Updates in Gastrointestinal Malignancies

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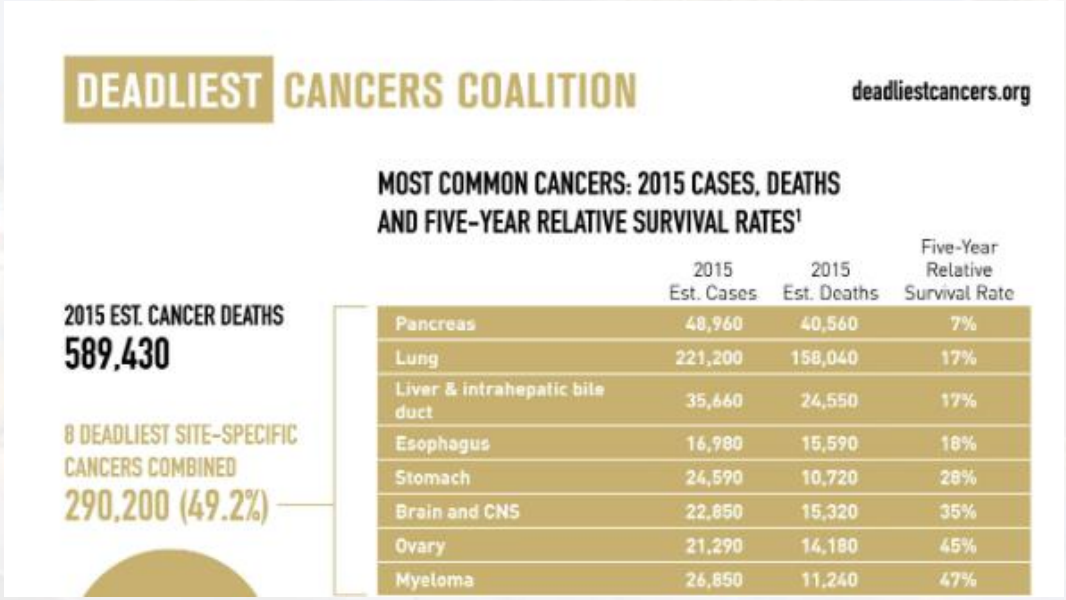
Gastrointestinal Malignancies

2023 estimates:

- ~ 340 k new Cases. ~ 166 k deaths in 2023 in USA.[1]
- ~ 12,260 cancer deaths out of 44,140 cancer deaths in Texas. (29%)[1]

Cancer Facts And Statistics. 2023

4 out of the top 5 cancers in the list of the deadliest Cancer coalition are GI malignancies



	2015 Est. Cases	2015 Est. Deaths	Five-Year Relative Survival Rate
Pancreas	48,960	40,560	7%
Lung	221,200	158,040	17%
Liver & intrahepatic bile duct	35,660	24,550	17%
Esophagus	16,980	15,590	18%
Stomach	24,590	10,720	28%
Brain and CNS	22,850	15,320	35%
Ovary	21,290	14,180	45%
Myeloma	26,850	11,240	47%

Presented By: Laith Abushahin MBBS
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TEXAS ONCOLOGY

Overview

Common Theme:

- No one-size- fit-all
  - Biology- tailored
  - Integration of multi disciplinary interventions

Disease	Recent Update or anticipated developments
Gastric Adenocarcinoma	Locoregional management in MSI-H disease Integration of other biomarkers: CLDN18.2, FGFR2b
Biliary Cancers	KEYNOTE966
HCC	RTOG1112. LAUNCH trial Integration of LDT and systemic therapy
Pancreatic Cancer	NAPOLI3
Colon Cancer	Biomarkers directed therapy FRESCO 2 trial

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Gastric Adenocarcinoma

Management of Locoregional disease

- Anticipated trials with ICI combination
- MSI-H disease

Management Metastatic Disease

Anticipated Advances

- Zolbetuximab
- Bemartuximab

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Gastric Adenocarcinoma

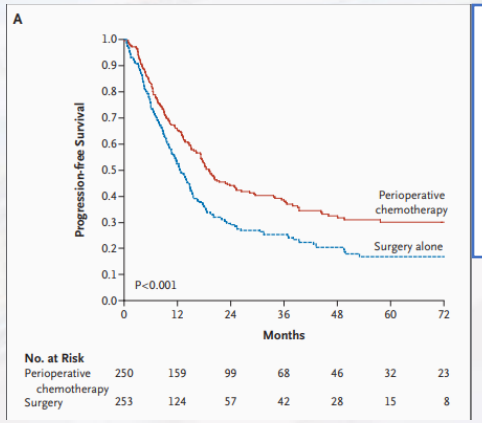
Locoregional Gastric Cancer(Western)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 6, 2006 VOL. 355 NO. 1

Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

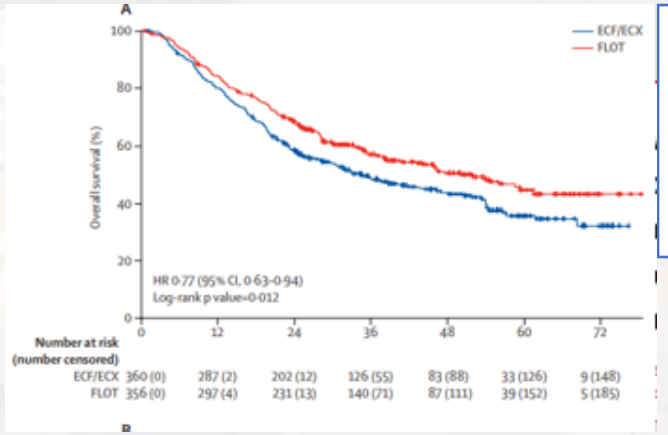
David Cunningham, M.D., William H. Allum, M.D., Sally P. Stenning, M.Sc., Jeremy N. Thompson, M.Chir., Cornelis J.H. Van de Velde, M.D., Ph.D., Marianne Nicolson, M.D., J. Howard Scarffe, M.D., Fiona J. Lofts, Ph.D., Stephen J. Falk, M.D., Timothy J. Iveson, M.D., David B. Smith, M.D., Ruth E. Langley, M.D., Ph.D., Monica Verma, M.Sc., Simon Weeden, M.Sc., and Yu Jo Chua, M.B., B.S., for the MAGIC Trial Participants*



- Median OS 35 m
- 5 Y survival 35%
- DFS 18 m
- pCR: ~ 6%

Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial

Salah-Eddin Al-Batran, Nils Homann, Claudia Pauligk, Thorsten O Goetze, Johannes Meiler, Stefan Kasper, Hans-Georg Kopp, Frank Mayer, Georg Martin Haag, Kim Luley , Udo Lindig, Wolff Schmiegel, Michael Pohl, Jan Stoehlmacher, Gunnar Folprecht, Stephan Probst, Nicole Prasnikar, Wolfgang Fischbach, Rolf Mahlberg, Jörg Trojan, Michael Koenigsmann, Uwe M Martens, Peter Thuss-Patience, Matthias Egger, Andreas Block,



- Median OS: 50 m
- 5 Y survival 45%
- DFS: 30 m
- pCR: 17%

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Gastric Adenocarcinoma

Adding Ramicurumab?

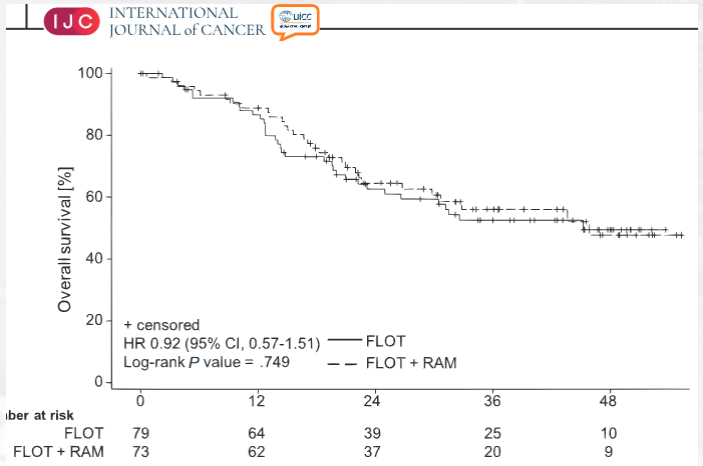
Received: 2 November 2022 | Revised: 31 January 2023 | Accepted: 14 February 2023
DOI: 10.1002/ijc.34495

CANCER THERAPY AND PREVENTION

IJC INTERNATIONAL JOURNAL of CANCER

Perioperative FLOT plus ramucirumab for resectable esophagogastric adenocarcinoma: A randomized phase II/III trial of the German AIO and Italian GOIM

Thorsten O. Goetze[1,2] | Ralf-Dieter Hofheinz[3] | Timo Gaiser[4] |



Phase 2 segment enrolled 152 patients.
Did not meet path response needed to move to phase 3.

OS : 46m

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TEXAS ONCOLOGY

Gastric Adenocarcinoma

Adding ICI?

Genesis:

- Checkmate 577 showed ICI role after trimodality therapy.

