Immunotherapy and Targeted Therapy in Colorectal Cancer

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- NICHE-2 trial
- ESMO GI Abstract SO-34
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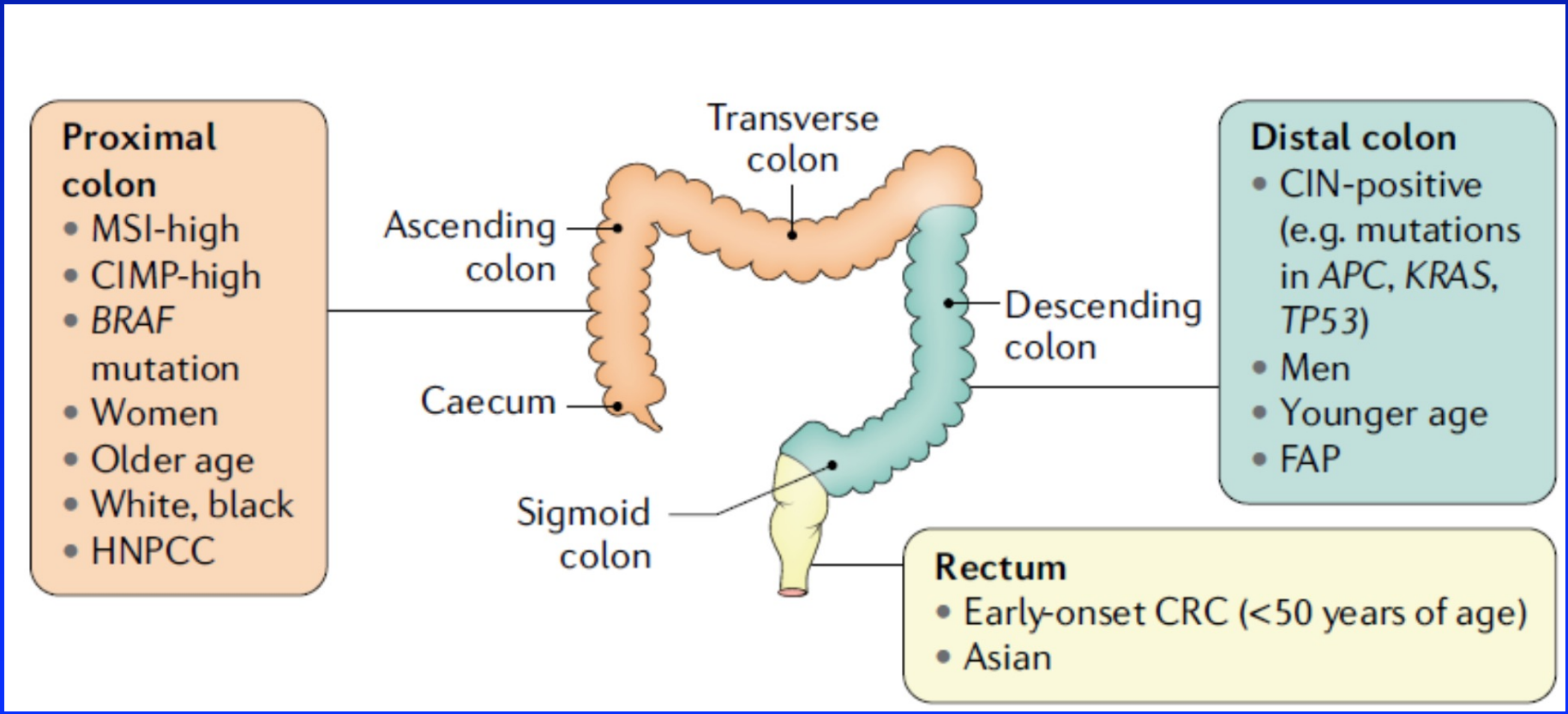
- CAIRO5
- MOUNTAINEER
- Krystal -1 trial

