Updates in Colorectal Cancer

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Disclosure

I **do not** have any commercial or financial relationship to any topics or products discussed.

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Colorectal Cancer

- Epidemiology
- Locoregional Colorectal Cancer
- Advanced Stage
- Future Directions

Epidemiology

- Third most common cancer
- 1.9 million new CRC occurred worldwide
- 2020 US 104,610 colon and 43,340 rectal – 53K deaths
- Incidence per 100,000 people decreased from 60.5 to 38.7
- Recent data shows decrease of 3.3% annually in age group of > 65 from 2011 to 2016

Epidemiology

- Conversely increase of 1% in age group 50-64
- 0.6% annual decline in mortality for individuals 50-64
- 2% increased incidence in age group <50 years
- 1.3% increased death rate in age <50 years
- Estimated that the incidence rate for colon and rectal cancer will increase 90 to 124% in patients 20-34 by 2030

Louisiana

Incidence Rate Report for Louisiana by Parish

Colon & Rectum (All Stages^), 2015-2019

All Races (includes Hispanic), Both Sexes, All Ages

Sorted by Rate

Parish	Age-Adjusted Incidence Rate† cases per 100,000 (95% Confidence Interval)	CI*Rank (95% Confidence Interval)	Average Annual Count	Recent Trend	Recent 5-Year Trend‡ in Incidence Rates (95% Confidence Interval)
Louisiana [7]	45.1 (44.3, 45.9)	N/A	2,429	stable →	0.4 (-1.6, 2.5)
US (SEER+NPCR) [1]	37.7 (37.6, 37.7)	N/A	143,166	falling ↓	-1.7 (-2.0, -1.3)

https://statecancerprofiles.cancer.gov/quick-profiles/index.php?statename=louisiana

Epidemiology

- 20% are associated with familial clustering
- 50-60% are diagnosed with metastases
- 20-34% have synchronous liver metastasis
- 10-15% are diagnosed as having locally advanced colon cancer – defined as T4, direct invasion of surrounding organs or extensive LN
- LACC is classified as stage IIB/C and stage IIIB/C

Cells **2022**, *11*(23), 3744; **https://doi.org/10.3390/cells11233744**
Version 3.2022 NCCN Guidelines Colon Cancer

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Colon Cancer

NCCN Guidelines Index
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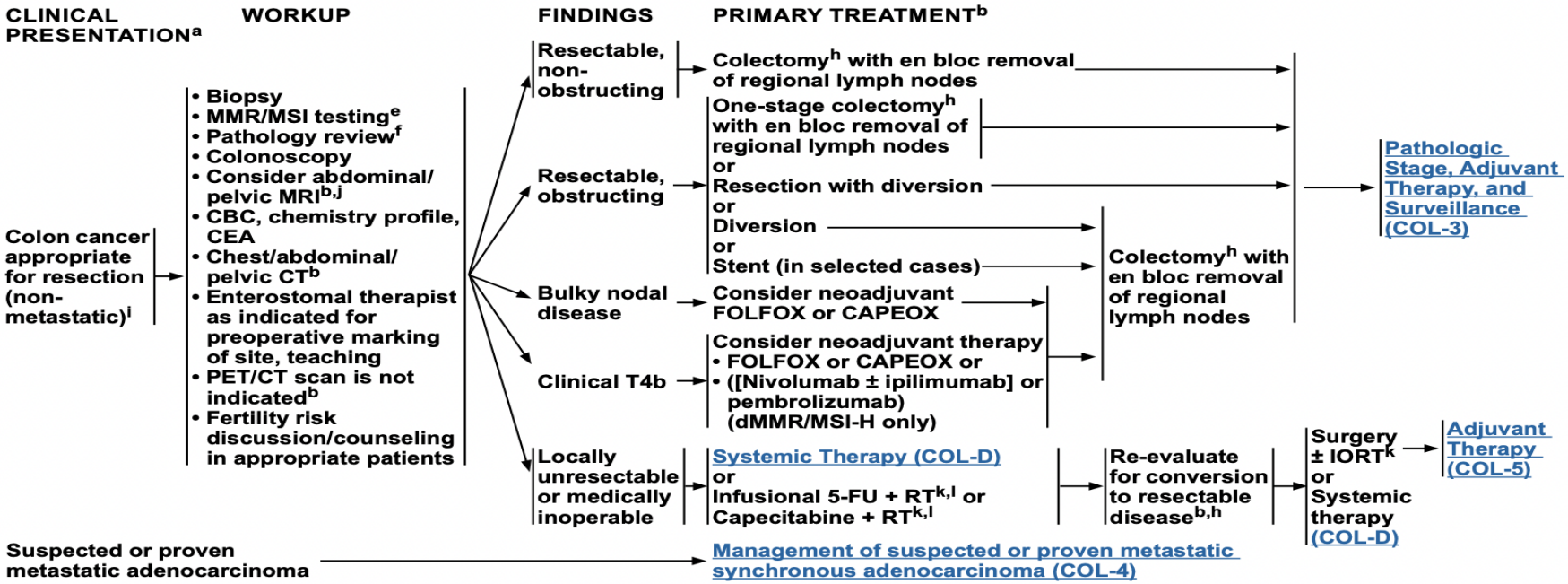


[a] All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected Lynch syndrome, FAP, and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[b] Principles of Imaging (COL-A).
[e] Principles of Pathologic Review (COL-B 4 of 8) - MSI or MMR Testing.
[f] Principles of Pathologic Review (COL-B) - Colon cancer appropriate for resection, pathologic stage, and lymph node evaluation.
[h] Principles of Surgery (COL-C 1 of 3).
[i] For tools to aid optimal assessment and management of older adults with cancer, see the NCCN Guidelines for Older Adult Oncology.
[j] Consider an MRI to assist with the diagnosis of rectal cancer versus colon cancer (eg, low-lying sigmoid tumor). The rectum lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI.
[k] Principles of Radiation and Chemoradiation Therapy (COL-E).
[l] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

LACC

- 5-year observed survival Stage IIb (T4aN0M0) and Stage IIc(T4bN0MO) of 60.6% and 45.7%
- Adjuvant chemo-therapy has been the mainstay of therapy
- A meta-analysis published in 2020 including 29k patients suggested that neoadjuvant chemotherapy significantly improved overall survival and DFS without increasing morbidity compared to upfront surgery in bulky disease or cT4 status

Cells **2022**, *11*(23), 3744; **https://doi.org/10.3390/cells11233744**

LACC

- Around 5% have advanced locally unresectable tumors caused by critical organ involvement or direct invasion
- Small studies support similar concepts of rectal chemoradiation that show success with downstaging

LACC

J Gastrointest Oncol. 2020 Oct;11(5):847-857. doi: 10.21037/jgo-20-220.

Neoadjuvant therapy in locally advanced colon cancer: a meta-analysis and systematic review

Chin Kai Cheong [1], Kameswara Rishi Yeshayahu Nistala [1], Cheng Han Ng [1], Nicholas Syn [1], Heidi Sian Ying Chang [2], Raghav Sundar [1 3 4], Soon Yu Yang [5], Choon Seng Chong [1 2]

Affiliations + expand

PMID: 33209481 PMCID: PMC7657836 DOI: 10.21037/jgo-20-220

Free PMC article

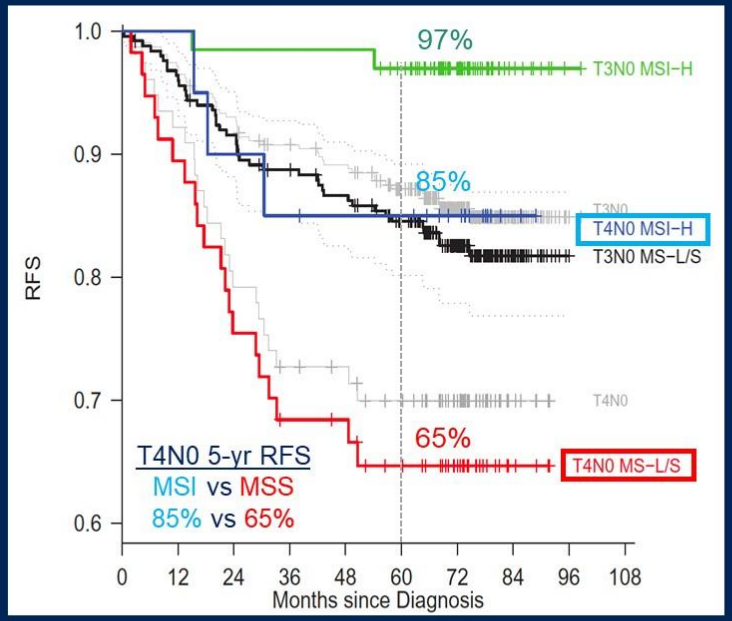
MMR –Mismatch Repair

- Mismatch report deficient cells produce truncated, nonfunction protein or exhibit loss of proteins ~ 15% of sporadic CRC cases
- Study evaluating PD1 in advanced dMMR in 12 different tumors showed benefit in dMMR-MSI-H CRC
- 35 patients with early-stage CRC receiving Ipi with nivo – had a pathological response of 100%
- In 2022 Chalabi et al. reported promising downstaging effect of neoadjuvant immunotherapy in dMMR LACC. Among 112 patients with cT3 or N+ colon cancer- 95% exhibited a major pathological response

Nat Med. 2020 Apr;26(4):566-576.

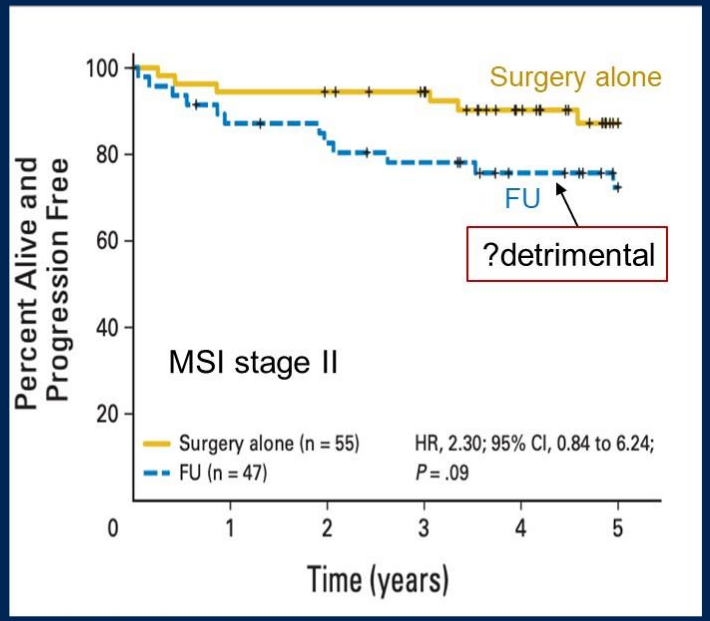
dMMR/MSI Stage II Colon Cancer

✓ Good prognostic marker



Roth et al. J Natl Cancer Inst 2012;104:1635–1646 (PETACC3)

✓ Lack of benefit with 5FU



Sargent et al. J Clin Oncol. 2010 Jul 10;28(20):3219-26

???

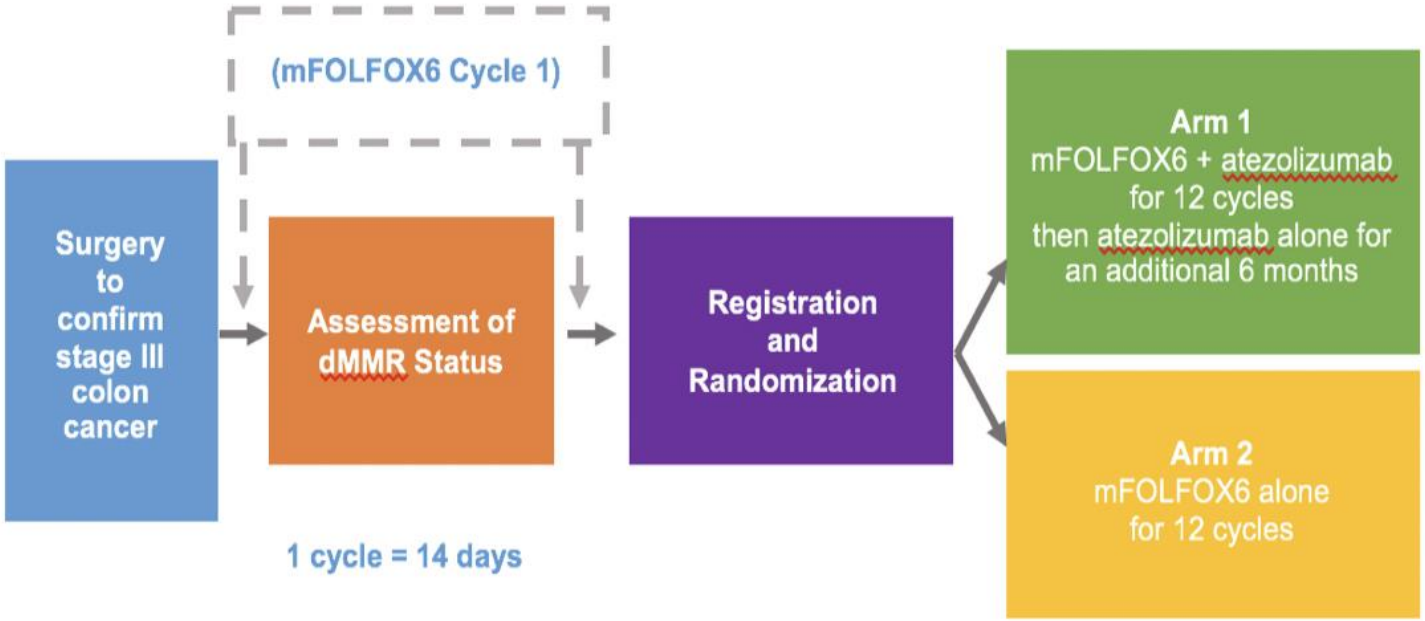
Role of oxaliplatin

ATOMIC

adjuvant trial of microsatellite instability colon cancer

- Active since September 12, 2017
- Targeted enrollment of 700
- Primary study endpoint is disease-free survival (DFS)

ATOMIC TRIAL



ASCO Gastrointestinal Cancers Symposium

Circulating Tumor DNA: Prime Time or Jumping Too Soon?