Trial	Phase/ #	Agent	How is going?
DANTE (Al-Batran ASCO 2022)	IIb/295	Atezo	
VESTIGE (Smyth ASCO 2023)	II/191	IPI/Nivo adj	
Keynote 585	III//1007	Pembro	
MATTERHORN	III/ 958	Durvalumab	

Adding ICI to all comers is NOT standard of care

Presented By: Laith Abushahin MBBS
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Gastric Adenocarcinoma

MSI-H :

JAMA Oncology | Original Investigation

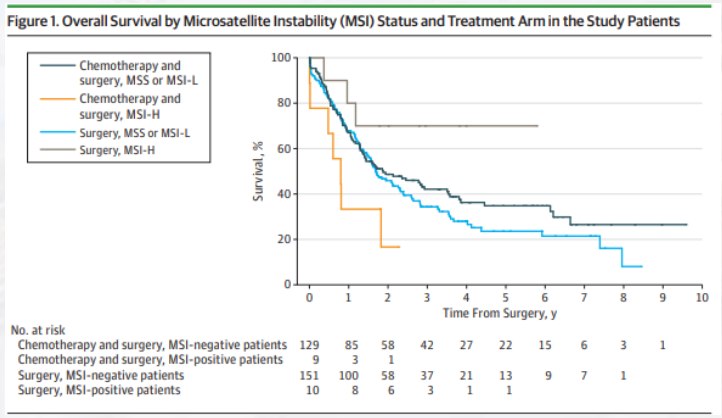
Mismatch Repair Deficiency, Microsatellite Instability, and Survival
An Exploratory Analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial

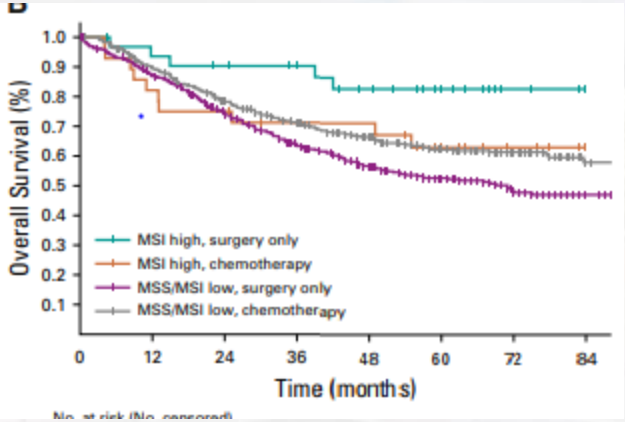
Elizabeth C. Smyth, MB, BCh, MSc; Andrew Wotherspoon, MD; Clare Peckitt, MSc; David Gonzalez, PhD; Sanna Hulkki-Wilson, BSc, MSc; Zakaria Eltahir, PhD; Matteo Fassan, MD, PhD; Massimo Rugge, MD, FACG; Nicola Valeri, MD, PhD; Alicia Okines, MD; Madeleine Hewish, MD, PhD; William Allum, MD; Sally Stenning, MSc; Matthew Nankivell, MSc; Ruth Langley, MD, PhD; David Cunningham, MD, FMedSci

Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer

Check for updates

Filippo Pietrantonio, MD[1,2]; Rosalba Miceli, PhD[1]; Alessandra Raimondi, MD[1]; Young Woo Kim, MD, PhD[3]; Won Ki Kang, MD[4]; Ruth E. Langley, MD, PhD[5]; ...





Upfront surgery

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Gastric Adenocarcinoma

Management of Locoregional in MSI-H disease

Trial	Phase/#	Regimen	Outcomes
NEONIPIGA[1]	II/32	Perioperative IPI/Nivo	59% pCR + 3 patients with cCR Zero relapse reported
INFINITY[2]	II/17	Neoadjuvant T/D	60%pCR+ 2 pts with cCR

André T et al. J Clin Oncol. 2023 Jan 10;41(2):255-265
Pietrantonio et al. J Clin Oncol. 41, no. 4_suppl (February 01, 2023) 358-358.

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Gastric Adenocarcinoma

NCCN panel made amendment on 8/29/2023

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Esophageal and Esophagogastric Junction Cancers

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Updates in Version 3.2023 of the NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers from Version 2.2023 include:

Squamous Cell Carcinoma and Adenocarcinoma

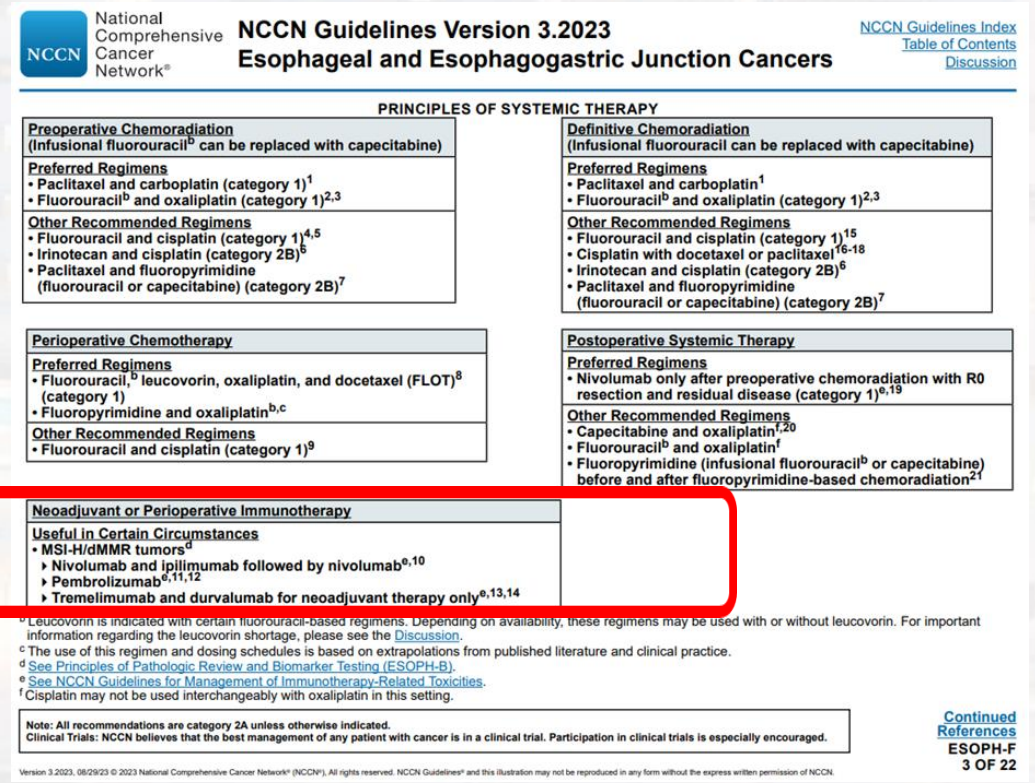
ESOPH-B Principles of Pathologic Review and Biomarker Testing

ESOPH-B 1 of 6

- The table was revised as follows:
  - Analysis/Interpretation/Reporting; New bullets added:
    - Biopsy: Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients
    - Endoscopic resection: Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients
    - Esophagogastrectomy, without prior chemoradiation: Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients, if not previously performed

ESOPH-B 4 of 6

- Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing; First bullet revised: "~~Testing for MSI by polymerase chain reaction (PCR)/NGS or MMR by IHC should be considered on locally advanced, recurrent, or metastatic esophageal and EGJ cancers in patients who are candidates for treatment with programmed cell death protein 1 (PD-1) inhibitors~~ *Universal testing for MSI by polymerase chain reaction (PCR), NGS, or MMR by IHC should be performed for all newly diagnosed esophageal and EGJ cancers.* The testing is performed..."



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Esophageal and Esophagogastric Junction Cancers

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PRINCIPLES OF SYSTEMIC THERAPY

Preoperative Chemoradiation
(Infusional fluorouracil[b] can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin (category 1)[1]
- Fluorouracil[b] and oxaliplatin (category 1)[2,3]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[4,5]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Definitive Chemoradiation
(Infusional fluorouracil can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin[1]
- Fluorouracil[b] and oxaliplatin (category 1)[2,3]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[15]
- Cisplatin with docetaxel or paclitaxel[16-18]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Perioperative Chemotherapy

Preferred Regimens
- Fluorouracil,[b] leucovorin, oxaliplatin, and docetaxel (FLOT)[8] (category 1)
- Fluoropyrimidine and oxaliplatin[b,c]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[9]

Postoperative Systemic Therapy

Preferred Regimens
- Nivolumab only after preoperative chemoradiation with R0 resection and residual disease (category 1)[e,19]

Other Recommended Regimens
- Capecitabine and oxaliplatin[f,20]
- Fluorouracil[b] and oxaliplatin[f]
- Fluoropyrimidine (infusional fluorouracil[b] or capecitabine) before and after fluoropyrimidine-based chemoradiation[21]

Neoadjuvant or Perioperative Immunotherapy

Useful in Certain Circumstances
- MSI-H/dMMR tumors[d]
  - Nivolumab and ipilimumab followed by nivolumab[e,10]
  - Pembrolizumab[e,11,12]
  - Tremelimumab and durvalumab for neoadjuvant therapy only[e,13,14]

[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[c] The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.
[d] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[f] Cisplatin may not be used interchangeably with oxaliplatin in this setting.

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.

Continued
References

ESOPH-F
3 OF 22

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TEXAS ONCOLOGY

Gastric Adenocarcinoma

Management Metastatic Disease

Current Biomarkers with therapy implications:

- HER2+ [1,2]
- MSI H [3]
- PD-1 CPS [4]

1. Bang YJ et al. Lancet. 2010 Aug 28;376(9742):687-97
2. Janjigian YY et al. Nature. 2021 Dec;600(7890):727-730.
3. Chao J et al. JAMA Oncol. 2021;7(6):895–902.
4. Janjigian YY et al. Lancet. 2021 Jul 3;398(10294):27-40.