CRC



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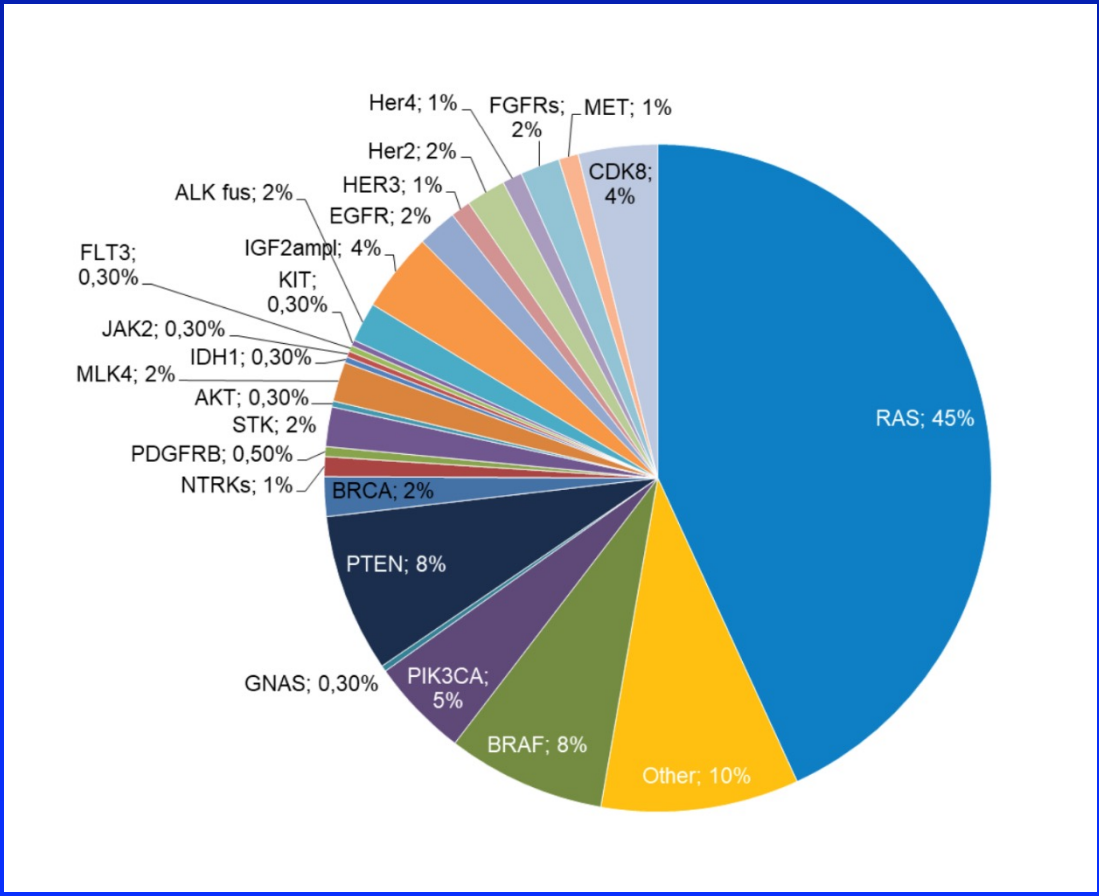
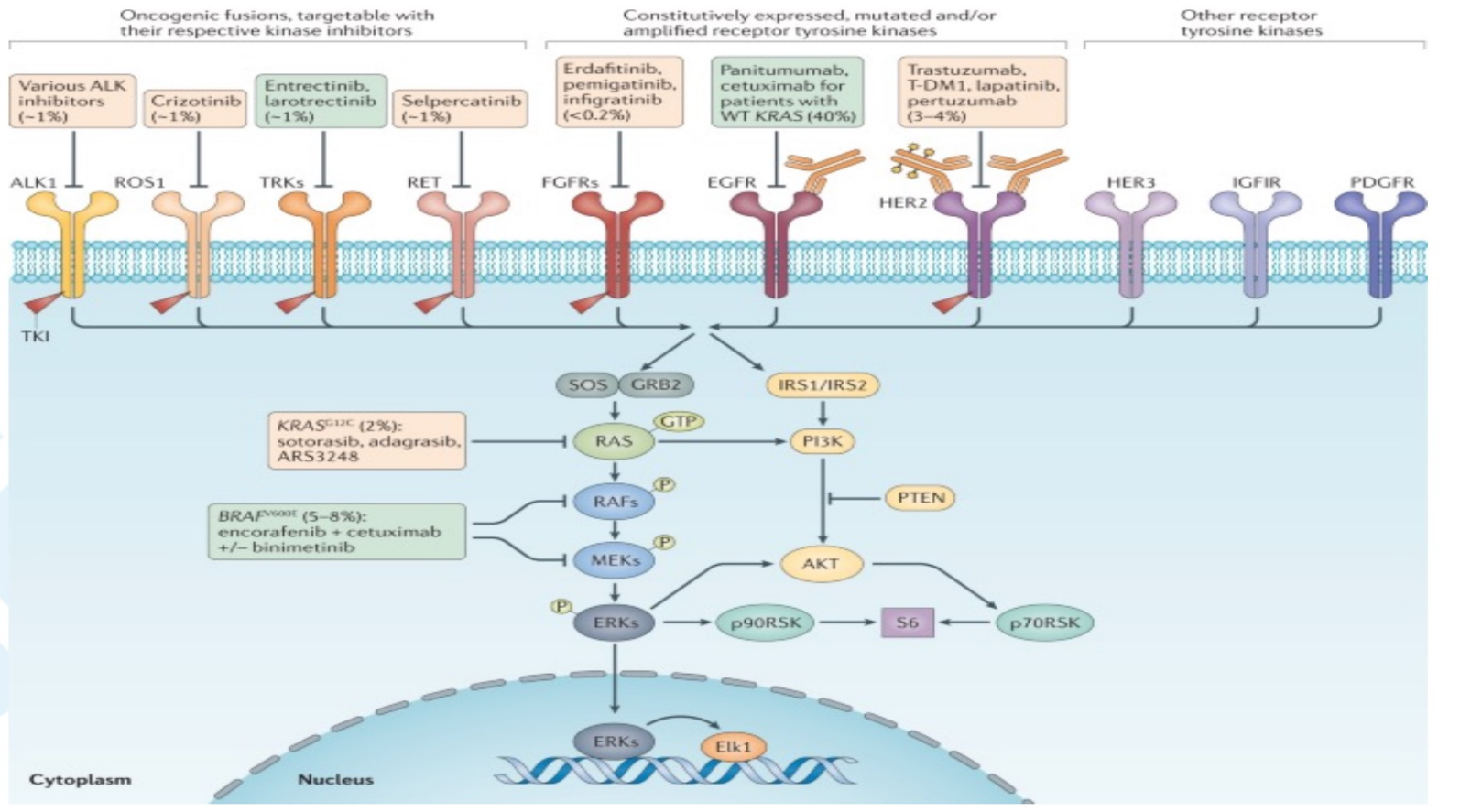
Molecular Subgroups



Precision Oncology



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A Comprehensive Comparison of Early-Onset and Average-Onset Colorectal Cancers

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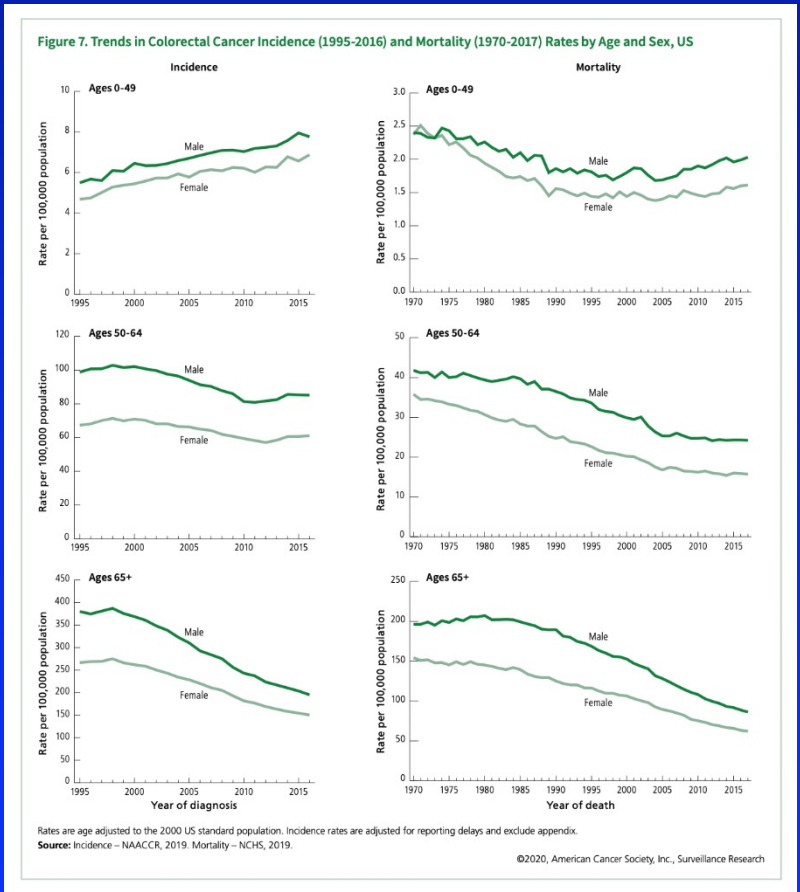
Incidence and Mortality



https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2020-2022.pdf

Is early-onset disease clinically or genomically distinct from average-onset colorectal cancer (AO-CRC)