Case Discussion

Adjuvant Therapy in Colon Cancer

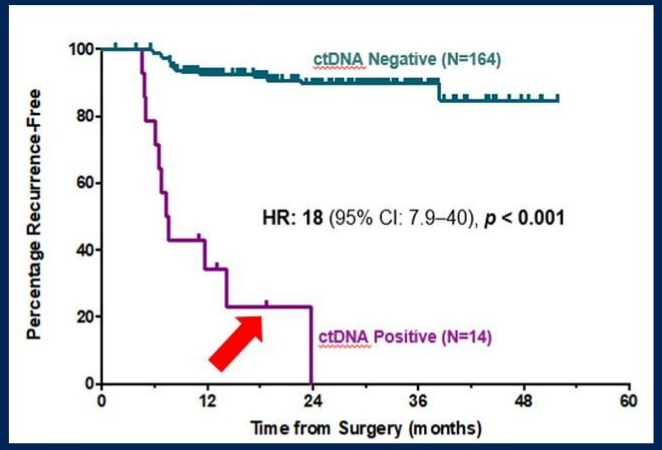
Jeanne Tie

Peter MacCallum Cancer Centre and Walter & Eliza Hall Institute
Melbourne, Australia

Post-op ctDNA is Highly Prognostic

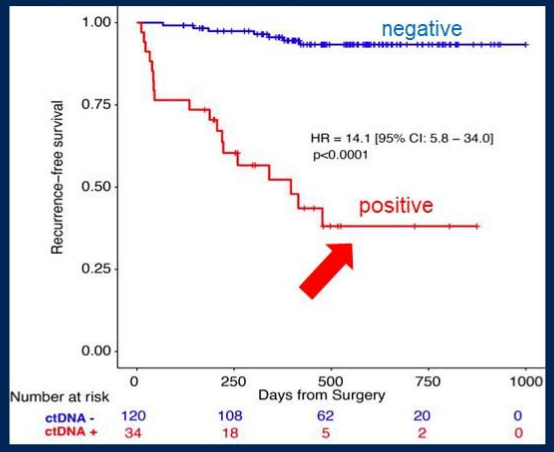
- ctDNA detection after curative-intent surgery for CRC
  → very high recurrence risk (~80%) especially without further treatment

AUSTRALIA: Week 4-10 post-op
(Stage II - no chemo)



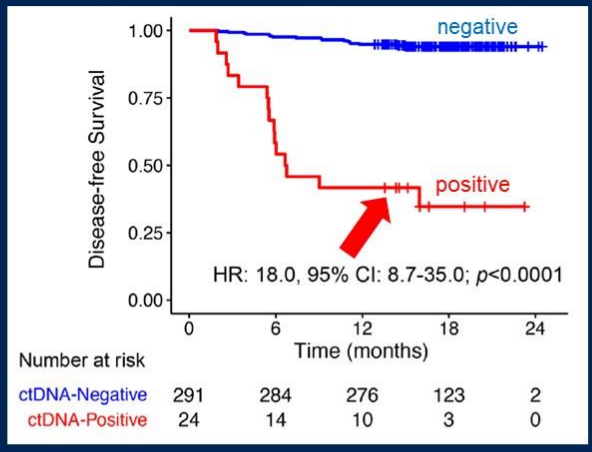
Tie J et al. *Sci Transl Med.* 2016 Jul 6;8(346):346ra92

US: Week 2-8 post-op
(Stage I-III +/- adjuvant chemo)



Cohen SA et al. *ESMO 2022.* Abstract 319MO.

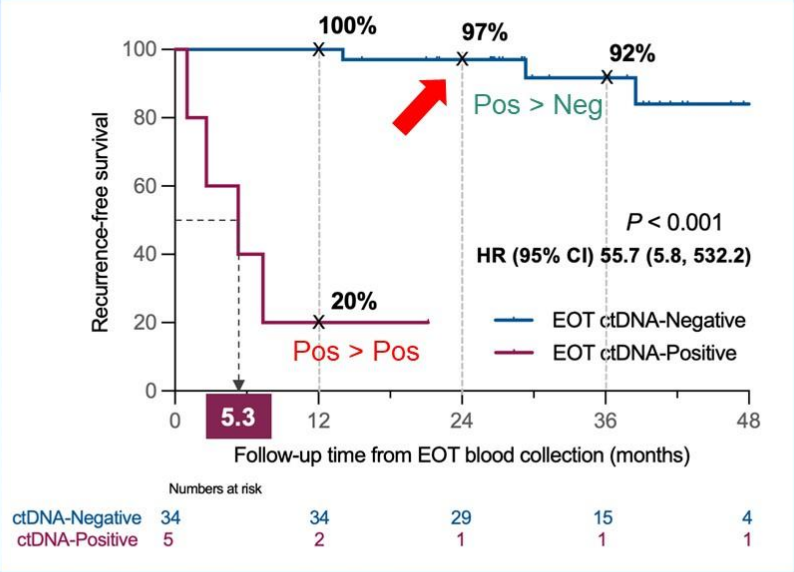
JAPAN: Week 4 post-op
(Stage II +/- adjuvant chemo)



Kotani D et al. *Nat Med* (2023). Online 16 Jan.

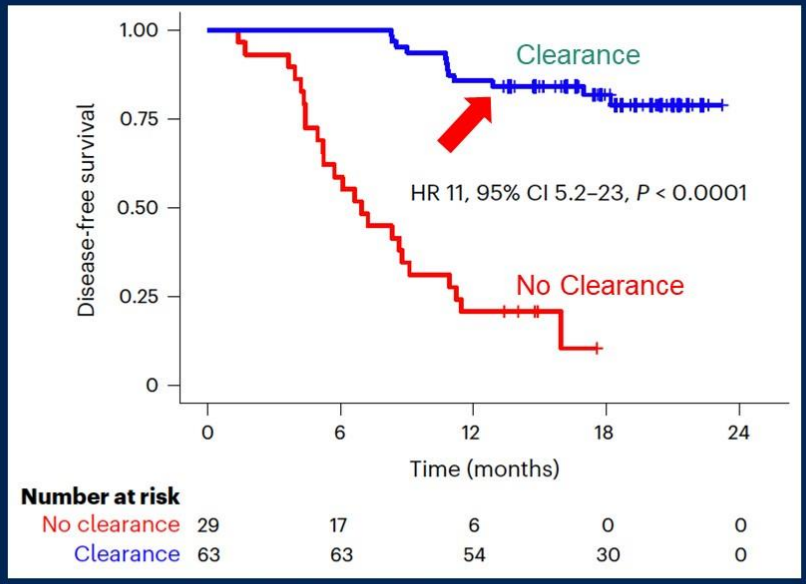
ctDNA Clearance After Treatment Predicts Outcome

DYNAMIC trial (stage II)
ctDNA cleared in 87% of patients at 4 weeks after completing chemotherapy



Tie *et al.*,*ESMO Congress 2022, 318MO*

GALAXY study (resected stage I-IV)
ctDNA cleared in 68% of chemo-treated patients by 6 months after surgery



Kotani D et al. *Nat Med* (2023). Online 16 Jan.

What to do with Post-Chemo ctDNA-Positive Patients?
Selected "2nd Line/Extended" Adjuvant Therapy Trial

Study	Population	Intervention
ACT3 *(MGH – A Parikh)*	Stage III colon cancer	BRAF mut: 6M Enco/Bini/Cetux MSI: 12M Nivolumab Other: FOLFIRI vs surveillance
ALTAIR *(CIRCULATE-JAPAN)*	Stage II/III/IV (resected mets)	After 3M adjuvant CAPOX: Trifluridine/tipiracil vs placebo
NSABP FC-12 *(T George, N Wolmark)*	Stage II/III	Gevokizumab (IL-1β)
NCT04486378	Stage III/high-risk stage II	mRNA vaccine (RO7198457) vs surveillance
CLAUDE	Stage II/III/IV (resected mets)	EO2040 (peptide vaccine) + Nivolumab

Conclusion/Takeaway

- Detection of ctDNA after curative intent surgery predicts for high risk of recurrence (prognostic)
  - Post-op ctDNA testing can be helpful to guide adjuvant therapy in scenarios where treatment benefit is uncertain/modest, e.g., low/intermediate risk or dMMR/MSI stage II
- Favorable RFS in treated ctDNA-positive patients and the high ctDNA clearance rate suggest potential benefit from adjuvant chemo
  - Ongoing randomized trials will provide more definitive evidence
- ctDNA detection post-chemotherapy or during surveillance is prognostic but its clinical utility remains the subject of ongoing trials
  - Caution: over-investigation, anxiety provoking without survival gain

Prognostic/Predictive Marker

Review

Comprehensive Review of Biomarkers for the Treatment of Locally Advanced Colon Cancer

Jen-Pin Chuang [1,2,3], Hsiang-Lin Tsai [4,5], Po-Jung Chen [4,6], Tsung-Kun Chang [4,6,7,8], Wei-Chih Su [4,7], Yung-Sung Yeh [9,10,11], Ching-Wen Huang [4,5] and Jaw-Yuan Wang [1,4,5,7,11,12,*]

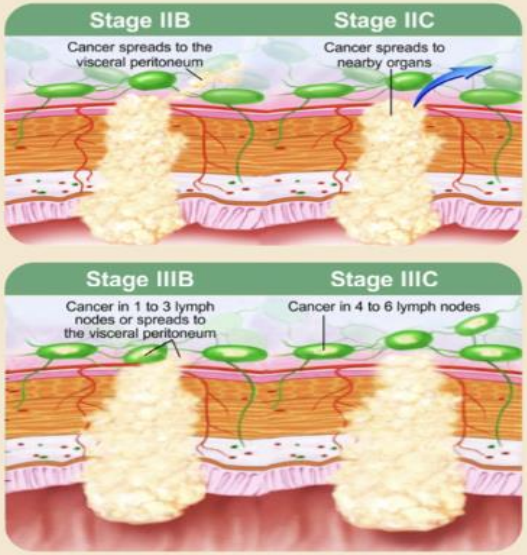
Other Biomarkers

- ERCC1 – expression of excision repair-cross complementing 1 investigated as negative predictive marker for FOLFOX neoadjuvant chemotherapy
- LINE-1 Methylation of long interspersed nucleotide elements as degree of methylation serves as an independent factor for oncology outcomes
- PIK3CA mutated colorectal cancer patients had lower recurrence rates treated with Aspirin

 Signal Transduction and Targeted Therapy(2020)5:22

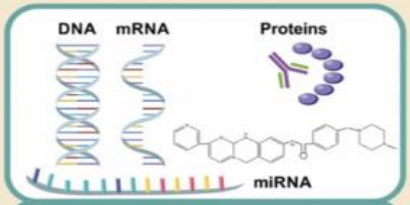
Predictive/Prognostic Biomarkers of LACC

dMMR
TS
GSTpi
dMMR
ERCC1 and ERCC2
Tumor differentiation
MMR
MSI-H
EGFR
KRAS BRAF
PIK3CA
CIMP
DCC
ERCC1
ct DNA
Blood sugar level



Favorable Prognosis in Clinicopathological Features

Early TNM stage
≥12 retrieved LNs
R0 resection
Age<70 year
Left side colon cancer



