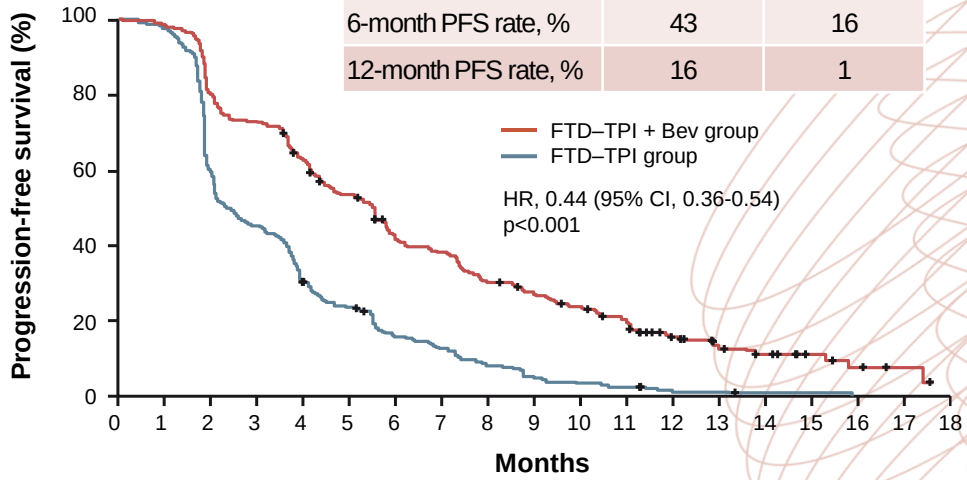
	FTD–TPI + Bev (N=246)	FTD–TPI (N=246)
Median OS, months	10.8	7.5
6-month OS rate, %	77	61
12-month OS rate, %	43	30



No. at risk																				
FTD–TPI + Bev group	246	244	239	230	217	203	183	160	149	131	119	104	88	69	52	37	24	13	2	0	0
FTD–TPI group	246	242	230	205	184	163	143	120	108	95	85	76	63	44	24	16	10	5	2	1	0

PROGRESSION-FREE SURVIVAL

	FTD–TPI + Bev (N=246)	FTD–TPI (N=246)
Median PFS, months	5.6	2.4
6-month PFS rate, %	43	16
12-month PFS rate, %	16	1



No. at risk																				
FTD–TPI + Bev group	246	242	198	179	153	128	99	89	70	61	52	43	25	18	13	7	4	2	0
FTD–TPI group	246	236	147	109	74	56	36	29	19	12	8	6	2	2	1	1	0	0	0

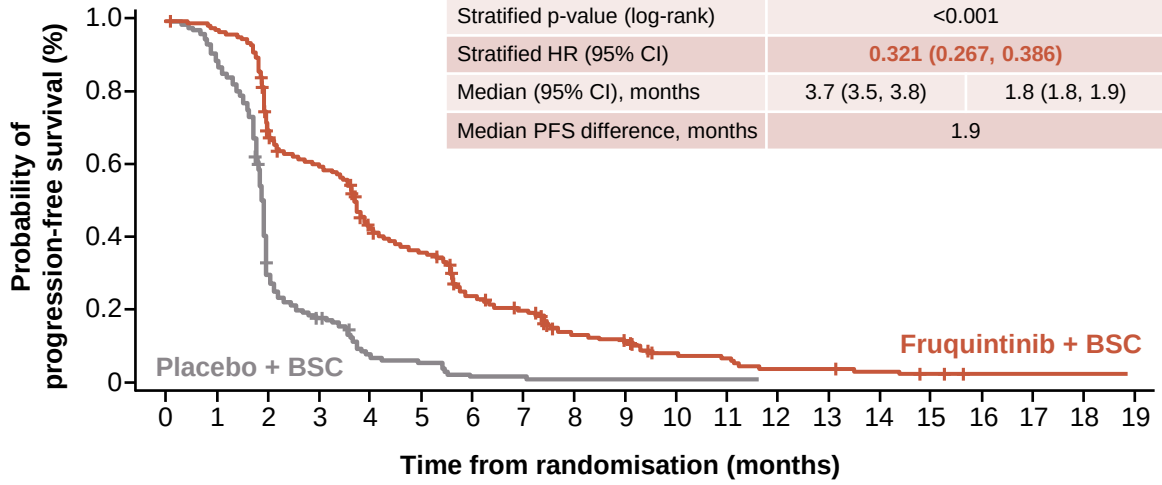
Bev, bevacizumab; CI, confidence interval; FTD-TPI, Trifluridine/Tipiracil; HR, hazard ratio; (m)CRC, (metastatic) colorectal cancer; OS, overall survival; PFS, progression-free survival