- Since 1990's incidence of CRC in patients < 50 has steadily increased by 1-2% annually
- Greatest increase in patients age 20-29 years – 3.8%
- Estimated that by 2030 10.9% of a colon and 22.9% of all rectal cancer will be diagnosed in patients < 50 years
- Established risk factors of obesity, diet, high red meat, low fiber, physical inactivity, smoking, ETOH do not adequately explain the increase

Methods

- Single institutional review study MSKCC 2014-2019
- Clinical, histopathologic and genomic characteristics of
- MSK impact 341-468 gene NGS assay & Germline analysis via blood derived DNA 76-88 gen MSK-impact panel
- Divided into < 35 (n=151) and >36-49 (n=608) and > 50 (n=687)
- MSI, CRI hereditary syndromes and IBS excluded

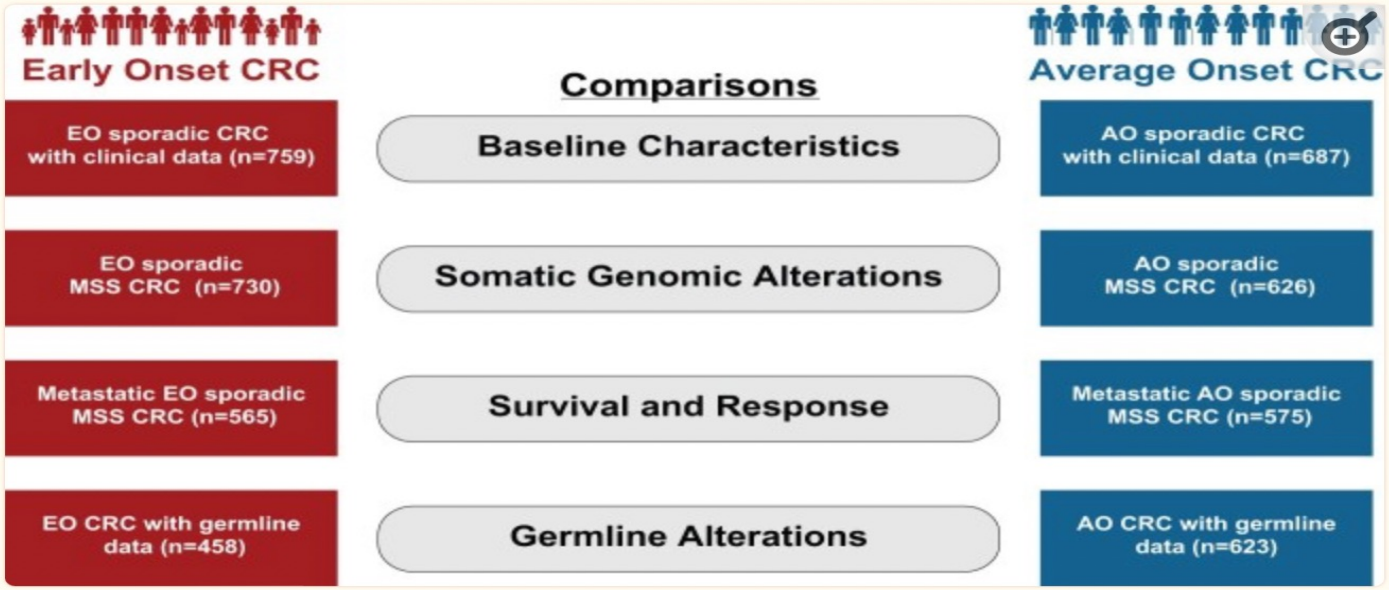


Figure 1.

Overview of comparison groups. The figure shows the comparisons made between patients with EO-CRC and AO-CRC. AO = average onset; CRC= colorectal cancer; EO = early-onset; MSS = microsatellite stable.

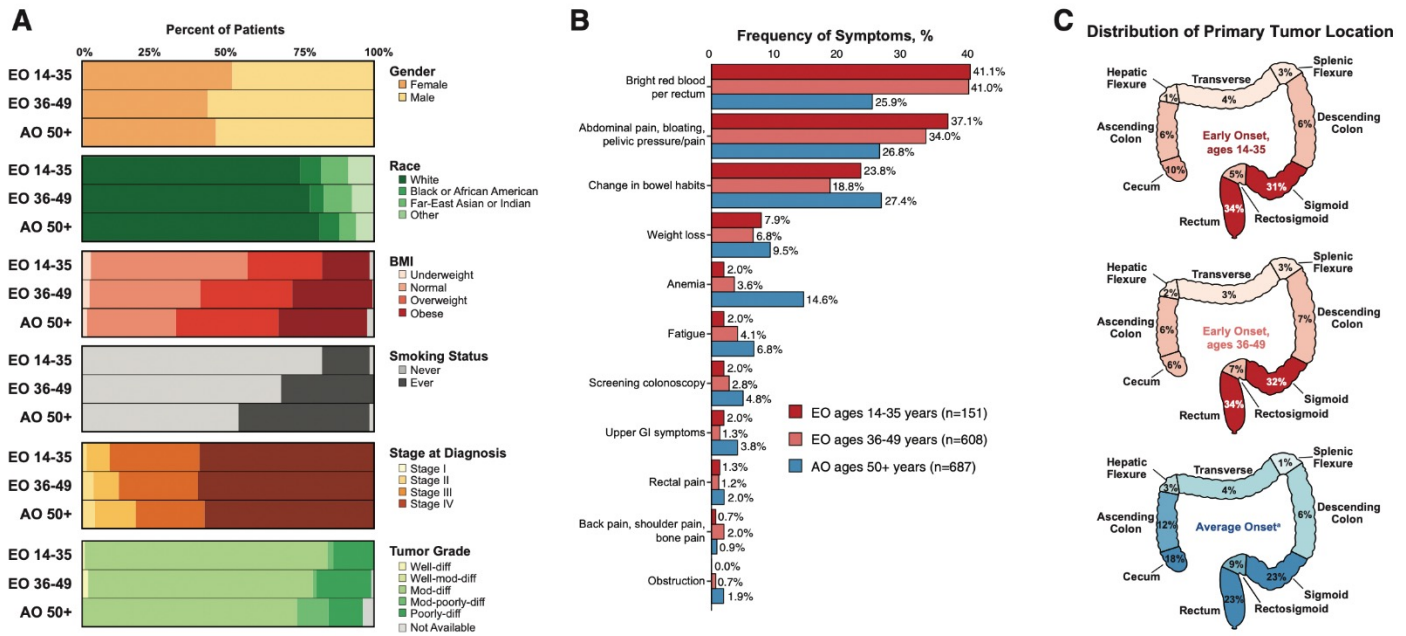
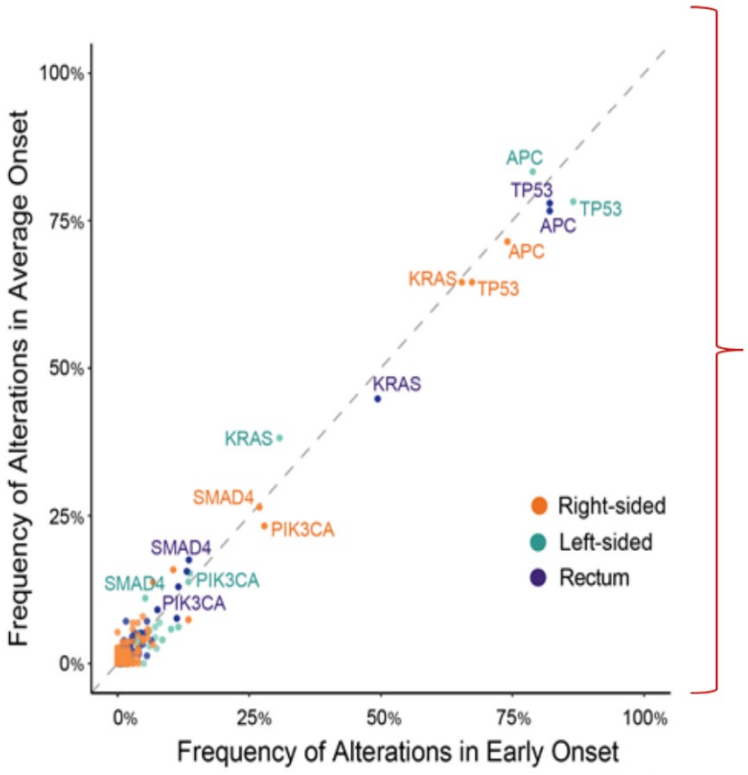