Potential Genetic and Epigenetic Prognostic Biomarkers

miRNAs

let-7g; miR-129; miR-217; miR-125a; miR-375; miR-328; miR-125b; miR-144; miR-194; miR-486; miR-1299; miR-140, miR-215, miR-494

lncRNAs

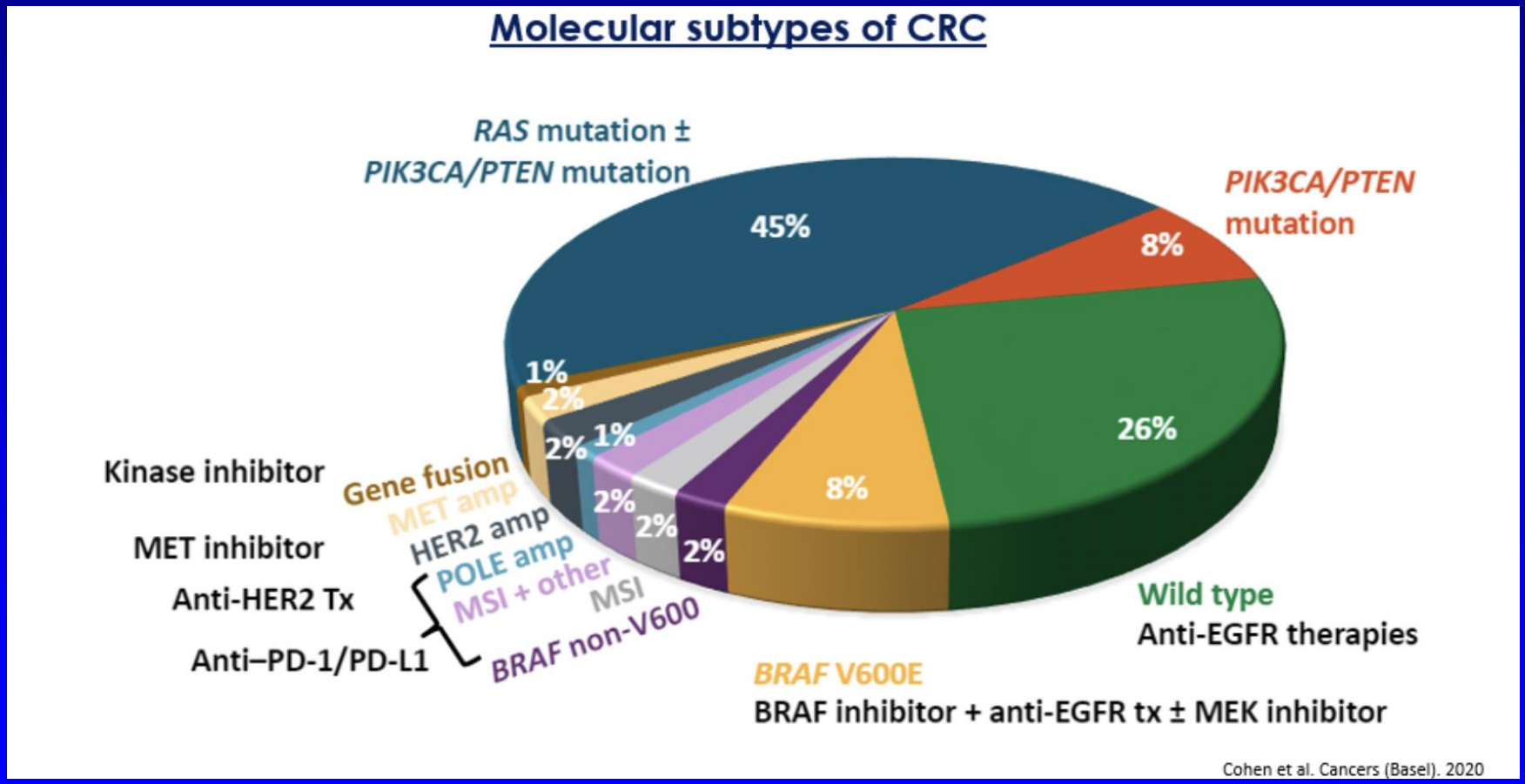
PVT1
CASC21
CASC15
HOTAIR
lncRNA-p21

Genomic & Metabolomic Landscape

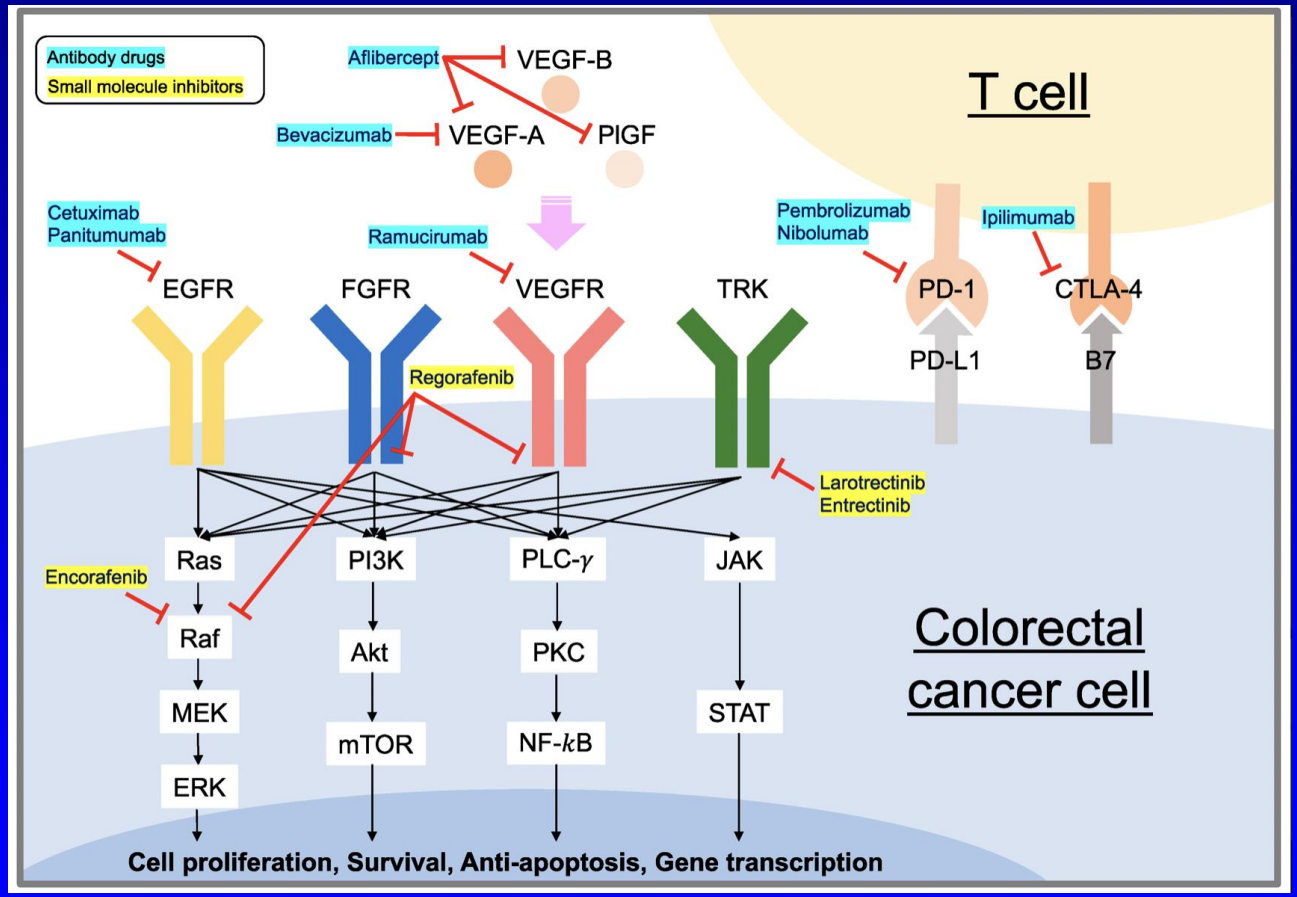
LINE-1 methylation

Signal Transduction and Targeted Therapy(2020)5:22

Metastatic Colon Cancer



Metastatic Colorectal Cancer



Int. J. Mol. Sci. **2023**, *24*(2), 1702; https://doi.org/10.3390/ijms24021702

Metastatic Disease

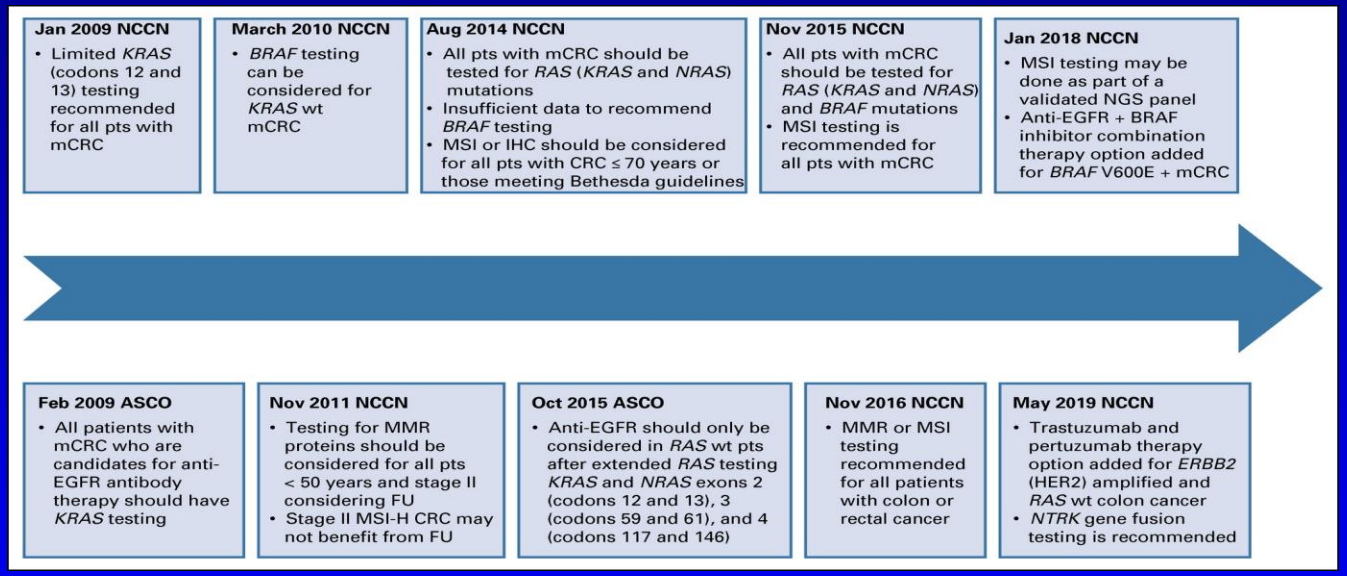
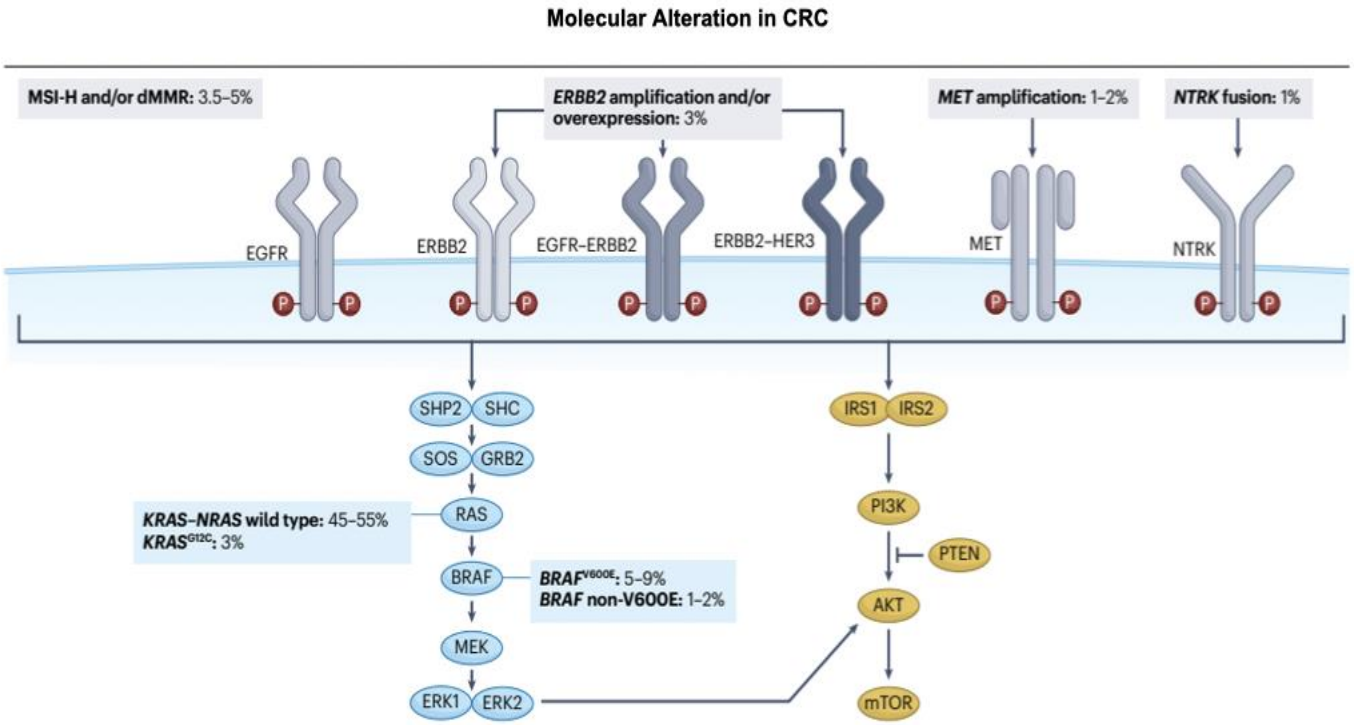


FIG 1. Evolution of guidelines for molecular testing in metastatic colorectal cancer (mCRC). FU, fluorouracil; IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability high; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; pts, patients; wt, wild type.