Biomarkers of interest:

- CLDN18.2 → Zolbetuximab
- FGFR2b → Bemartuximab

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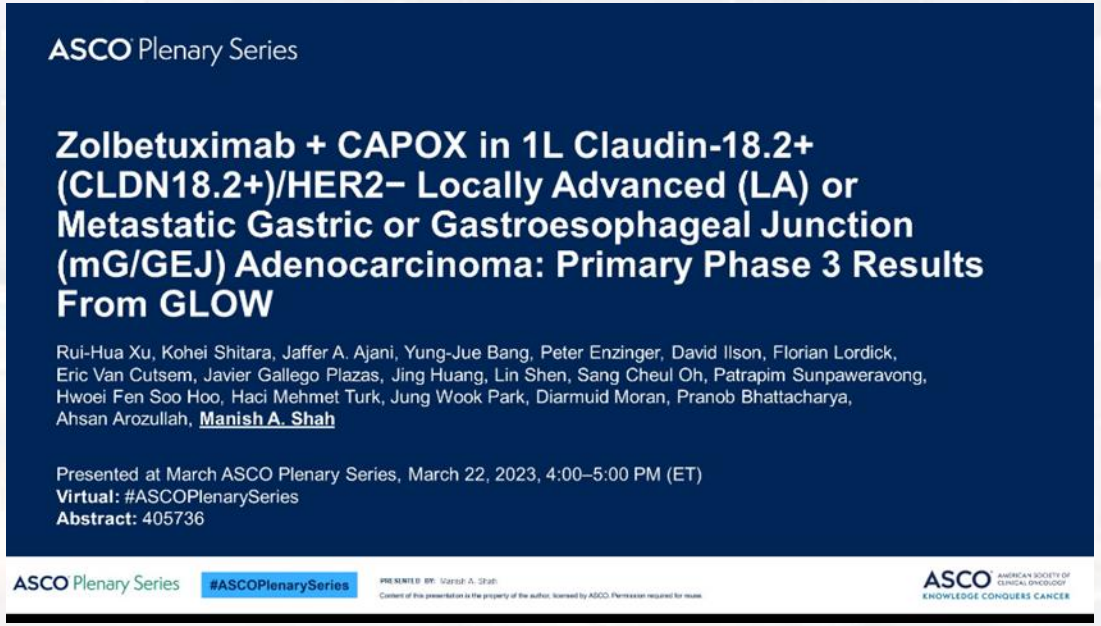
Gastric Adenocarcinoma

Zolbetuximab :



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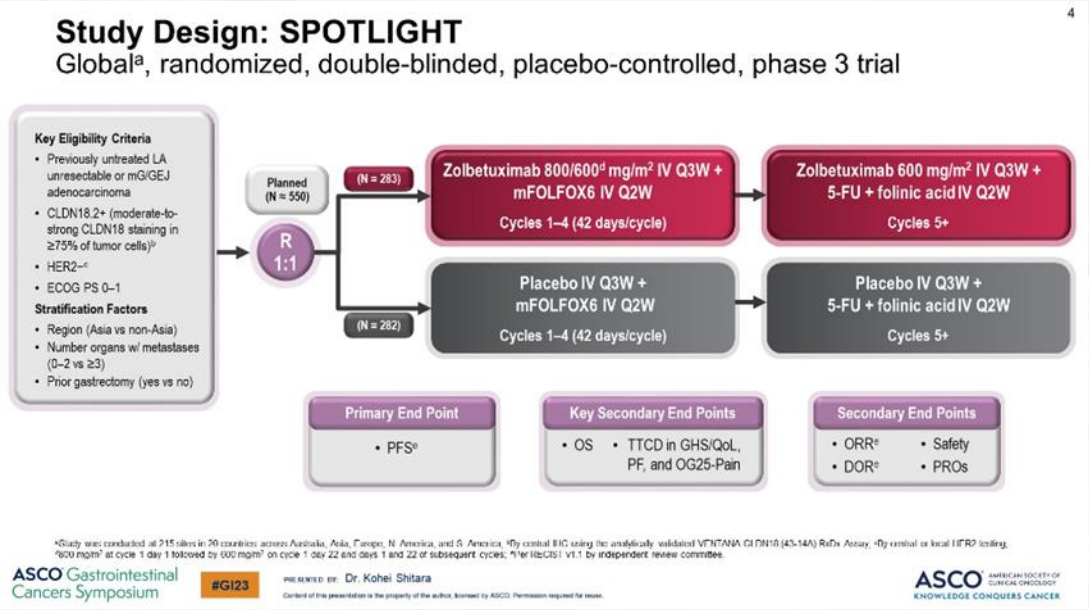
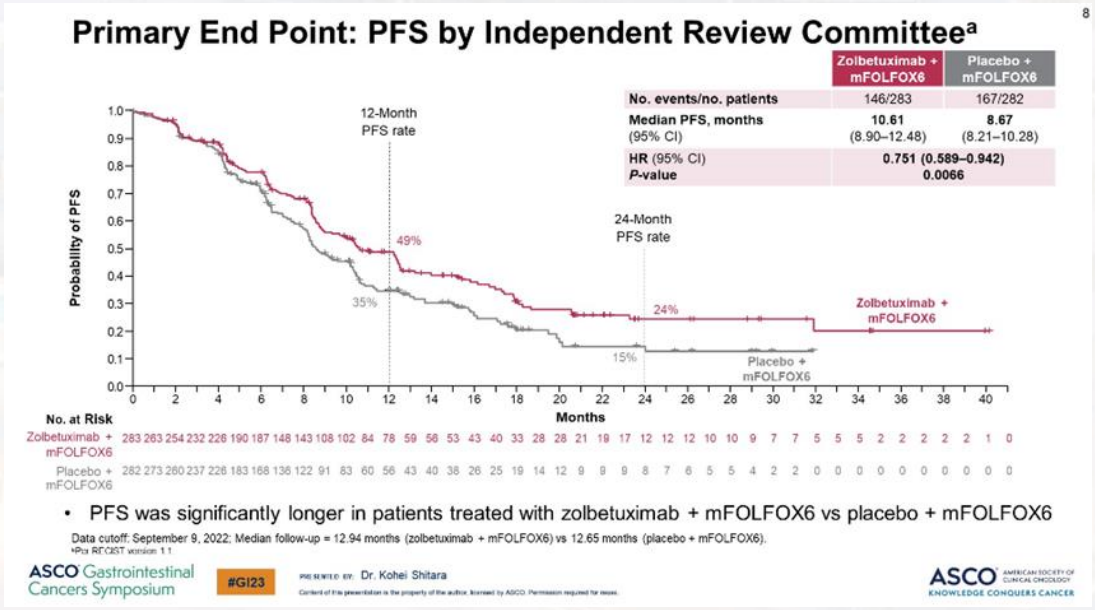
TEXAS ONCOLOGY