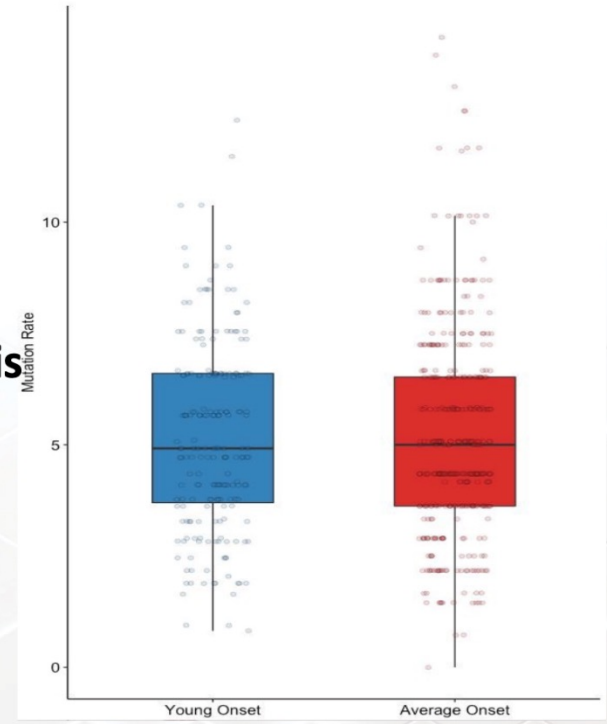
Figure 2. Clinical and tumor characteristics. Cancer-specific features of early-onset colorectal EO-CRC and AO-CRC by age at diagnosis: 35 years and younger, 36-49 (EO-CRC) and 50 years and older AO-CRC. **A)** Comparison of demographic, clinical, and tumor characteristics demonstrates that there is no significant difference in several characteristics, including sex and tumor grade distribution. Median body mass index was lower in the 35 years and younger cohort than in the AO-CRC cohort. **B)** Frequency of cancer-related presenting symptoms. **C)** Colorectal primary tumor location. AO = average onset; CRC = colorectal cancer; EO = early-onset; NOS = not otherwise specified.

Cerek et al., N Natl Cancer Inst. 2021 Dec, 113 (12): 1683-1692



No significant differences in molecular genomics when tumor location is accounted for

Mutation Burden



Cerek et al., N Natl Cancer Inst. 2021 Dec, 113 (12): 1683-1692

Conclusion

- Grade, genomic tumor nor clinical outcome data support the hypothesis that sporadic EO-CRC is distinct from AO
- 80% presented with left sided CRC and nearly 1/3 with RC
- EO patients presented with rectal bleeding and abdominal pain, less likely with anemia (routine evaluation in older adults)
- External factors are likely driving earlier CRC development

Neoadjuvant Localized Disease Trial

Neoadjuvant Immunotherapy in dMMR

- Neoadjuvant chemotherapy in dMMR population has approximately 7% pathologic response
- Initiated after NICHE-1 trial (NCT03026140) showed 100% pathologic responses and 60% pCRs to immune check point blockage
- NICHE 2 Primary endpoint 3-year disease free survival (DFS) and safety, secondary endpoints included MPR and pCR

NICHE-2

- Non-randomized, multicenter trial (n=112) intention-to-treat (ITT) 3 mg/kg of nivolumab plus 1 mg/kg of ipilimumab in cycle 1 and single agent nivolumab in 2 weeks later followed by surgery within 6 weeks
- No-metastatic, previously untreated dMMR cT3 and/or node positive disease based on radiologic staging, no perforation or obstruction
- 97 had Lynch status available - 65 had sporadic dMMR and 32 Lynch syndrome
- Median age 60 years (range 20-82 years), 74% radiologic stage of high risk III, right sided 68%, left 17% and 15% transverse

NICHE 2

- 95% of patients had a major PR, 67% demonstrated pCR and 93% DFS at 3 years – no recurrence to date
- Sporadic tumors had a 58% pCR rate and Lynch 78%
- One patient no pathologic response
- Of 14 patients with + LN after treatment, 3 received adjuvant chemotherapy, 6 refused and 5 not eligible for chemotherapy

T

NICHE 2 Safety

- No new safety signals
- 61% experienced any grade irAEs; 4% Grade III/IV
- Most common grade I/II AE were infusion reactions, dry mouth, thyroid abnormalities, fatigue and flue like symptoms
- 21% had any-grade-surgery related AE, 13% grade III or higher 5% including anastomotic leakage or wound infections

Conclusion

- NICHE-2 confirmed previously reported pathologic responses to short-term neoadjuvant nivolumab plus ipilimumab in a large cohort of dMMR CC pts
- The first survival data suggest a strong potential for neoadjuvant immunotherapy to become standard of care and allow further exploration of organ-sparing approaches

BRAF Mutation

- $BRAF^{V600E}$ mutation is found in 8–10% of metastatic colorectal cancer (mCRC) patients
- Recognized as a poor prognostic factor with a median overall survival inferior to 20 months