Published in: Martin E. Gutierrez; Kristin S. Price; Richard B. Lanman; Rebecca J. Nagy; Irfan Shah; Shivam Mathura; Michael Mulcahy; Andrew D. Norden; Stuart L. Goldberg; *JCO Precision Oncology* 2019 31-9.
DOI: 10.1200/PO.19.00274

Metastatic Colon Cancer

Molecular alterations in metastatic colorectal cancer (CRC)

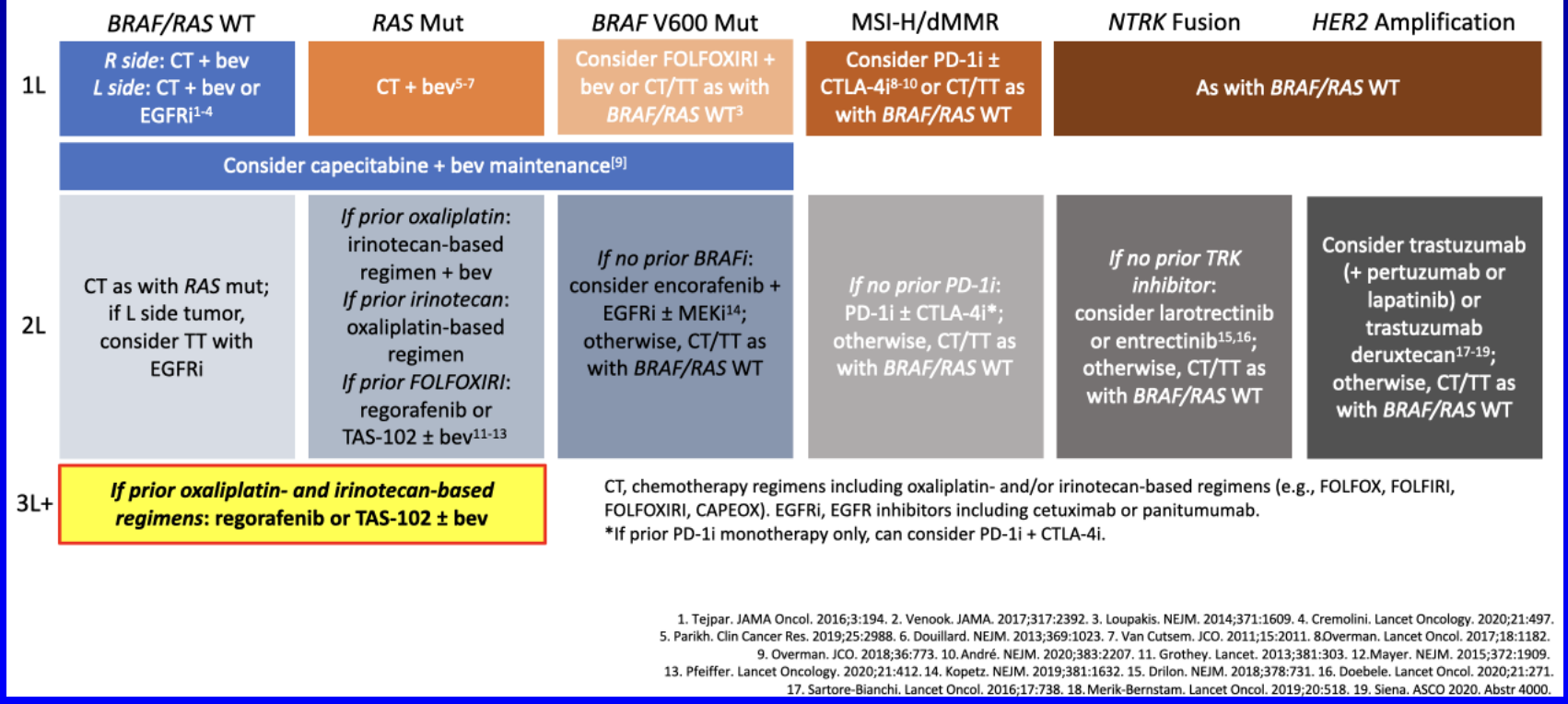


- ***HER2 (ERBB2)*** **is rarely amplified and/or overexpressed in mCRC, at an estimated 3% (5–7% in *RAS* and *BRAF* wild-type tumors).**
- **HER2 amplification status (HER2+) should be assessed in all mCRC patients with RASwt.**

Bando et al., Nat Rev Gastroenterol Hepatol, 2023

Metastatic Colorectal Cancer

General Treatment Algorithm for Metastatic CRC



CT, chemotherapy regimens including oxaliplatin- and/or irinotecan-based regimens (e.g., FOLFOX, FOLFIRI, FOLFOXIRI, CAPEOX). EGFRi, EGFR inhibitors including cetuximab or panitumumab.
*If prior PD-1i monotherapy only, can consider PD-1i + CTLA-4i.

1. Tejpar. JAMA Oncol. 2016;3:194. 2. Venook. JAMA. 2017;317:2392. 3. Loupakis. NEJM. 2014;371:1609. 4. Cremolini. Lancet Oncology. 2020;21:497.
5. Parikh. Clin Cancer Res. 2019;25:2988. 6. Douillard. NEJM. 2013;369:1023. 7. Van Cutsem. JCO. 2011;15:2011. 8.Overman. Lancet Oncol. 2017;18:1182.
9. Overman. JCO. 2018;36:773. 10. André. NEJM. 2020;383:2207. 11. Grothey. Lancet. 2013;381:303. 12.Mayer. NEJM. 2015;372:1909.
13. Pfeiffer. Lancet Oncology. 2020;21:412. 14. Kopetz. NEJM. 2019;381:1632. 15. Drilon. NEJM. 2018;378:731. 16. Doebele. Lancet Oncol. 2020;21:271.
17. Sartore-Bianchi. Lancet Oncol. 2016;17:738. 18. Merik-Bernstam. Lancet Oncol. 2019;20:518. 19. Siena. ASCO 2020. Abstr 4000.

Metastatic Colon Cancer

Overview

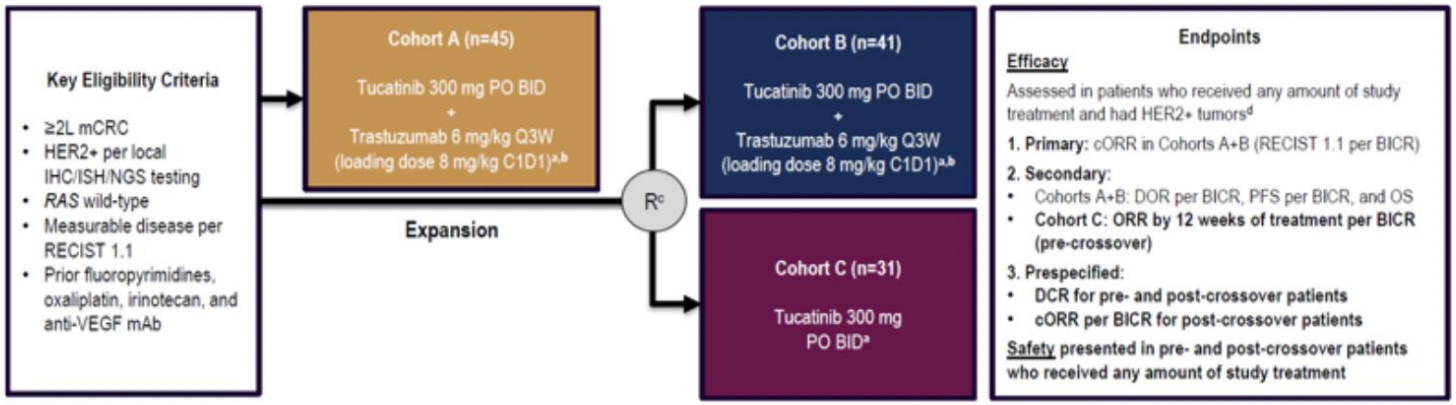
Overview of Metastatic CRC
- Key Molecular Subtypes
- Mutation-adapted Treatment Options

Key Trials for Approved Agents
- BEACON: Encorafenib (BRAF)
- MOUNTAINEER: Tucatinib + Trastuzumab (HER2)
- CORRECT: Regorafenib (Mutation Agnostic)
- Regorafenib + Immune Checkpoint Inhibition
- ReDOS: Regorafenib Dose Optimization

Conclusions

HER2 Positive

MOUNTAINEER: *Tucatinib Plus Trastuzumab in HER2+ mCRC*



Patients treated with tucatinib monotherapy were allowed to cross over and receive tucatinib and trastuzumab if they experienced radiographic progression at any time point or if they had not achieved a PR or CR by week 12

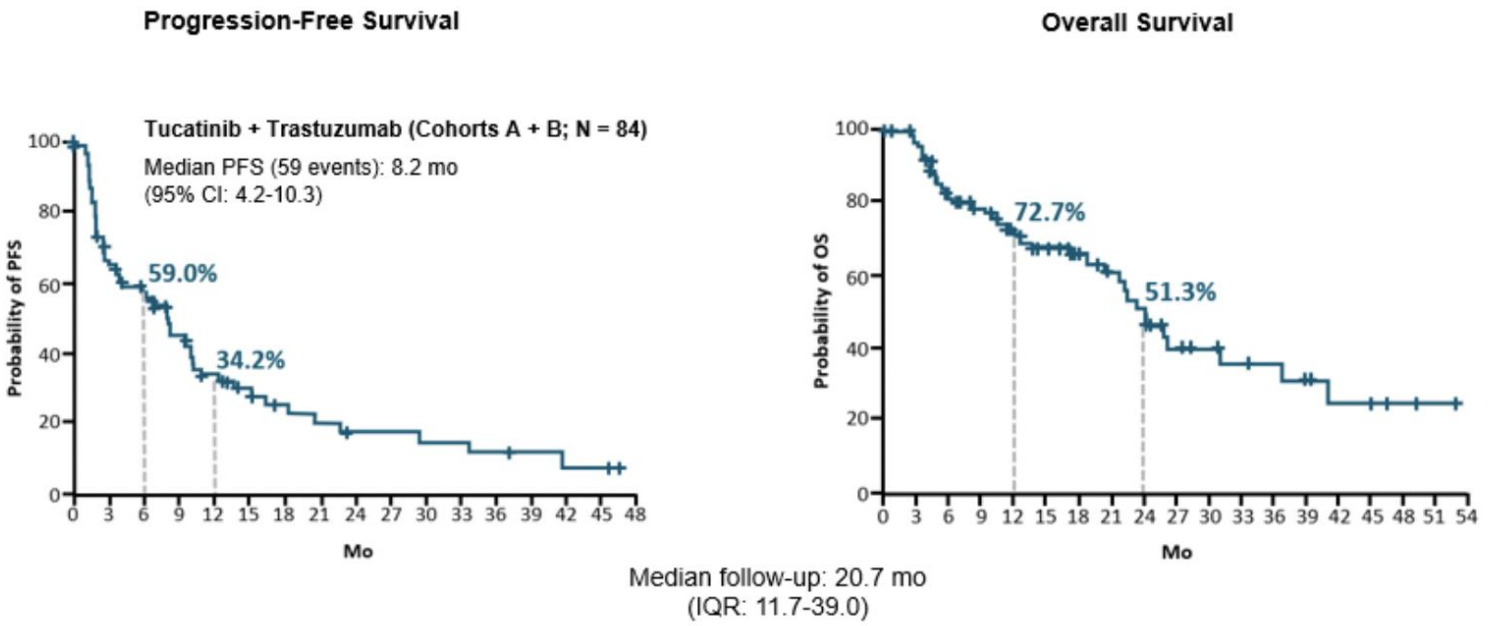
a Each treatment cycle is 21 days; b Patients remained on therapy until evidence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or study closure; c Stratification: Left sided tumour primary vs other; d

Investigators concluded that the tucatinib and trastuzumab combination has the potential to become a standard of care in patients with HER2-positive mCRC

Adapted from Strickler et al. ESMO-World GI 2022. Oral presentation no. LBA-2.; Strickler et al. ESMO 2022#LBA27

MOUNTAINEER

MOUNTAINEER (Cohorts A+B): *PFS and OS per BICR*



Median follow-up: 20.7 mo
(IQR: 11.7-39.0)

After median follow-up of 20.7 mo, the median PFS and OS were 8.2 mo and 24.1 mo, respectively

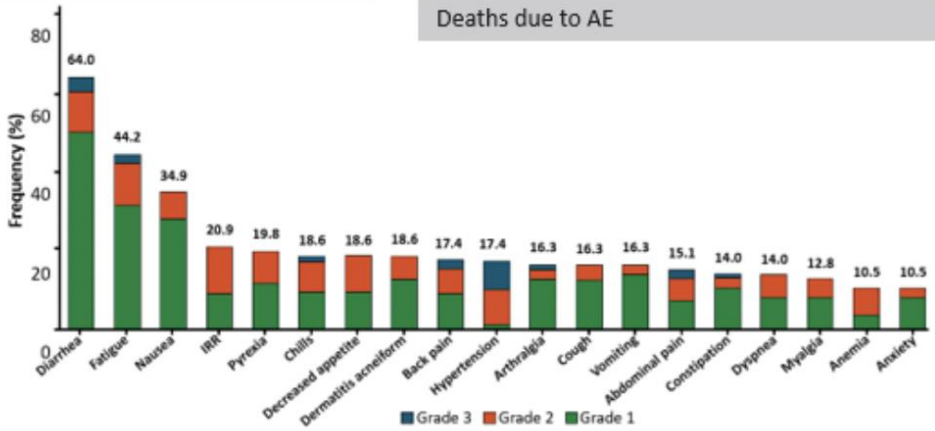
Strickler et al. ESMO-World GI 2022. Oral presentation no. LBA-2.

MOUNTAINEER

MOUNTAINEER (Cohorts A+B): *Treatment-Emergent AEs*

TEAE, n (%)	Tucatinib + Trastuzumab Cohorts A + B (N = 86)
Any grade	82 (95.3)
▪ Tucatinib related	63 (63.3)
▪ Trastuzumab related	58 (67.4)
Grade ≥3 AEs	33 (38.4)
▪ Tucatinib related	8 (9.3)
▪ Trastuzumab related	6 (7.0)

TEAE, n (%)	Tucatinib + Trastuzumab Cohorts A + B (N = 86)
SAEs	19 (22.1)
▪ Tucatinib related	3 (3.5)
▪ Trastuzumab related	2 (2.3)
AEs leading to	
▪ Treatment discontinuation	5 (5.8)
▪ Tucatinib dose modification	22 (25.6)
Deaths due to AE	0



The combination of tucatinib and trastuzumab was well tolerated with diarrhea, fatigue, and nausea as the most frequent TRAEs; there were no deaths related to AEs

Strickler et al. ESMO-World GI 2022. Oral presentation no. LBA-2.