Tabernero J, et al. J Clin Oncol. 2023;41(suppl 4; abstr 4) (ASCO GI 2023, oral presentation); Prager G, et al. N Engl J Med. 2023; 388:1657-1667

FRESCO-2: FRUQUINTINIB PROLONGED OS AND PFS IN PATIENTS WITH REFRACTORY mCRC

PROGRESSION-FREE SURVIVAL

	Fruquintinib	Placebo
Events/patients (%)	392/461 (85.0%)	213/230 (92.6%)
Stratified p-value (log-rank)	<0.001	
Stratified HR (95% CI)	0.321 (0.267, 0.386)	
Median (95% CI), months	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)
Median PFS difference, months	1.9	



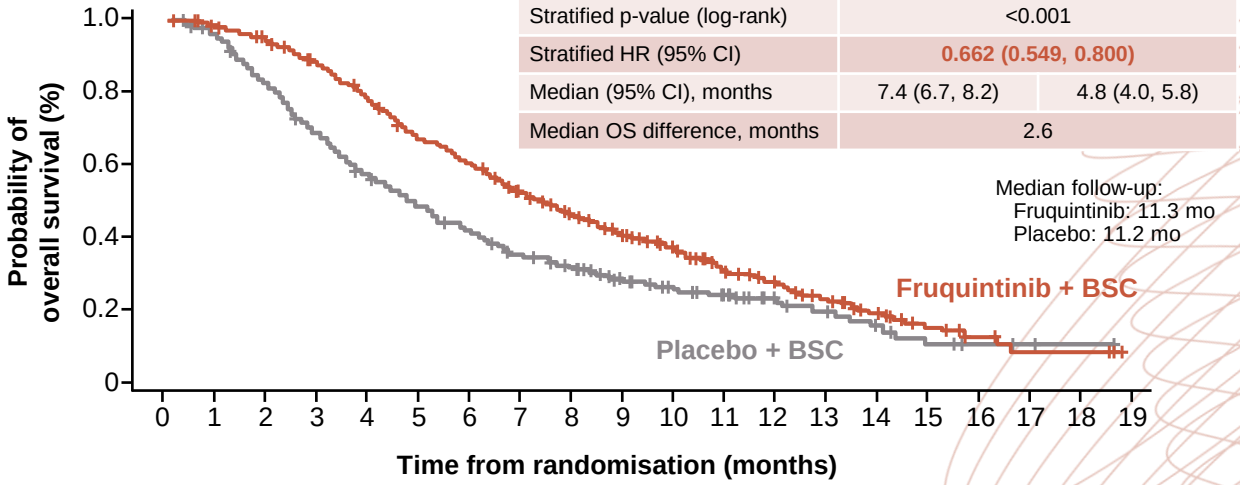
Patients at risk

Fruquintinib	461	430	291	256	170	146	89	71	43	36	21	17	10	9	6	4	2	2	2
Placebo	230	194	60	36	12	10	2	2	1	1	1	1	0						

PFS: 3.7 mo vs. 1.8 mo (HR 0.32; p<0.001)

OVERALL SURVIVAL

	Fruquintinib	Placebo
Events/patients (%)	317/461 (68.8%)	173/230 (75.2%)
Stratified p-value (log-rank)	<0.001	
Stratified HR (95% CI)	0.662 (0.549, 0.800)	
Median (95% CI), months	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)
Median OS difference, months	2.6	



Patients at risk

Fruquintinib	461	449	429	395	349	297	266	224	184	143	113	79	58	41	23	14	7	4	4	0
Placebo	230	216	184	153	125	105	89	73	63	45	37	31	20	15	10	6	3	2	1	0

OS: 7.4 mo vs. 4.8 mo (HR 0.66; p<0.001)

<u>Tumour response:</u>

ORR: 1.5% vs. 0.0% (p=0.059)