MSI-H

- Found in 10-15% of all sporadic colorectal Cancer
- Predicts a good outcome
- Survival rate is up to 15% higher compared with that of CRC patients with MSS

Analysis of the Impact of Mutated *BRAF*^{V600E} on TME and Genomic Alterations in MSI-H/dMMR CRC

- *BRAF*^{V600E} mutations with MSI-H tumors occur in ~2% of the total CRC population, but effects of *BRAF*^{V600E} on TME and genomic alterations in MSI-H/dMMR CRC, not well described
- Retrospective review of patients with MSI-H/dMMR CRC and either wild-type *BRAF* (n = 336) or *BRAF*^{V600E} (n = 123) who underwent NGS
  - MSI-H assessed using 239 loci; dMMR assessed by IHC
  - Other assessments: TMB, neoantigen tumor burden, PD-L1 expression, immune infiltration, and canonical immuno-metabolomic pathways
  - Comparison between wild-type *BRAF* and *BRAF*^{V600E}
    - Prevalence of other oncogenes
    - Immunometabolomic pathway enrichment scores

- **Primary endpoint:** effect of *BRAF*^{V600E} on immunologic characteristics of TME in MSI-H/dMMR CRC
- **Secondary endpoints:** describe *BRAF*^{V600E}-associated genomic alterations, relationship between *BRAF*^{V600E} and IO biomarkers, effect of mutated *KRAS* on TME in MSI-H/dMMR CRC

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Analysis of Mutated *BRAF*^{V600E} Impact on TME in MSI-H/dMMR CRC: Clinical Characteristics

Characteristic	Overall (N = 459)	*BRAF*^{WT} (n = 336)	*BRAF*^{V600E} (n = 123)
Female, n (%)	269 (59)	185 (55)	84 (69)
▪ Unknown, n	1	0	0
Median age, yr (IQR)	69 (57-78)	62 (51-73)	76 (70-85)
▪ Unknown, n	126	108	18
Race, n (%)			
▪ White	227 (49.4)	170 (50.8)	57 (46.4)
▪ Black	20 (4.3)	16 (4.7)	4 (3.2)
▪ Asian	3 (0.6)	3 (0.9)	0
▪ Other	24 (5.2)	19 (5.6)	5 (4)
▪ Unknown	185 (40.5)	128 (38)	57 (46.4)
Disease stage, n (%)			
▪ Stage I	19 (4.2)	17 (5)	2 (1.5)
▪ Stage II	81 (17.7)	60 (17.8)	21 (17)
▪ Stage III	90 (19.6)	63 (18.8)	27 (22)
▪ Stage IV	190 (41.3)	141 (42)	49 (40)
▪ Unknown	79 (17.2)	55 (16.4)	24 (19.5)

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Analysis of Mutated *BRAF*^{V600E} on TME in MSI-H/dMMR CRC: Oncogenic Comutations

Genomic Comutation, %	*BRAF*^{V600E}	*BRAF*^{WT}
*MSH6**	42	20
*B2M**	33	16
*ATM**	23	12
*TP53**	30	19
*MSH2**	11	3.3

**q* <.05 by *BRAF* mutation status.

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Analysis of Mutated *BRAF*^{V600E} on TME in MSI-H/dMMR CRC: Laboratory Results

- Impact on CRC tumor immune microenvironment
  - Proportion of NK cells significantly higher with *BRAF*^{V600E} vs *BRAF*^{WT}: median of 21% vs 15% (*P* <.001)
  - No significant differences in proportion of CD4+ and CD8+ T-cells (*P* = .50)
  - Significant upregulation of IMMUNE_TH1_GALON in *BRAF*^{V600E} tumors

- Significant *downregulation* of cancer stem cell pathways in *BRAF*^{V600E} tumors
  - NOTCH_REACTOME enrichment score for *BRAF*^{V600E} vs *BRAF*^{WT}: *P* = .001
  - TRANSLATION_RIBOS_REACTOME enrichment score for *BRAF*^{V600E} vs *BRAF*^{WT}: *P* = .003
  - WNT_BIOCARTA enrichment score for *BRAF*^{V600E} vs *BRAF*^{WT}: *P* = .001

- Significant *upregulation* of 4 pathways among *BRAF*^{V600E} tumors
  - Cyclin-dependent cell signaling (*P* <.001)
  - Glycerophospholipid metabolism (*P* <.001)
  - Galactose metabolism (*P* = .024)
  - Nucleotide metabolism (*P* = .043)

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Analysis of Mutated *BRAF*^{V600E} on TME in MSI-H/dMMR CRC: Conclusions

- Mutation tumor burden, CD4 and CD8 were same, inflammatory status was similar
- BRAF mutant tumors had low stemness and differentiation, but higher growth and metabolic reprogramming, suggestive of more aggressive biology
- Similarity in some immunologic characteristics within the TME of the *BRAF*^{WT} and *BRAF*^{V600E} MSI-H/ dMMR CRC indicates both subtypes likely derive similar benefit from IO therapy

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Metastatic Disease

CAIRO5: Background

- No current consensus on criteria for resectability of CRC liver metastases or the optimal systemic induction regimen in patients with potentially resectable liver metastases

- Retrospective or prospective studies with limitations in study design/analysis
  - No or varying criteria for resectability
  - Long-term outcomes analyses after liver resections lacking
  - Heterogeneous population, study designs, or use of *RAS/BRAF* mutation status

- Phase III CAIRO5 trial was designed to prospectively compare current active systemic induction regimens in patients with initially unresectable colorectal liver metastases based on predefined criteria by a central liver expert panel

1. Bolhuis. Eur J Cancer. 2020;141:225. 2. Punt. ASCO 2022. Abstr LBA3506.

CAIRO5: Protocols for Expert Panel

- Liver expert panel
  - 15 liver surgeons and 3 abdominal radiologists
  - CT scans (and MRI if available) evaluated at baseline and follow-up
  - If no consensus reached with CT scan evaluation among 3 liver surgeons, 2 additional liver radiologists evaluated the scan
    - Decision made by majority vote