HER2 Targeted Therapy

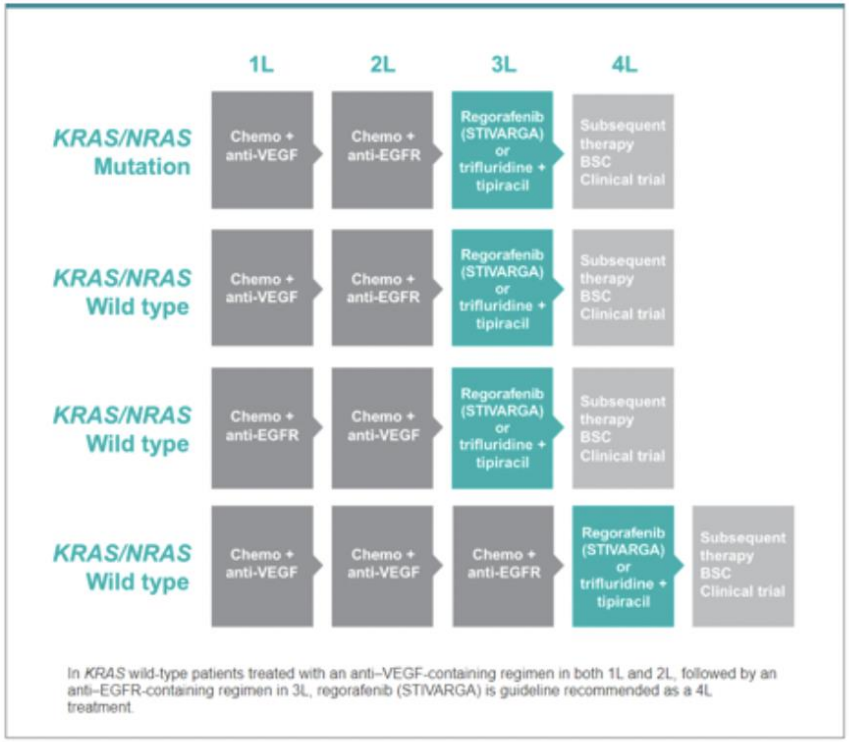
Recent Data of HER2-targeted Therapies In Patients With Advanced or Metastatic CRC

Regimen	Trial (n) – year	ORR	PFS	OS	Most common Grade 3+ AEs
Trastuzumab + lapatinib	HERACLES-A (n=32) – 2016	28%	4.7m	10m	Fatigue 16% Decreased LVEF 6%
Trastuzumab + pertuzumab	MyPathway (n=84; 57 evaluable) – 2019	32%	2.9m	11.5m	Hypokalemia 5% Abdominal pain 5%
Pertuzumab and T-DM1	HERACLES-B (n=31) – 2020	9.7%	4.1m	Not reported	Thrombocytopenia 7%
Trastuzumab deruxtecan	DESTINY-CRC01 (N=78; 53 HER2+) – 2021	45.3%	6.9m	15.5m	Neutropenia 15% Anemia 13%
Tucatinib + trastuzumab	MOUNTAINEER (n=117; 84 Cohorts A+B) - 2022	38.1%	8.2m	24.1m	Hypertension 7% Diarrhea 3.5%

1. Tosi F, et al. *Clin Colorectal Cancer*. 2020;19(4):256-262.e2. 2. Meric-Bernstam F, et al. Lancet Oncol. 2019;20(4):518-530. 3. Sartore-Bianchi A, et al. ESMO Open. 2020;5(5):e000911. 4. Siena S, et al; Lancet Oncol. 2021;22(6):779-789. 5. Meric-Bernstam et al. ASCO 2021. Abstract 3004. 6. Yoshino T et al. ASCO GI 2022. Abstract 119.

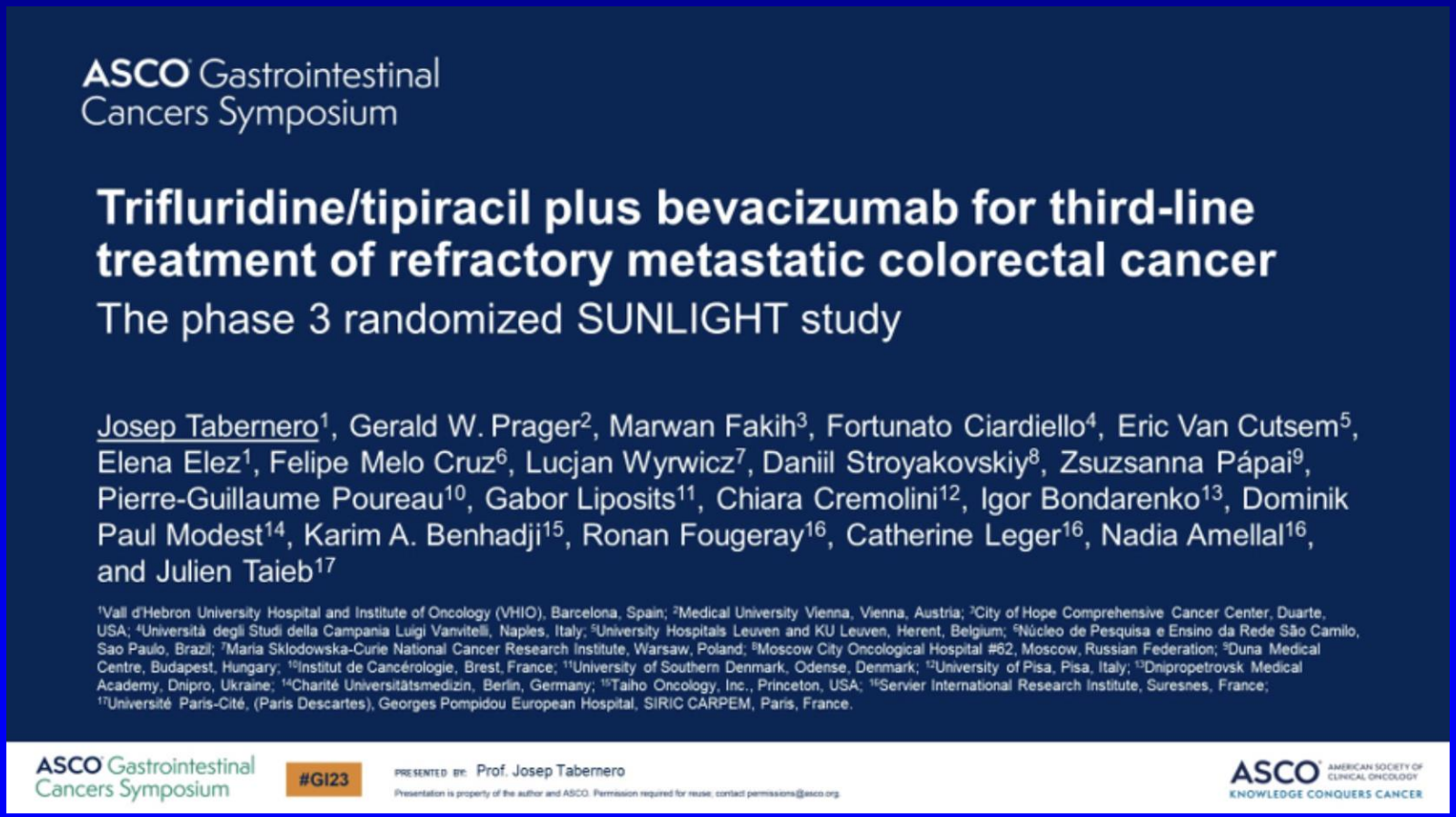
THIRD LINE THERAPY

NCCN Guidelines®, ESMO Guidelines, and JSCCR Guidelines for 3+L treatment option in appropriate patients



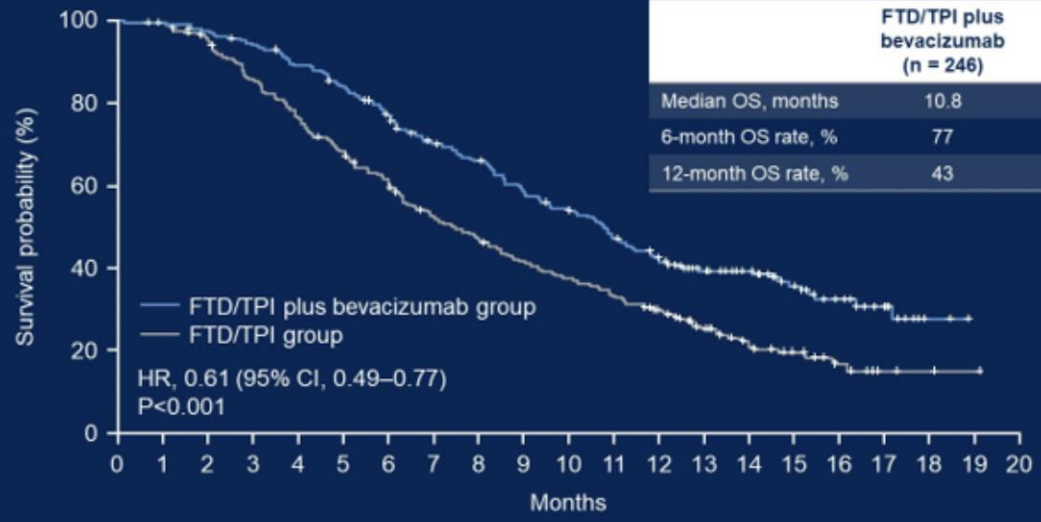
https://www.stivarga.com/mcrc/treatment-planning; Accessed Feb 7, 2023

SUNLIGHT Study



SUNLIGHT Study

OS in full analysis set (primary endpoint)



	FTD/TPI plus bevacizumab (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 plus bevacizumab 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

CI, confidence interval; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; OS, overall survival.

ASCO Gastrointestinal Cancers Symposium #GI23

PRESENTED BY: Prof. Josep Tabernero

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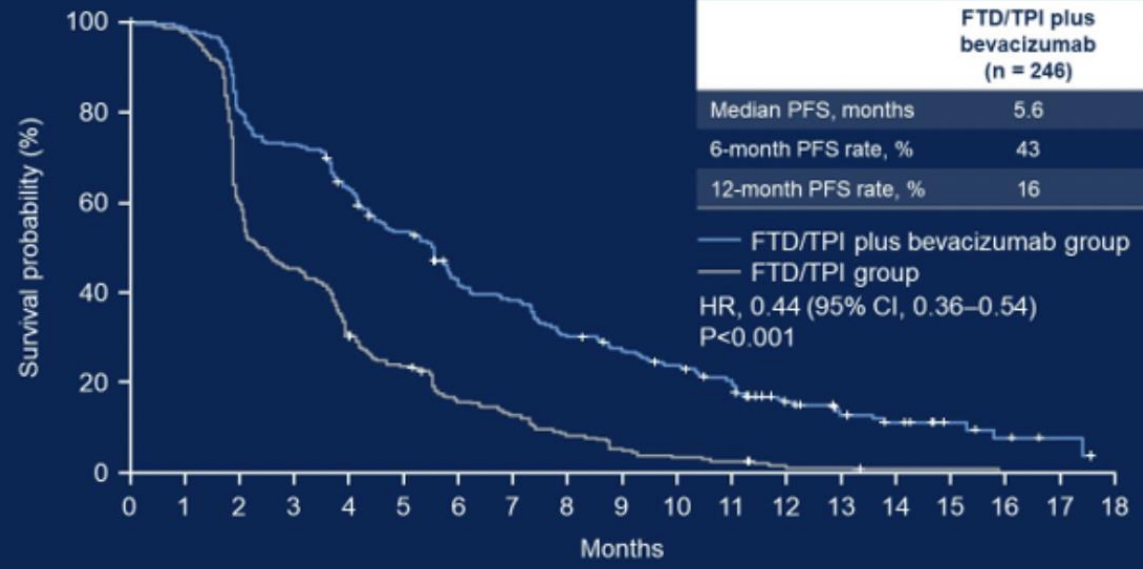
SUNLIGHT Study