DCR: 55.5% vs. 16.1% (p<0.001)

BSC, best supportive care; CI, confidence interval; DCR, disease control rate; HR, hazard ratio; mCRC, metastatic colorectal cancer; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

Dasari NA, et al. Ann Oncol. 2022;33(suppl_7):S808-S869 (ESMO 2022 oral presentation)

ASCO GI 2024 SELECT LATER-LINE REAL-WORLD DATA FOR mCRC

mCRC, metastatic colorectal cancer

REAL-WORLD USE AND OUTCOMES OF REGORAFENIB FLEXIBLE DOSING IN PATIENTS WITH mCRC IN EUROPE[1]

- Patients receiving **REG flexible dosing regimens** (ReDOS-like,[2] dose-adjusted) had **longer DoT compared with a standard dosing regimen** despite having a higher frequency of adverse prognostic factors
- Study confirms **flexible dosing strategies are viable options for optimising REG treatment** and outcomes in patients with mCRC

	Total (N=355)	ReDOS-like (n=173)	Dose-adjusted (n=67)	Standard (n=115)
Stage IVC, n (%)	181 (51)	77 (45)	37 (55)	67 (58)
ECOG PS 0-1, n (%)	240 (68)	112 (65)	47 (70)	81 (70)
Metastatic sites ≥3, n (%)	169 (48)	77 (45)	43 (64)	49 (43)
Liver metastases, n (%)	302 (85)	150 (87)	63 (94)	89 (77)
Lung metastases, n (%)	198 (56)	103 (60)	39 (58)	56 (49)
Line of REG = 2-3, n (%)	294 (83)	138 (80)	55 (82)	101 (88)
Line of REG = ≥4, n (%)	60 (17)	35 (20)	12 (18)	14 (12)
Median DoT,[a] months	1.4	1.4	1.9	1.0
REG cycles ≥3, n (%)	252 (71)	116 (67)	62 (93)	74 (64)

[a] From REG initiation to last dose date prior to first >2-week gap in patients who were not censored

DoT, duration of treatment; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRC, metastatic colorectal cancer; REG, regorafenib

1. Peeters A, et al. J Clin Oncol. 2024;42 (no. 3_Suppl):47 (Poster presentation); 2. Bekaii-Saab T, et al. Lancet Oncol. 2019;20:1070-1082

REAL-WORLD STUDY IN PATIENTS WITH mCRC WITH LONG-TERM RESPONSES TO REGORAFENIB IN THE USA

- Study used the Flatiron Health Electronic Health Record-derived database in the USA to evaluate characteristics of patients with a long-term response (LTR) to REG using DoT as a surrogate for treatment response

Characteristics at index	LTR of ≥4 months (n=503)	LTR of ≥5 months (n=346)
Male sex, n (%)	281 (56)	185 (53)
ECOG PS 0-1, n (%)	332 (66)	237 (68)
Prior BEV, n (%)	341 (68)	221 (64)
Median CEA level (IQR), ng/mL	40 (9, 152)	35 (9, 139)
KRAS mutation, n (%)[a]	127/234 (54)	84/164 (51)
BRAF mutation, n (%)[a]	18/319 (6)	12/219 (5)
Median time from initial CRC diagnosis to index date (IQR), mos	38.6 (24.8, 62.8)	39.2 (25.1, 64.1)
Stage IV at initial CRC diagnosis, n (%)[b]	241 (48)	160 (46)

[a] Denominator is patients tested at index with available data; [b] at diagnosis not index

- 15% of REG treated patients received treatment for ≥5 months and 22% received treatment for ≥4 months. Patients with LTR5 and LTR4 had similar demographic and clinical characteristics, including favorable ECOG PS and similar biomarker status

BEV, bevacizumab; BRAF, proto-oncogene B-Raf; CEA, carcinoembryonic antigen; DoT, duration of treatment; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; (m)CRC, (metastatic) colorectal cancer; mos, months; REG, regorafenib; USA, United States of America

Kim RD, et al. J Clin Oncol. 2024;42 (no. 3_Suppl):48

PROSPECTIVE OBSERVATIONAL STUDY INVESTIGATING THE IMPACT OF TREATMENT SEQUENCE USING REG AND FTD/TPI ± BEV FOR mCRC ON OVERALL SURVIVAL (OSERO STUDY)