Gastric Adenocarcinoma

Zolbetuximab :

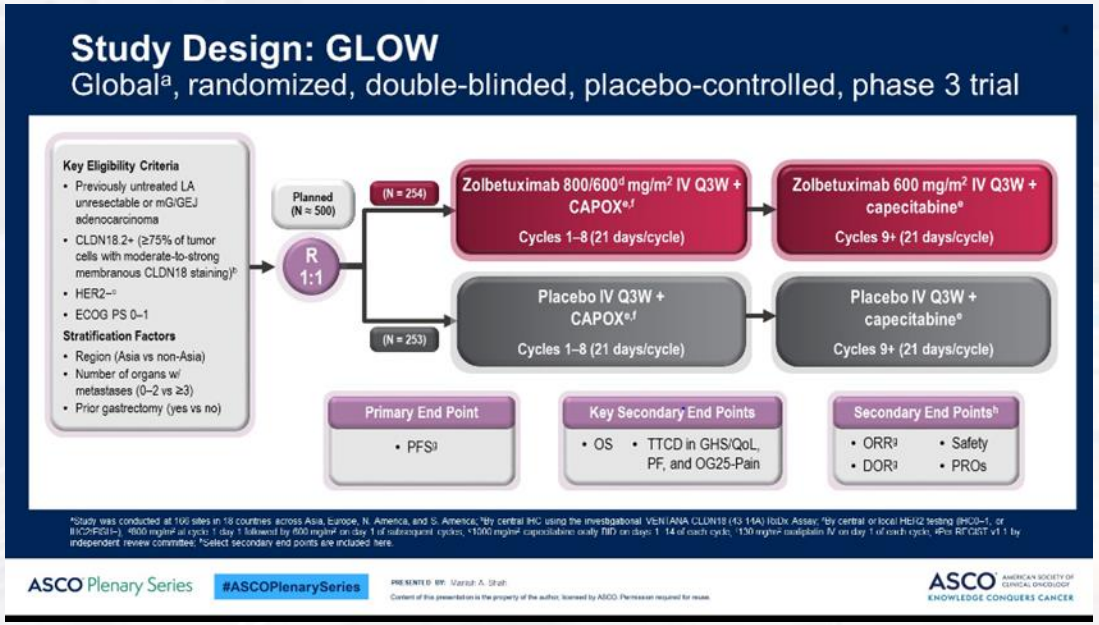


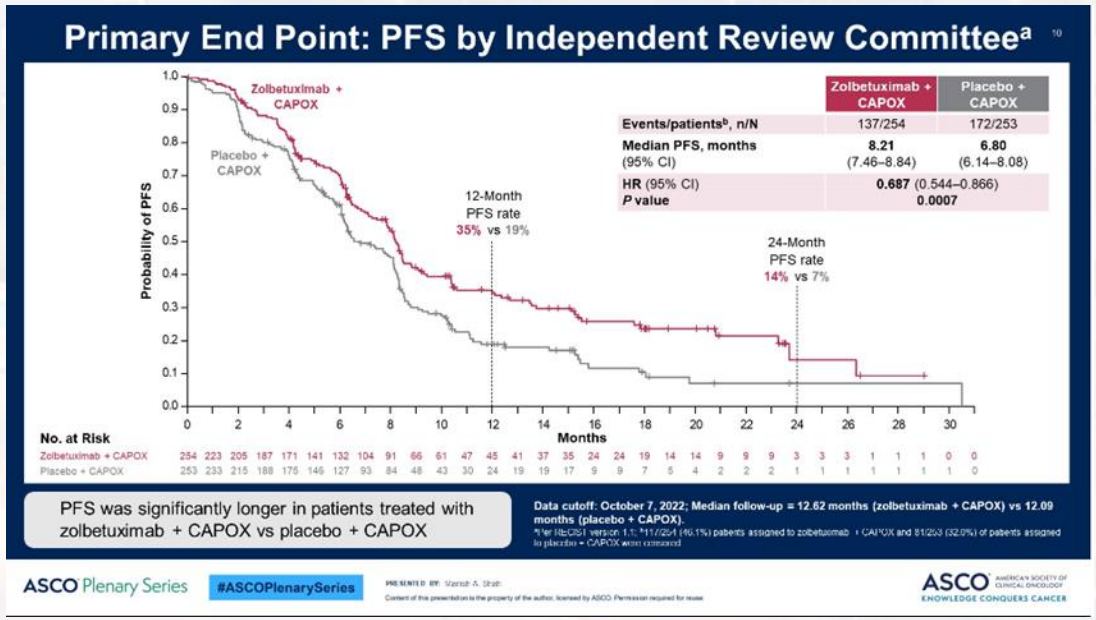


OS~ 19 months

Gastric Adenocarcinoma

Zolbetuximab :





The FDA has granted a priority review with a target action date of January 12, 2024.

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TEXAS ONCOLOGY

Gastric Adenocarcinoma

Bemartuzumab:

FIGHT Trial Design

Presented : Dr Weinberg ASCO 2021

Key Eligibility Criteria
- No prior therapy for unresectable locally advanced or metastatic gastric/GEJ adenocarcinoma
- RECIST v1.1 evaluable disease
- FGFR2b overexpression by IHC and/or *FGFR2* gene amplification by ctDNA[1]
- ECOG 0/1
- HER2 not positive
- May receive 1 dose of mFOLFOX6

Stratification Factors
- Geographic region
- Single dose of mFOLFOX6 during screening
- Prior adjuvant or neo-adjuvant chemotherapy