PFS in full analysis set



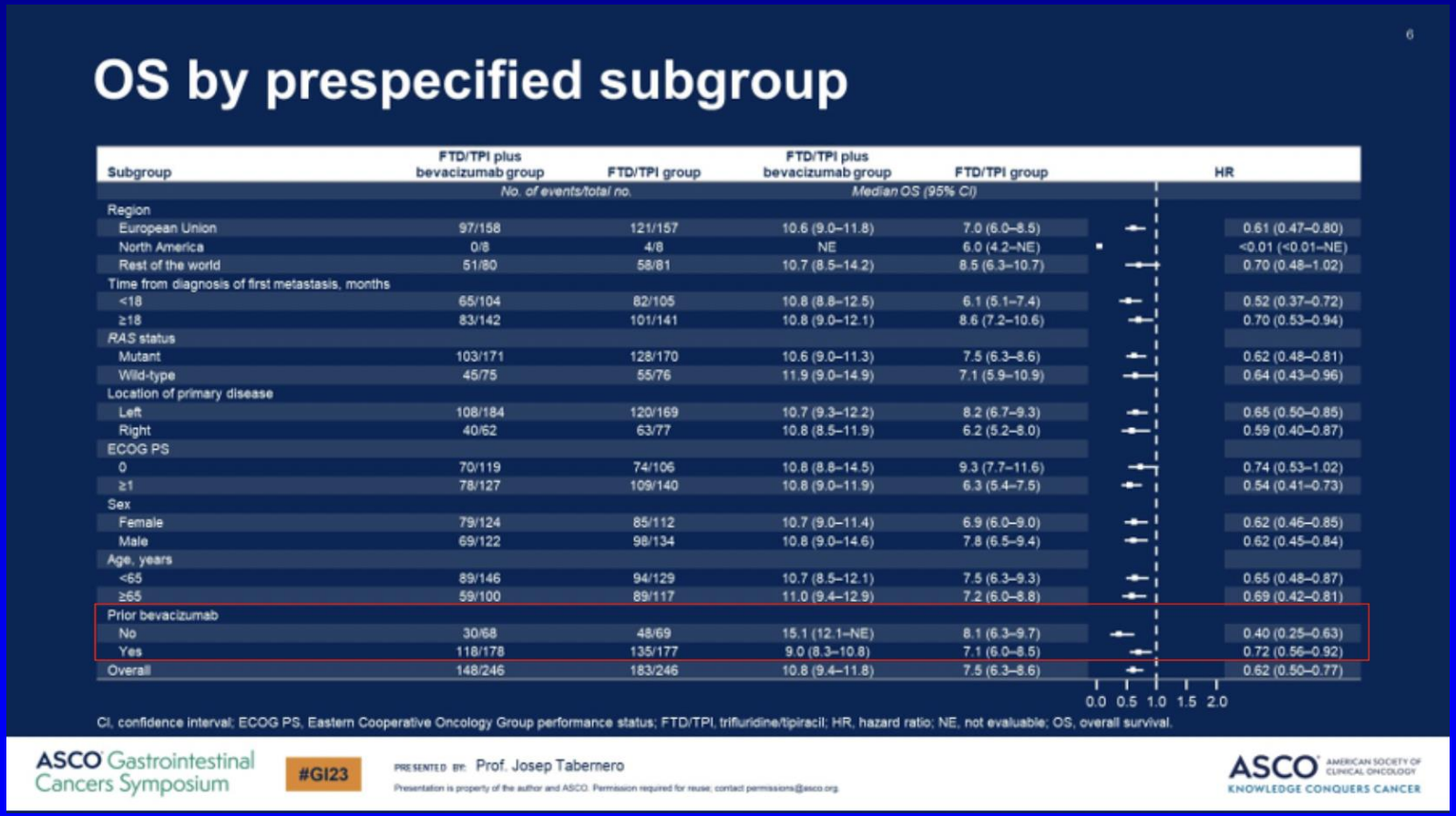
	FTD/TPI plus bevacizumab (n = 246)	FTD/TPI (n = 246)
Median PFS, months	5.6	2.4
6-month PFS rate, %	43	16
12-month PFS rate, %	16	1

No. at risk

FTD/TPI plus bevacizumab 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

CI, confidence interval; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; PFS, progression-free survival.

SUNLIGHT Study



Subgroup	FTD/TPI plus bevacizumab group	FTD/TPI group	FTD/TPI plus bevacizumab group	FTD/TPI group	HR
	No. of events/total no.		*Median OS (95% CI)*		
Region					
European Union	97/158	121/157	10.6 (9.0–11.8)	7.0 (6.0–8.5)	0.61 (0.47–0.80)
North America	0/8	4/8	NE	6.0 (4.2–NE)	<0.01 (<0.01–NE)
Rest of the world	51/80	58/81	10.7 (8.5–14.2)	8.5 (6.3–10.7)	0.70 (0.48–1.02)
Time from diagnosis of first metastasis, months					
<18	65/104	82/105	10.8 (8.8–12.5)	6.1 (5.1–7.4)	0.52 (0.37–0.72)
≥18	83/142	101/141	10.8 (9.0–12.1)	8.6 (7.2–10.6)	0.70 (0.53–0.94)
RAS status					
Mutant	103/171	128/170	10.6 (9.0–11.3)	7.5 (6.3–8.6)	0.62 (0.48–0.81)
Wild-type	45/75	55/76	11.9 (9.0–14.9)	7.1 (5.9–10.9)	0.64 (0.43–0.96)
Location of primary disease					
Left	108/184	120/169	10.7 (9.3–12.2)	8.2 (6.7–9.3)	0.65 (0.50–0.85)
Right	40/62	63/77	10.8 (8.5–11.9)	6.2 (5.2–8.0)	0.59 (0.40–0.87)
ECOG PS					
0	70/119	74/106	10.8 (8.8–14.5)	9.3 (7.7–11.6)	0.74 (0.53–1.02)
≥1	78/127	109/140	10.8 (9.0–11.9)	6.3 (5.4–7.5)	0.54 (0.41–0.73)
Sex					
Female	79/124	85/112	10.7 (9.0–11.4)	6.9 (6.0–9.0)	0.62 (0.46–0.85)
Male	69/122	98/134	10.8 (9.0–14.6)	7.8 (6.5–9.4)	0.62 (0.45–0.84)
Age, years					
<65	89/146	94/129	10.7 (8.5–12.1)	7.5 (6.3–9.3)	0.65 (0.48–0.87)
≥65	59/100	89/117	11.0 (9.4–12.9)	7.2 (6.0–8.8)	0.69 (0.42–0.81)
Prior bevacizumab					
No	30/68	48/69	15.1 (12.1–NE)	8.1 (6.3–9.7)	0.40 (0.25–0.63)
Yes	118/178	135/177	9.0 (8.3–10.8)	7.1 (6.0–8.5)	0.72 (0.56–0.92)
Overall	148/246	183/246	10.8 (9.4–11.8)	7.5 (6.3–8.6)	0.62 (0.50–0.77)

SUNLIGHT Study

Overall safety summary

Event (any cause), n (%)	FTD/TPI plus bevacizumab (n = 246)	FTD/TPI (n = 246)
Overall AEs	241 (98)	241 (98)
FTD/TPI-related AEs	221 (90)	200 (81)
Bevacizumab-related AEs	119 (48)	NA
Severe (grade ≥3) AEs	178 (72)	171 (70)
Serious AEs	61 (25)	77 (31)
Treatment-related deaths	0	0
AEs leading to withdrawal from the study	31 (13)	31 (13)

Dose modification, n (%)	FTD/TPI plus bevacizumab (n = 246)	FTD/TPI (n = 246)
Dose reductions	40 (16)	30 (12)
Dose delays	171 (70)	131 (53)

AE, adverse event; FTD/TPI, trifluridine/tipiracil; NA, not applicable.

FRUQUINTINIB

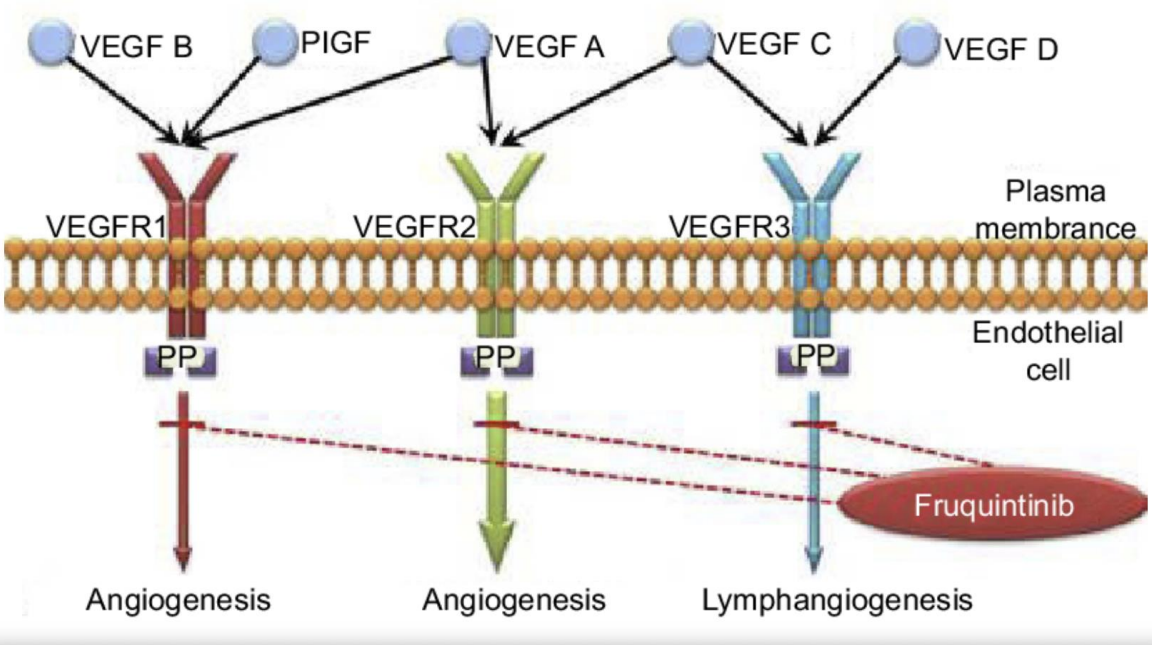


Figure 1 Molecular targets of fruquintinib.

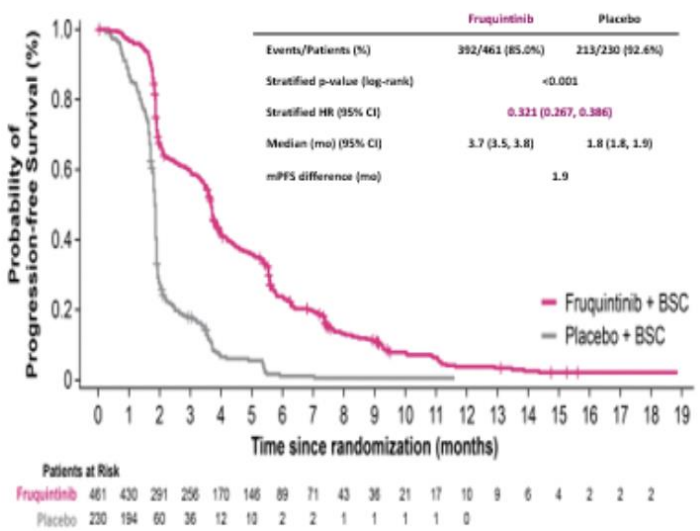
Published in 2019
CMAR_A_215533 7787..7803

Ying Zhang, Jia Zou, Zhe Wang, Ying Wang

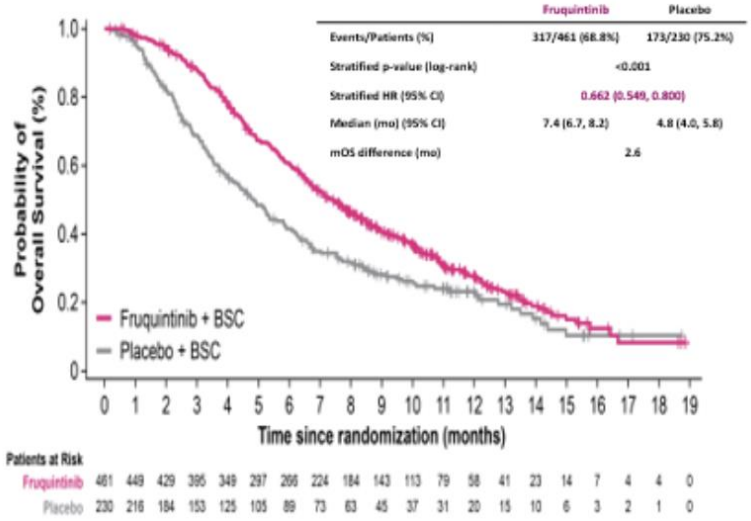
FRUQUINTINIB

FRESCO 2 : Phase III study of fruquintinib in pts with refractory mCRC

Progression Free Survival



Overall Survival



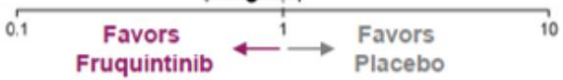
Prior TAS-102 and/or regorafenib	TAS-102	240 (52.1)	121 (52.6)
	Regorafenib	40 (8.7)	18 (7.8)

FRUQUINTINIB

Subgroup Analyses: OS and PFS

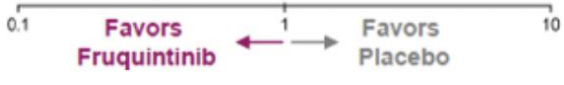
Overall Survival Subgroup Analysis

		Fruquintinib n/N	Placebo n/N	
Prior VEGFi	Yes	306/445	167/221	0.683 (0.565, 0.827)
	No	11/16	6/9	0.193 (0.024, 1.557)
Prior EGFRi	Yes	127/180	64/88	0.689 (0.507, 0.936)
	No	190/281	109/142	0.666 (0.524, 0.846)
Prior TAS-102 and Regorafenib	TAS-102	165/240	88/121	0.723 (0.557, 0.938)
	Regorafenib	25/40	12/18	0.772 (0.379, 1.573)
	Both	127/181	73/91	0.600 (0.447, 0.805)
Liver metastases	Yes	255/339	132/156	0.576 (0.465, 0.713)
	No	62/122	41/74	0.771 (0.513, 1.158)



Progression Free Survival Subgroup Analysis

		Fruquintinib n/N	Placebo n/N	
Prior VEGFi	Yes	377/445	206/221	0.335 (0.278, 0.402)
	No	15/16	7/9	0.020 (0.001, 0.385)
Prior EGFRi	Yes	154/180	79/88	0.325 (0.239, 0.440)
	No	238/281	134/142	0.310 (0.247, 0.391)
Prior TAS-102 and Regorafenib	TAS-102	210/240	111/121	0.367 (0.287, 0.470)
	Regorafenib	29/40	16/18	0.292 (0.139, 0.611)
	Both	153/181	86/91	0.285 (0.212, 0.382)
Liver metastases	Yes	297/339	149/156	0.291 (0.234, 0.362)
	No	95/122	64/74	0.334 (0.235, 0.476)