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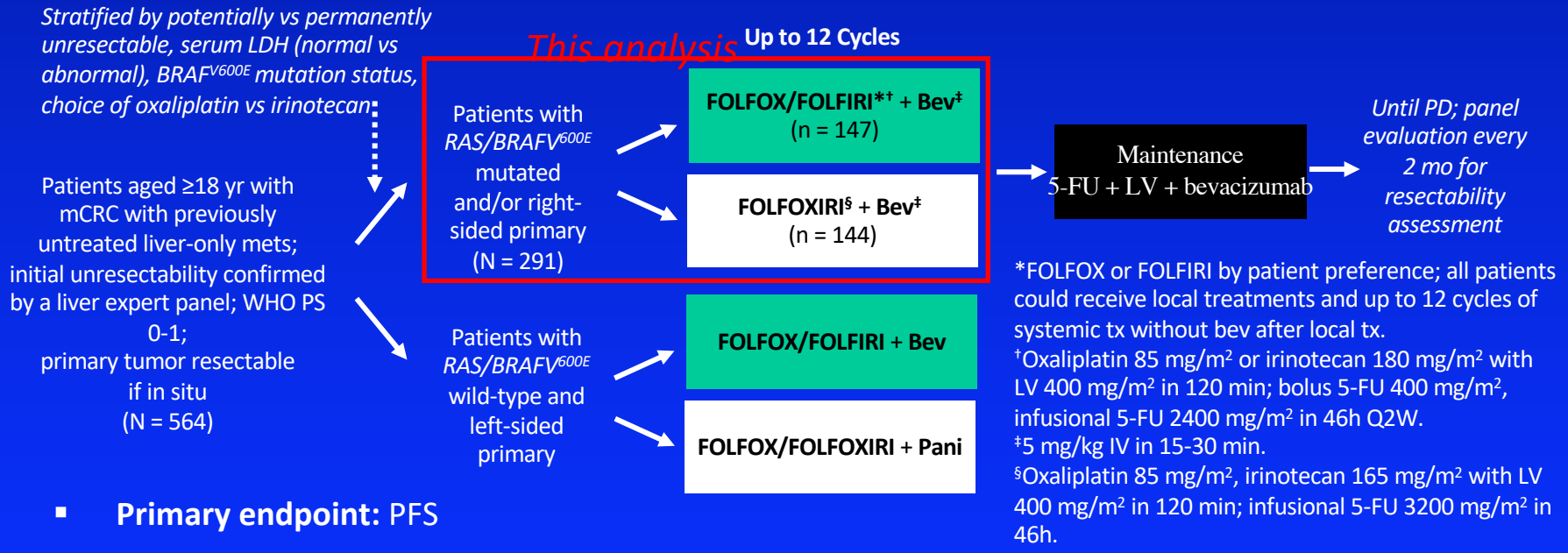
CAIRO5: Study Design

- Prospective, randomized phase III trial



*FOLFOX or FOLFIRI by patient preference; all patients could receive local treatments and up to 12 cycles of systemic tx without bev after local tx.
†Oxaliplatin 85 mg/m^2 or irinotecan 180 mg/m^2 with LV 400 mg/m^2 in 120 min; bolus 5-FU 400 mg/m^2, infusional 5-FU 2400 mg/m^2 in 46h Q2W.
‡5 mg/kg IV in 15-30 min.
§Oxaliplatin 85 mg/m^2, irinotecan 165 mg/m^2 with LV 400 mg/m^2 in 120 min; infusional 5-FU 3200 mg/m^2 in 46h.

- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, ORR, toxicity, rates of R0/1 resection, postoperative morbidity

NCT02162563. Punt. ASCO 2022. Abstr LBA3506

CAIRO5: Baseline Characteristics

Characteristic	FOLFOX/FOLFIRI + Bevacizumab (n = 147)	FOLFOXIRI + Bevacizumab (n = 144)
Median age, yr (range)	61 (39-79)	65 (35-81)
Male, %	64	60
WHO PS 0, %	64	69
Right-sided primary, %	41	42
RAS mutation, %	86	86
$BRAF^{V600E}$ mutation, %	7	8
Synchronous metastases, %	86	90
Prior adjuvant chemotherapy, %	5	5
Median no. CRC liver metastases, n (range)	12 (7-24)	12 (7-22)
Normal serum LDH, %	52	52
Preference for oxaliplatin, %	93	94
Potentially resectable CRLM (panel), %	88	86

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CAIRO5: Efficacy Summary

Parameter	FOLFOX/FOLFIRI + Bevacizumab (n = 147)	FOLFOXIRI + Bevacizumab (n = 144)	HR (95% CI)	*P* Value
Median PFS, mo	9.0	10.6	0.77 (0.60-0.99)	.038
Median no. of cycles,* n (range)	8 (1-16)	8 (1-15)	--	
ORR, %	33.3	53.5	--	<.001

*Excluding maintenance cycles and any adjuvant chemotherapy.

- At a median follow-up of 41 mo, OS data not yet mature
- PFS subgroup analyses showed no significant interaction between baseline unresectability or mutation status (*RAS*, $BRAF^{V600E}$, WT, and right-sided) and PFS

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CAIRO5: Local Treatment

Parameter	FOLFOX/FOLFIRI + Bevacizumab (n = 147)	FOLFOXIRI + Bevacizumab (n = 144)	*P* Value
Resection with or without ablation, %	46	57	.08
Postoperative complications, %			
Any	40	51	.19
Grade ≥3 Clavien-Dindo	15	27	.08
Death	0	2*	
Median no. of induction cycles, n (range)	7 (4-12)	6 (2-12)	--
Adjuvant chemotherapy, %	38	45	--
Median no. of adjuvant cycles, n (range)	6 (1-8)	4 (1-8)	--
Rate of R0/1 resection ± ablation, %			
▪ Any	37	51	.02
▪ 2-stage surgery ± PVE	16	32	.04

*Total of 3 patients.

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CAIRO5: Conclusions

- First prospective trial evaluating systemic induction regimens in patients with unresectable mCRC with liver-only metastases as determined by an expert panel
- In patients with initially unresectable colorectal liver metastases and right-sided and/or *RAS/BRAF*^{V600E}-mutated primary tumors, triplet chemo + bevacizumab was associated with efficacy improvements vs doublet chemo + bevacizumab
  - Including PFS, ORR, and frequency of R0/1 resection with or without ablation
- Triplet chemotherapy + bevacizumab was associated with increased but manageable toxicity
- This study demonstrated feasibility of using a liver expert panel, which increased the number of patients eligible for local, potentially curative treatment

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Novel Immunotherapy: Phase I C-800

- Patients with treatment resistant MSS CRC lack effective therapy options
- Multicenter –first in human Phase I C-800 trial
- 41 patients heavily pretreated patients
- Median follow-up of 5.8 months

Novel Immunotherapy Combination in MSS CRC

- Botensilimab is a novel fragment crystallizable-engineered anti-CTLA-4 and balastilimab an anti-PD-1 antibody
- Botensilimab has an enhanced Fc region that increases binding to Fc gamma receptor on antigen presenting and NK cells – tightening the ”immune synapse” (unique properties compared to first generation)
- Botensilimab at 1 mg/kg or 2 mg/kg every 6 weeks (n=34) in combination with balstilimab 3 mg/kg (n=34) every 2 weeks
- Patient needed at least one restaging scan at 6 weeks