R 1:1

Double blind, placebo controlled

Bema + mFOLFOX6 (n = 77)

VS

Placebo + mFOLFOX6 (n = 78)

Treatment Q2W[2]

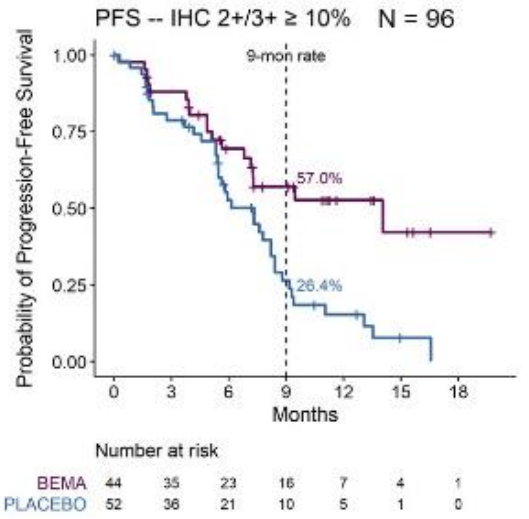
Primary endpoint
- Investigator-Assessed Progression-Free Survival

Secondary endpoints
- Overall Survival
- Response Rate

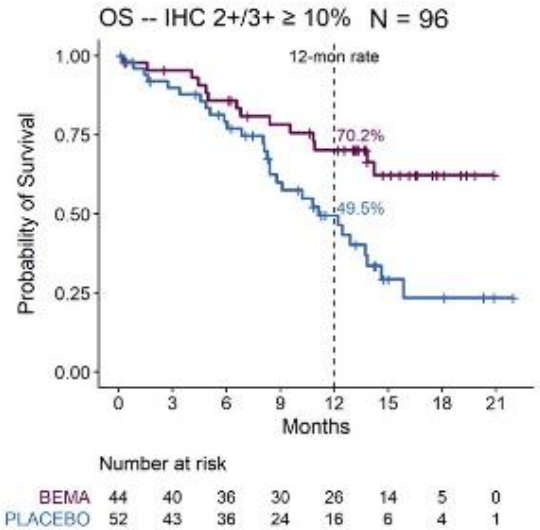
Statistical Plan

Trial initially designed as registrational Phase 3 (n=548) with 2-sided α 0.05
Amended after enrolling n = 155 to a proof-of-concept Phase 2 with pre-specified statistical assumptions of:
- Hierarchical sequential testing: PFS, then OS/ORR
- ≥84 events to demonstrate benefit at a HR≤0.76 for PFS at 2-sided α of 0.2

1 Central testing: Immunohistochemical stain (Ventana): cut-off any 2+/3+; circulating tumor DNA (PGDx): cut-off 1.5X
2 15mg/kg Q2W with a single 7.5mg/kg dose on Cycle 1 Day 8[2]