Abstr # TPS258

NRG-GI004/SWOG-S1610: Colorectal Cancer Metastatic dMMR Immuno-Therapy (COMMIT) Study: A Randomized Phase III Study of Atezolizumab with or without mFOLFOX6/Bevacizumab Combination Chemotherapy in the First-line Treatment of Patients with Deficient DNA Mismatch Repair (dMMR) or Microsatellite Instability High (MSI-H) Metastatic Colorectal Cancer

MJ Overman[1*], G Yothers[2], SA Jacobs[3], HK Sanoff[4], DJ Cohen[5], KA Guthrie[6], NL Henry[7], PA Ganz[8], S Kopetz[1], PC Lucas[9], CD Blanke[10], TS Hong[11], N Wolmark[9], HS Hochster[12], TJ George[13], CM Rocha Lima[14*]

[1]University of Texas MD Anderson Cancer Center, Houston, TX; [2]NRG SDMC and The University of Pittsburgh, Pittsburgh, PA; [3]NSABP Foundation, Pittsburgh, PA; [4]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC; [5]Icahn School of Medicine at Mount Sinai, New York, NY; [6]Fred Hutchinson Cancer Research Center, and SWOG SDMC, Seattle, WA; [7]University of Michigan Medical School Department of Internal Medicine, Ann Arbor, MI;; [8]UCLA Jonsson Comprehensive Cancer Center at UCLA, Los Angeles, CA; [9]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA; [10]OHSU School of Medicine Knight Cancer Center, Portland, OR; [11]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; [12]Rutgers-Cancer Institute of New Jersey, New Brunswick, NJ; [13]University of Florida Health Cancer Center, Gainesville, FL; [14]Atrium Health Wake Forest University Baptist Medical Center, Winston-Salem, NC

**Drs. Rocha Lima and Overman contributed equally to the management of this trial*

BACKGROUND

- ~5% of mCRCs are hypermutated due to dMMR by MLH1 promoter hypermethylation, biallelic somatic MMR mutations, or germline MMR mutations (Lynch syndrome).
- Pembrolizumab has been FDA approved for use as front-line therapy for dMMR/MSI-H MCRC based on KEYNOTE 177 results.
  - However, more pts had progressive disease as the best response in the anti-PD1 monotherapy arm compared with the standard of care (29.4% *vs* 12.3%).
  - Additionally, approximately 45% of pts on the pembrolizumab arm progressed at 12 mos.
- Synergistic Anti-tumor Activity of PD-1 Blockade in Combination with Oxaliplatin/5-FU and anti-VEGF (Lieu C, et al. ESMO 2014).
- The antiVEGF + IO first line standard for RCC and HCC. Chemotherapy + IO a first-line option in selected NSCLC pts.
- Atezo (MPDL3280A) is a monoclonal antibody that inhibits the interaction of PD-L1 and its receptors, PD-1 and B7-1.
- AtezoTRIBE subgroup analyses of 8 pts with dMMR metastatic colon cancer treated with FOLFOXIRI+bev+atezo reported the first cancer progression at 16 mos (Cremolini C, et al. ESMO 2021).
- As of 11/29/22, 89/211 pts have been enrolled to the two open treatment arms. Twenty additional pts were enrolled in Arm 1, which has been discontinued with Amendment #6 (09/15/2020).

OBJECTIVES

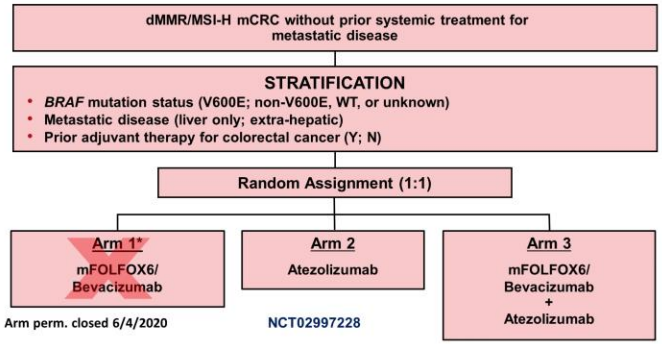
Primary
- Determine efficacy, based on PFS, of mFOLFOX6/bev+atezo compared to atezo monotherapy (control)

Secondary
- Compare overall survival
- Compare the ORR per RECIST 1.1
- Determine safety profiles of the combination of mFOLFOX6/bev/atezo + atezo in pts with dMMR/MSI-H mCRC
- Compare disease control rate (CR + PR + SD) at 12 mos
- Rate of PFS at 12 mos
- Determine duration of objective response and SD

Exploratory Objective
- Compare HRQoL and pt-reported symptoms

Translational Objective
- Bank tissue and blood samples for future correlative studies

STUDY DESIGN



Arm 2: Atezo monotherapy until progression or up to and including a maximum of 48 cycles
- Atezo 840 mg IV on Day 1 of every cycle (1 cycle = 2 wks)

Arm 3: mFOLFOX6/bev/atezo until progression
- Oxaliplatin 85 mg/m^2 IV + leucovorin 400 mg/m^2 IV + bev 5 mg/kg IV+ 5-FU 400 mg/m^2 IV bolus on Day 1, followed by 5-FU 2400 mg/m^2 IV over 46 hrs (Days 1 and 2), (1 cycle = 2 wks)
- Atezo 840 mg IV on Day 1 of every cycle
- Discontinue Oxaliplatin after Cycle 10
- Discontinue atezo after Cycle 48

NOTE:
- Upon progression, study therapy will be discontinued. Further treatment is at investigator's discretion; however, pts will continue to be followed for survival
- For Arm 3, in the event of unacceptable toxicity (including grade ≥3 neuropathy) without progression, individual components of mFOLFOX6/bev/atezo may be discontinued at investigator's discretion. All other components of mFOFOX6/bev/atezo may be continued at their current dose and schedule

***Summary of prior protocol changes:**
- Elimination of FOLFOX/bev arm (Arm 1); 1:1 randomization between Arm 2 and Arm 3; allowance for either dMMR or MSI-H via local lab determination; removal of mandatory tumor tissue requirement; reduction in the total number of pts to be enrolled; administrative updates to the protocol; allowance of biosimilars for bev.

ELIGIBILITY

- Metastatic CRC without prior chemotherapy for advanced disease
- Tumor determined to be dMMR or MSI-H by local institution:
  - *dMMR by* CLIA-certified IHC assay with a panel of all four IHC markers, including *MLH1, MSH2, PMS2,* and *MSH6*
  - *MSI-H by* CLIA-certified *PCR-based assessment of microsatellite alterations (either Bethesda markers or Pentaplex panel) or by NGS*
- ECOG Performance status of 0,1, or 2
- Measurable disease per RECIST 1.1
- Optional submission of archived tumor tissue, either from primary CRC site or metastatic lesions

STATISTICAL PLAN

- Analyses Populations
  - Intent to treat (ITT): The ITT population will include all randomly assigned pts.
  - Safety: The Safety population will include only pts who began their randomly assigned treatment.
- Analyses of Data on the Primary Endpoint
  - Analysis set is ITT. Experimental arm (ARM 3) will be compared to control arm (ARM 2) for primary endpoint of PFS by log-rank test.
- 121 PFS events are required to provide 80% power to detect a true hazard ratio (HA, alternative hypothesis) of 0.60 (equivalent to 64.4% PFS at 24 mos for experimental arm) with log-rank test at alpha 0.025 one-sided.
- Target accrual is 211 pts to Arms 2 and 3. Total target accrual, including the 20 pts previously randomized to Arm1, is 231.
- Estimated accrual time from Dec 2020 is 33 mos of additional accrual (assuming 5 pts/mo) with an additional 16 mos for additional follow-up. Estimates assume 1.0% dropout per mo on all arms.

CONCLUSIONS

- Active since November 2017
- Enrollment through CTSU is ongoing with a redesigned two-arm trial because Arm 1 lacked equipoise in the context of Keynote 177
- Amendment under review to modify eligibility criteria, allow one dose of chemotherapy prior to enrollment, and reduce sample size

SUPPORT: U10CA180868, -180822, -180888, -180819, UG1CA189867, U24CA196067, and Genentech, Inc.

Trial in progress: A phase II study (with safety run-in) of evorpacept (ALX148), cetuximab, and pembrolizumab in patients with refractory microsatellite stable metastatic colorectal cancer (AGICC-ALX148 21CRC01, NCT05167409)

Robert W. Lentz[1], Junxiao Hu[2], Patrick Blatchford[3], Todd M. Pitts[1], Alexis Leal[1], Sunnie Kim[1], S. Lindsey Davis[1], Christopher H. Lieu[1], Aaron J. Scott[4], Patrick Boland[5], Howard Hochster[5], & Wells A. Messersmith[1]

1. Division of Medical Oncology, Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado. 2. Department of Biostatistics and Informatics, Colorado School of Public Health, University of Colorado Denver, Aurora, Colorado. 3. Independent.
4. Division of Hematology and Oncology, Department of Medicine, College of Medicine, The University of Arizona Cancer Center, Tucson, Arizona. 5. Division of Medical Oncology, Department of Medicine, Robert Wood Johnson Medical School, Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey.

BACKGROUND AND PRECLINICAL DATA

- Metastatic colorectal cancer (mCRC) is the third most common cause of cancer and cancer-related deaths in the United States, with nearly 53,000 deaths predicted for 2022[1]
- Despite improvements in systemic therapy, average 5-year survival is only 12%[1]
- Approximately 95% of refractory mCRC patients have immunologically cold microsatellite stable (MSS) disease, and standard of care immunotherapy treatments are ineffective[2]

- Evorpacept (ALX148) is an engineered fusion protein containing two high affinity CD47 binding domains of SIRPα linked to an inactive Fc region of human immunoglobulin (**Figure 1**). Evorpacept blocks the CD47/signal regulatory protein alpha (SIRPα) innate immune inhibitory checkpoint, expressed on CRC and myeloid phagocytic cells, respectively
- The evorpacept inactive Fc does not bind to Fcγ receptors, minimizing CD47-targeted antibody-dependent cellular phagocytosis of red blood cells (which express CD47; **Figure 2**)[3]. Evorpacept is designed to be given in combination

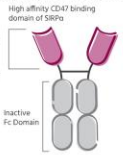


Figure 1: Evorpacept structure[5]

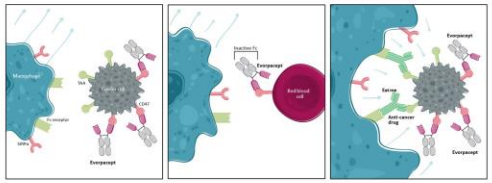


Figure 2: Evorpacept blocks the CD47/SIRPα axis, minimizes anemia, and is designed to be given with anti-cancer antibodies[5]

- In CT26 CRC syngeneic models, evorpacept ± anti-PD-1 monoclonal antibody decreases tumor growth, reduces myeloid immunosuppression, increases dendritic cell activation, and increases T cell activation (**Figure 3**)[3]
- In vitro, evorpacept enhances the antibody-dependent cellular phagocytosis (ADCP) activity of cetuximab[3]

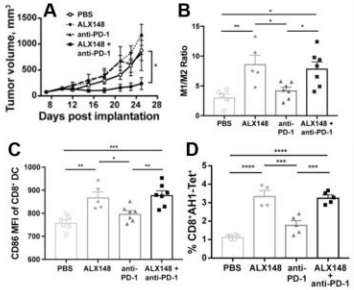


Figure 3: In syngeneic CRC models (CT26, BALB/c mice), evorpacept ± anti-PD-1, compared to control (PBS), decreases tumor growth (A), increases the ratio of M1 (CD45+CD11b+CD38+EGR2-) to M2 (CD45+CD11b+CD38-EGR2+) macrophages in the tumor (B), increases dendritic cell activation (CD86+) in the spleen (C), and increases antigen-specific (AH1+, the immunodominant antigen from CT26) CD8+ T cells in the spleen (D). *p< 0.05, **p<0.01, ***p<0.001 and ****p<0.0001 (A: day 25 two-tail student's t-test; B-D: One-Way ANOVA, Tukey-Kramer).[3]

- In the first-in-human clinical trial, evorpacept + pembrolizumab was well-tolerated (**Table 1**)[4]

Event	Grade 1-2 (%)	Grade 3-4 (%)
AST increase	17	0
ALT increase	12	2
Fatigue	12	0
Pruritus	10	0
Anemia	8	2
Leukopenia	6	2

Table 1: Most common evorpacept treatment-related adverse events in patients receiving evorpacept and pembrolizumab (N=52) in the first-in-human trial[4]

- Evorpacept, cetuximab, and pembrolizumab are hypothesized to generate synergistic innate and adaptive anti-tumor immune activation in MSS CRC:
  1. Evorpacept blocks the inhibitory "don't eat me" SIRPα/CD47 phagocytic checkpoint
  2. Cetuximab provides a pro-phagocytic "eat me" signal by binding to EGFR on CRC and engaging FcR on phagocytes to promote ADCP (necessary due to Fc inactivating mutation in evorpacept; cetuximab is NOT intended to inhibit signaling pathways downstream of EGFR)

STUDY DESIGN & METHODS

- This trial is a phase 2, single-arm, two-stage, multicenter, open-label, investigator-initiated trial evaluating the combination of evorpacept, cetuximab, and pembrolizumab in patients with refractory MSS mCRC:
  - Evorpacept 15 mg/kg weekly
  - Cetuximab 400 mg/m^2 followed by 250 mg/m^2 weekly
  - Pembrolizumab 200 mg every 3 weeks

Primary Objectives
- Recommended dose (RD) of evorpacept with cetuximab and pembrolizumab
- Objective response rate per RECIST v1.1 (by one-sided exact test with α=0.05, H_0 p ≤ 3% [historical controls], H_A p ≥ 15%; power is 87%).
  - The study will close for futility if there are no responses (partial or complete) in the first 24 evaluable patients (by MinMax design with α=0.025 [1-sided]; power is 87%).