- **Study demonstrates that OS are comparable regardless of whether REG, FTD/TPI, or FTD/TPI + BEV is administered first[a]**

Demography	Starting Regimen		
	Cohort A REG N=149	Cohort B FTD/TPI N=80	Cohort C FTD/TPI + BEV N=226
Median age, years	64.0	65.5	67.0
Male, %	53.0	52.5	55.3
ECOG PS 0, %	52.3	31.3	48.7
Right-sided tumour, %	33.6	27.5	20.4
RAS wild-type, %	35.6	41.3	43.4
BRAF V600E mutant, %	6.7	7.5	4.0

Outcomes	Starting Regimen		
	Cohort A REG N=149	Cohort B FTD/TPI N=80	Cohort C FTD/TPI + BEV N=226
Median OS, months	11.8	7.1	10.3
HR (95% CI) p value (comparison with cohort A)		0.72 (0.52-0.99) p=0.043	1.03 (0.79-1.33) p=0.828

- Patients who received subsequent treatment with FTD/TPI+BEV in cohort A (62.4%), REG in cohort B (37.5%), REG in cohort C (62.8%)

[a] Patients were refractory or intolerant to standard chemotherapies, anti-VEGF or anti-EGFR and who were scheduled to receive REG or FTD/TPI +/- BEV first.

BEV, bevacizumab; BRAF, proto-oncogene B-Raf; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival; REG, regorafenib

Chida A, et al. J Clin Oncol. 2024;42 (no. 3_Suppl):103 (Poster presentation)

REAL-WORLD ANALYSIS OF PATIENT CHARACTERISTICS AND OUTCOMES AMONG mCRC PATIENTS RECEIVING FTD/TPI PLUS BEV VERSUS FTD/TPI MONOTHERAPY

- This real-world study **supports the value of FTD/TPI+BEV combination** therapy vs FTD/TPI monotherapy as seen in the SUNLIGHT trial
- Patients with FTD/TPI+BEV were treated for longer duration with improved OS and no difference in trends for HCRU and associated costs

Demography	FTD/TPI + BEV N=122	FTD/TPI N=75
Mean age, years	60.2	61.8
Male, %	66	63
Mean Charlson Comorbidity Index	8.9	8.5
Mean BMI, kg/m^2	26.9	27.3
Received treatment in 3L/4L setting, %	65	75
Median follow-up, months	5.3	4.6

Characteristic	FTD/TPI + BEV N=122	FTD/TPI N=75
Mean length of treatment, mo	3.7	2.7
Median OS, mo	11.5	9.6
Mean outpatient visits, n	20.5	13.9
Mean ER visits, n	0.5	0.5
Mean hospitalisations, n	1.1	1.2
Mean healthcare event costs, USD	27,175	27,891

3L/4L, third-/fourth-line; BEV, bevacizumab; BMI, body mass index; ER, emergency room; FTD/TPI, trifluridine-tipiracil; HCRU, healthcare resource use; mCRC, metastatic colorectal cancer; mo, months; OS, overall survival; USD, United States dollars

Hubbard J, et al. J Clin Oncol. 2024;42 (no. 3_Suppl):34

SUMMARY

- RWE is being increasingly used to assist decision-making for regulators, payers, HCPs and patients
- Randomised controlled trials remain the ‘gold-standard’ to determine causal effect but RWE can provide complementary data in a patient population more representative of clinical practice
- RWD can be collected from a variety of sources, including administrative claims databases, EHRs, registries, and multimodal data sources
- Several limitations of RWE (e.g., risk of bias, data quality and confounding factors) must be considered and controlled through statistical and design methodology
- Regulatory guidance on the use of RWE will improve the perception of RWE by various stakeholders
- Real-world evidence on the use of regorafenib and trifluridine-tipiracil as later-line treatments for mCRC patients generally supports data from RCTs
- Additional later-line treatments for molecularly unselected mCRC patients should also be considered, such as fruquintinib
- RWE will provide useful information on the use of fruquintinib in routine clinical practice, as it becomes more widely available

EHR, electronic health record; HCP, healthcare professional; mCRC, metastatic colorectal cancer’ RCT, randomised-controlled trial; RWD, real-world data; RWE, real-world evidence

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