Botensilimab + Balstilimab in Previously Treated MSS mCRC: Response

Response	N = 41
ORR, % (95% CI)	24 (14-39)
BOR, n (%)	
▪ CR	0 (0)
▪ PR	10 (24)
▪ SD	20 (49)
▪ PD	11 (27)
DCR (PR + SD), % (95% CI)	73 (58-84)
Median follow-up, mo (range)	5.8 (1.6-24.4)

- 8 of 10 objective responses ongoing
- 3 responses >1 yr
- Median DoR: not reached
- Exploratory analysis in patients without active liver metastases (n = 24)
  - ORR: 42% (95% CI: 25-61)
  - DCR: 96% (95% CI: 80-99)

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Botensilimab + Balstilimab in Previously Treated MSS mCRC: Safety

TRAE, n (%)	Any Grade	Grade 1/2	Grade 3
Any	31 (76)	21 (51)	10 (24)
Gastrointestinal			
▪ Diarrhea/colitis	16 (39)	12 (29)	4 (10)
▪ Nausea	7 (17)	7 (17)	0
▪ Vomiting	4 (10)	4 (10)	0
Constitutional			
▪ Fatigue	9 (22)	8 (20)	1 (2)
▪ Decreased appetite	9 (22)	9 (22)	0
▪ Chills	7 (17)	7 (17)	0
▪ Pyrexia	4 (10)	5 (12)	1 (2)
Hepatic			
▪ ALT increased	5 (12)	5 (12)	0
▪ AST increased	4 (10)	3 (7)	1 (2)
Musculoskeletal			
▪ Arthralgia	5 (12)	4 (10)	1 (2)
▪ Myalgia	5 (12)	5 (12)	0
Skin			
▪ Pruritus	4 (10)	4 (10)	0
▪ Rash	4 (10)	4 (10)	0

- No hypophysitis and rare pneumonitis
- No grade 4/5 TRAEs
- Investigator-assessed irAEs
  - Any grade: 46%
  - Grade 3: 17%
- Discontinuation due to TRAE
  - Botensilimab only: 10%
  - Botensilimab and Balstilimab: 10%

Bullock. ESMO World GI 2022. Abstr LBA_09.

Botensilimab + Balstilimab in Previously Treated MSS mCRC: Conclusion

- In heavily pretreated MSS mCRC, the novel FC-enhanced CTLA-4 antibody botensilimab in combination with the PD-1 antibody balstilimab produced an ORR of 24% with evidence of some durable responses
  - The ORR was 42% in patients without active liver metastases
- The combination was well tolerated with most AEs of grade 1/2 and no cases of hypophysitis

- Conclusion: botensilimab and balstilimab combination warrants further investigation

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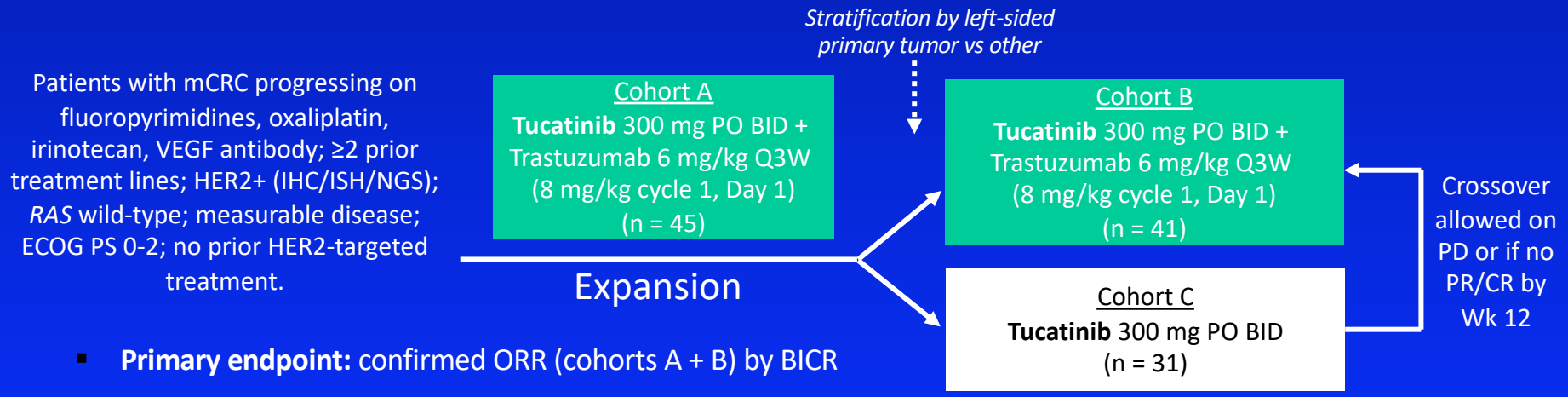
MOUNTAINEER TRIAL

- U.S. and European multicenter open-label randomized phase II trial enrolled 86 patients into the combination cohorts
- Patients had received a median of three prior lines of therapy. Approximately 85% of patients had tumors in the left side of the colon or rectum
- 64.3% of the patients had liver metastases and 70.2% had lung metastases

MOUNTAINEER: Tucatinib + Trastuzumab in Previously Treated HER2+ Metastatic Colorectal Cancer

- Randomized, multicenter, open-label phase II study; expanded globally from single cohort



- **Primary endpoint:** confirmed ORR (cohorts A + B) by BICR
- **Secondary endpoints:**
  - Cohorts A + B: DoR (BICR), PFS (BICR), OS
  - Cohort C: ORR by Wk 12 (BICR)
- Safety: cohorts A + B with any amount of treatment

Strickler. ESMO WCGIC 2022. Abstr LBA-2.

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MOUNTAINEER: Baseline Characteristics

Characteristic	Tucatinib + Trastuzumab Cohorts A + B (n = 84)	Tucatinib Cohort C (n = 30)
Median age, yr (range)	55.0 (24-77)	59.5 (29-75)
Male/female, n (%)	51 (60.7) / 33 (39.3)	15 (50) / 15 (50)
ECOG PS 0/1/2, %	59.5/36.9/3.6	56.7/43.3/0
Primary tumor site, n (%)		
▪ Left colon and rectum	71 (84.5)	27 (90.0)
▪ All other primaries	13 (15.5)	3 (10.0)
– Transverse colon	7 (8.3)	0
– Right colon	5 (6.0)	3 (10.0)
– Multiple/overlapping sites	1 (1.2)	0
Stage IV at initial diagnosis, n (%)	50 (59.5)	19 (63.3)
Metastases at study entry, n (%)		
▪ Liver	54 (64.3)	15 (50.0)
▪ Lung	59 (70.2)	20 (66.7)