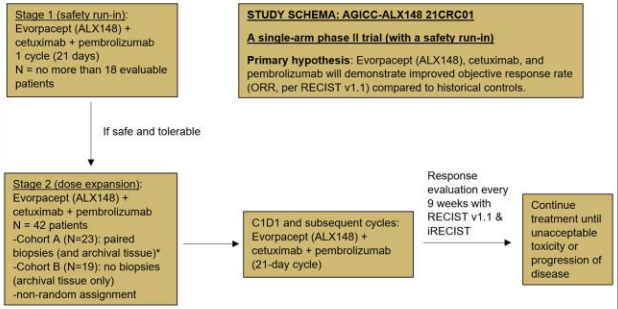
Secondary Objectives
- Disease control rate, duration of response, and progression-free survival per RECIST v1.1
- Overall survival
- First cycle dose-limiting toxicities in Stage 1
- Safety and tolerability

Exploratory Objectives
- Response per iRECIST
- Immune modulation in the peripheral blood (mass cytometry) and tumor (IHC and mRNA expression) pre- and post-treatment, and correlate with response
- Relationship between baseline PD-L1, EGFR, and CD47 tumor expression and efficacy (IHC)

ELIGIBILITY CRITERIA

- Adults with unresectable MSS/proficient mismatch repair CRC refractory to oxaliplatin, irinotecan, and a fluoropyrimidine, regardless of tumor sidedness and RAS/BRAF mutational status
  - Exception: left-sided RAS/BRAF wild-type mCRC who are EGFR inhibitor naïve
  - Measurement of EGFR expression by immunohistochemistry is not required
- ECOG performance status 0-1 and adequate hematologic/end organ function
- Absence of prior immunotherapy (checkpoint inhibitor or immune stimulatory agent)
- Absence of significant autoimmune disease

SCHEMA



*A subset of patients in Stage 2 (Cohort A) will undergo paired (pre- and on-treatment) biopsies. All patients in Stage 2 (Cohorts A & B) will receive identical treatments (evorpacept, cetuximab, and pembrolizumab)

CONCLUSIONS

- AGICC-ALX148 21CRC01 is a phase 2, single-arm, multicenter, open-label, investigator-initiated immunotherapy trial evaluating the combination of evorpacept, cetuximab, and pembrolizumab in patients with refractory microsatellite stable colorectal cancer
- The study is open to enrollment through the Academic Gastrointestinal Cancer Consortium (AGICC)

CONTACT INFORMATION

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- The authors acknowledge ALX Oncology Inc., Eli Lilly USA, and Merck & Co, Inc. for providing evorpacept, cetuximab, and pembrolizumab, respectively
- The authors acknowledge Criterium, Inc., dba Academic Gastrointestinal Cancer Consortium (AGICC) for clinical trial support services and all participating sites

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Abstract TPS267

STELLAR-303: a phase 3 study of XL092 in combination with atezolizumab versus regorafenib in patients with previously treated metastatic colorectal cancer

J. Randolph Hecht,[1] Josep Tabernero,[2] Aparna Parikh,[3] Yijia Wang,[4] Zhong Wang,[4] Martin Schwickart,[4] Dominic Curran,[4] Anwaar Saeed[5]

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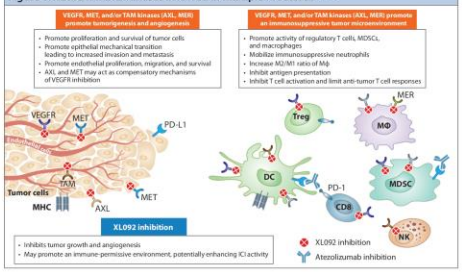
BACKGROUND

- The prognosis of patients with metastatic colorectal cancer (mCRC) is poor, with a 5-year survival rate of 14%[1]
- Patients who have progressed following front- and second-line chemotherapy have limited treatment options[2]
- Regorafenib and trifluridine-tipiracil are approved for patients in the third- or later-line setting, but the survival benefit is limited (median overall survival [OS] 6.4 and 7.1 months, respectively)[3,4]
- Immune checkpoint inhibitor (ICI) therapy (nivolumab ± ipilimumab and single-agent pembrolizumab) is approved in patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) mCRC[5,6]; however, the MSI-H phenotype is limited to ~5% of patients with mCRC,[7] highlighting an unmet need in the majority of patients
- In phase 1/2 trials, ICIs in combination with VEGFR2 tyrosine kinase inhibitors (TKIs) have demonstrated encouraging clinical activity in patients with mCRC that was not MSI-H or dMMR; cabozantinib in combination with either atezolizumab or durvalumab showed clinical activity with a greater benefit in *RAS* wild-type (wt) versus mutant (mut) disease[7,8]
- XL092 is a novel TKI that targets MET, VEGFR2, and the TAM kinases AXL and MER, which are involved in tumor growth, metastasis, angiogenesis, and immunosuppression of the tumor microenvironment (**Figure 1**)[9]
  - Given its immunomodulatory activity, XL092 may enhance ICI response[10]
  - The relatively short half-life (16–22 hours) of XL092 is favorable for once-daily (QD) dosing and dose modification to manage tolerability[11]
- In a phase 1 dose-escalation study, the recommended dose of XL092 was 100 mg when used in combination with atezolizumab based on a manageable toxicity profile, response outcomes, and pharmacodynamic data[11]
- STELLAR-303 (NCT05425940) is evaluating the efficacy and safety of XL092 in combination with the ICI atezolizumab versus regorafenib in patients with microsatellite stable (MSS) or microsatellite instability low (MSI-low) mCRC who have progressed after or are intolerant to standard of care (SOC) therapy

Figure 1. XL092 Inhibits Kinases Involved in Multiple Processes[9,12,13]



STUDY DESIGN

- STELLAR-303 is a global, open-label, randomized phase 3 study
- The planned sample size is ~600 patients, with 400 *RAS*wt and 200 *RAS*mut patients
- Patients must not have MSI-H or dMMR disease
- *RAS* mutation status and MSI/MMR status must be determined by tissue-based analysis prior to enrollment
- Eligible patients will be randomized 1:1 to receive XL092 in combination with atezolizumab or regorafenib alone, with randomization stratified by geographical region, presence of liver metastasis, and *RAS* status
- The primary endpoint is OS in all randomized patients with *RAS*wt
- OS and other efficacy endpoints (**Figure 2**) will be analyzed in the *RAS*wt population, the *RAS*mut population, and in all randomized patients
- Safety will be analyzed in safety populations (all patients who receive any amount of study treatment) corresponding to the efficacy analyses populations
- Additional endpoints include health-related quality of life (HRQoL), biomarkers, pharmacokinetics, immunogenicity, and healthcare utilization

Figure 2. Study Design of STELLAR-303

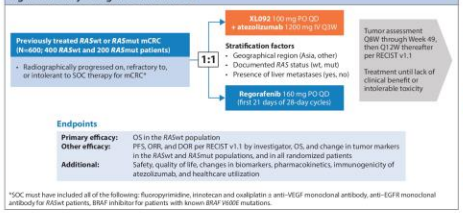


Table 1. Key Eligibility Criteria

Inclusion	Exclusion
• Histologically/cytologically confirmed adenocarcinoma of the colon or rectum • Measurable disease per RECIST v1.1 by investigator • ECOG performance status 0 or 1 • Radiographically progressed on, refractory to, or intolerant to SOC therapy for mCRC • Progressed during treatment with or within 3 months of most recent SOC therapy • Documented *RAS* status by tissue-based analysis • Archival or fresh tumor tissue • Age ≥18 years	• Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) mCRC by tissue-based analysis • Prior treatment with XL092, regorafenib, trifluridine-tipiracil, or PD-L1/PD-1 targeting ICIs • Receipt of a TKI ≤2 weeks before randomization • Receipt of any anticancer antibody therapy, systemic chemotherapy, or hormonal anticancer therapy ≤3 weeks (bevacizumab ≤4 weeks) before randomization • Radiation therapy ≤4 weeks (≤2 weeks for bone metastasis) before randomization • Uncontrolled, significant intercurrent or recent illness

ASSESSMENTS

Tumor Response

- Radiographic response and progression will be determined by the investigator using RECIST v1.1
- CT of chest/abdomen/pelvis or CT of chest and MRI of abdomen/pelvis is performed at screening, every 8 weeks (Q8W) during first 49 weeks, and then every 12 weeks (Q12W) thereafter
- MRI/CT of the brain is performed at screening in patients with known or suspected brain metastases. After randomization, patients with documented or suspected brain metastases will be assessed Q8W during first 49 weeks and then Q12W thereafter

Safety

- Safety evaluations will include assessments of adverse events defined by the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0, physical examination, vital signs, performance status, electrocardiograms, hematology, serum chemistries, coagulation tests, urine tests, and thyroid function tests

Biomarker and Tumor Marker Assessments

- Archival or fresh tumor tissue will be obtained for assessment of tumor tissues
- ctDNA plasma samples will be collected on Week 9, then Q8W through Week 49 and Q12W until radiographic assessments cease
- Biomarker analyses may include PD-L1 expression and mutational status
- Samples for the CRC tumor markers carbohydrate antigen 19-9 and carcinoembryonic antigen will be collected on Week 9, then Q8W through Week 49 and Q12W until radiographic assessments cease
- Tumor marker assessments will not be used to determine progressive disease

Pharmacokinetic and Immunogenicity Assessments

- Blood samples of patients receiving XL092 plus atezolizumab will be collected per protocol-defined schedule to assess pharmacokinetics and immunogenicity (antidrug antibodies against atezolizumab)

Quality of Life Assessments

- HRQoL assessments will be performed prior to the first dose of study treatment, on Weeks 4 and 7, and then on the same schedule as radiographic assessments until treatment discontinuation, using the EuroQoL Health questionnaire instrument EQ-5D-5L and the EORTC questionnaires QLQ-C30 and the CRC-specific QLQ-CR29

STATISTICAL DESIGN

- The study is designed to provide adequate power to assess OS in the *RAS*wt population
- All other analyses will be descriptive

STUDY SITES

- The study is being conducted at approximately 136 sites globally
- The study began enrolling patients in September 2022 and is ongoing

Commitment to Clinical Study Diversity

- Clinical study diversity will be achieved by the use of geomapping and other technology to ensure selection of representative sites
- Social media engagement will support enrollment of ethnic minority populations

Figure 3. STELLAR-303 Study Sites

SUMMARY

- The phase 3 STELLAR-303 study will evaluate the efficacy and safety of XL092 in combination with atezolizumab versus regorafenib in patients with MSS/MSI-low mCRC who have progressed after or are intolerant to SOC therapies
- Planned enrollment is ~600 patients: 400 *RAS*wt and 200 *RAS*mut
- The study is powered to assess the primary endpoint of OS in the *RAS*wt population
- Other endpoints include PFS, ORR, DOR, change in tumor markers, HRQoL, and safety
- The study is open for enrollment at sites in the United States, Belgium, France, Germany, Hungary, Poland, Portugal, Spain, United Kingdom, Australia, Hong Kong, New Zealand, Singapore, South Korea, Taiwan, and Thailand

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ABBREVIATIONS

dMMR, mismatch repair deficient; CT, computed tomography; DC, dendritic cell; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EORTC, European Organisation for Research and Treatment of Cancer; HRQoL, health-related quality of life; ICI, immune checkpoint inhibitor; IV, intravenously; Mϕ, macrophage; mCRC, metastatic colorectal cancer; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; MRI, magnetic resonance imaging; MSI-H, microsatellite instability-high; MSI-low, microsatellite instability-low; MSS, microsatellite stable; mut, mutant; NK, natural killer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; PO, orally; QD, once daily; Q3W, every 3 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SOC, standard of care; TKI, tyrosine kinase inhibitor; Treg, regulatory T cell; wt, wild type; VEGFR, vascular endothelial growth factor receptor

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SUMMARY

Targeted treatment options based on molecular subtypes of CRC

Molecular Subtypes	Targeted Therapies
MSI, whatever the *RAS*/*RAF* mutational status	Immune checkpoint inhibitor(s)
RAS/*RAF* wild-type	Anti-EGRF mAbs
BRAF^{V600E} mutated	Encorafenib + cetuximab +/− binimetinib
RAS mutated	No current targeted therapy, ongoing trials with new-generation KRAS inhibitors
HER2 amplified/mutated	Anti-HER2 mAbs/inhibitors (trastuzumab, pertuzumab, lapatinib), anti-HER2 antibody-drug conjugate (trastuzuab deruxtecan)
NTRK fusion-positive	TRK inhibitor (Larotrectinib, entrectinib)

Cohen et al. Cancers (Basel). 2020

SUMMARY

- Mutational workup is more important and evolving
- Consider Neoadjuvant Therapy in T4b
- Circulating tumor DNA is evolving
- Consider VEGF+Trifluridine/Tipiracil according to SUNLIGHT Study in third line – especially in patient with on prior VEGF
- FRESCO 2 study FRUQUINTINIB VGEF Inhibition