Strickler. ESMO WCGIC 2022. Abstr LBA-2

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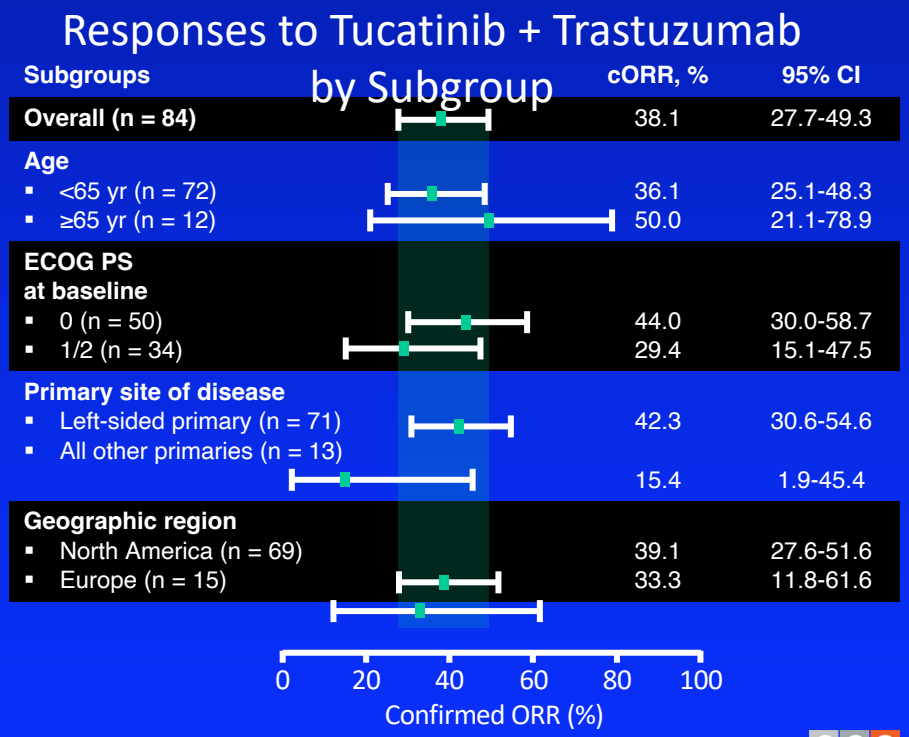
MOUNTAINEER: Response

Response	Tucatinib + Trastuzumab Cohorts A + B (N = 84)
Best response per BICR, n (%)	
▪ CR	3 (3.6)
▪ PR	29 (34.5)
▪ SD	28 (33.3)
▪ PD	22 (26.2)
▪ NA	2 (2.4)
Confirmed ORR, % (95% CI)	
▪ BICR	38.1 (27.7-49.3)
▪ Investigator review	42.9 (32.1-54.1)
Median time to ORR per BICR, mo (range)	2.1 (1.2-9.8)
DCR per BICR, n (%)	60 (71.4)
Median DoR per BICR, mo (95% CI)	12.4 (8.5-20.5)



Strickler. ESMO WCGIC 2022. Abstr LBA-2. Reproduced with permission.

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MOUNTAINEER: Conclusions

- In patients with previously treated HER2-positive mCRC tucatinib & trastuzumab produced a confirmed ORR of 38%
- After median follow-up of 20.7 mo, the median PFS and OS were 8.2 mo and 24.1 mo, respectively
- Well tolerated with diarrhea, fatigue, and nausea as the most frequent TRAEs. No deaths related to AEs
- Tucatinib and trastuzumab has the potential to become a standard of care in patients with HER2-positive mCRC

Strickler. ESMO WCGIC 2022. Abstr LBA-2

KRYSTAL Trial

- KRAS G12C mutation occur in 3-4% of patients with CRC serves as negative predictor of efficacy with cetuximab
- Mutation is linked to poor prognosis vs other KRAS mutations
- Krystal-1 evaluated the efficacy of the KRAS G12C inhibitor MRTX849 both as a single agent and in combination with cetuximab in patients who received prior systemic therapy

KRYSTAL 1 Trial

- KRYSTAL-1 trial, 78 patients with previously treated colorectal cancer received MRTX849 at 600 mg twice daily as a monotherapy (n = 46) or in combination with cetuximab (n = 32).
- More than half the patients had received three or more prior lines of therapy; mutations in *TP53* were found in 69%, and other mutations were identified in 15% to 20% of patients.
- Median follow-up was 8.9 months for the monotherapy cohort and 7.0 months for the combination group.

Krystal Trial

- 1b portion – patient received 600 mg of oral MRTX849 BID and cetuximab 400 mg/m2 followed by 250 mg every week or 500 mg/m2 every 2 weeks – primary endpoint safety, secondary endpoint ORR per Recist 1.1, DOR, PFS and OS
- Phase 2 – patient was administered 600 mg of oral MRTX849 BID twice daily with primary endpoint ORR, secondary end point DOR, PFS, OS and safety
- Baseline characteristics in both groups similar, median age 59 (range 29-74), median prior lines of therapy 3 (1-9)

KRYSTAL TRIAL Results

- Phase 1 b - at a median follow up of 17.5 months n=28 patients experienced an objective response of ORR 46 % and disease control 100%
- Median duration of response (DOR) wit the combination was 7.6 months, and the median time to response TTR 1.4 months
- Phase 2 – median follow up of 20.1 months (n=49) ORR of 19% and disease control rate of 89%. 6 patients experienced disease progression

Data derived from Klempner SJ, et al. Abstract LBA24. Presented at: European Society for Medical Oncology Congress; Sept. 9-13, 2022; Paris.

Krystal Trial Safety

- 16% of patients discontinued cetuximab, all patients in combination arm experienced at least 1 any degree treatment related adverse effect (TRAE)
- 9% had grade III and 2 patients had grade IV (infusion related)
- 93% in the monotherapy arm reported any degree AE- 30% grade III
- Most common any grade AE included nausea (63%), diarrhea (56%), vomiting (53%), dermatitis (47%), fatigue (47%)
- Grade III diarrhea (3%), acneiform rash (3%) and stomatitis (3%)

Conclusion

- Combination treatment resulted in numerically higher response rates and longer PFS compared to monotherapy cohort
- Small patient cohort
- Limitations include study design - Phase 1 and 2

SUMMARY

- No biological identifiable difference early versus average age CRC
- Neoadjuvant combination IO therapy might become standard of care in MSI-H patients
- Liver only disease metastatic patients might benefit from triple agent chemotherapy compared to doublet
- BRAF and MSI-H mutation are biologically similar and may benefit from immunotherapy treatment

SUMMARY

- A novel IO combination treatment shows efficacy in heavily pretreated MSS cancer
- Tucatinib in combination with trastuzumab shows efficacy in HER pretreated CRC
- Cetuximab and KRASG12c blockage shows promising results