	Bema N = 44	Placebo N = 52
mPFS, mo (95% CI)	14.1 (6.8, NR)	7.3 (5.4, 8.2)
HR (95% CI)	0.44 (0.25, 0.77)	



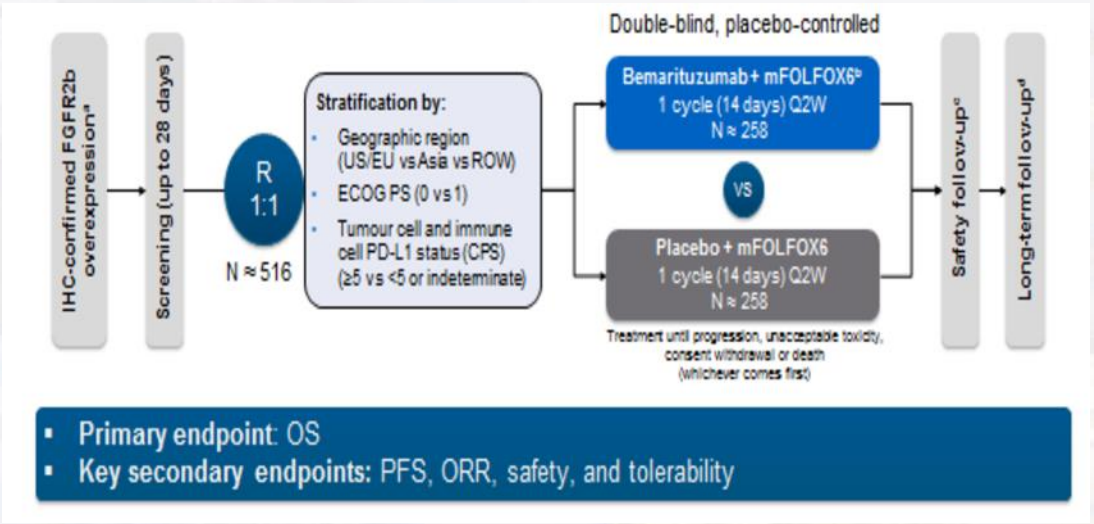
	Bema N = 44	Placebo N = 52
mOS, mo (95% CI)	NR (13.8, NR)	11.1 (8.4, 13.8)
HR (95% CI)	0.41 (0.22, 0.79)	

- 30% of prescreening deemed positive
- ~ 61% of positive meet high expression > 10% of tumor

Wainberg et al. J Clin Oncol 39, 2021 (suppl 3; abstr 160)

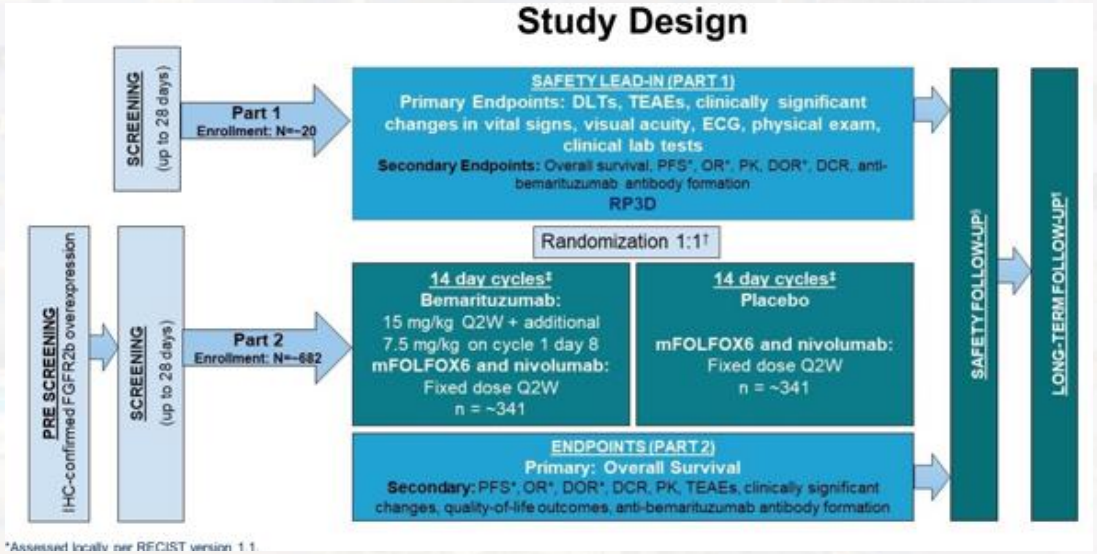
Gastric Adenocarcinoma

Bemartuzumab:



Smyth et al. J Clin Oncol 40, 2022 (suppl 16; abstr TPS4164)

FORTITUDE 101



Wainberg et al. J Clin Oncol 40, 2022 (suppl 16; abstr TPS4165)

FORTITUDE 102

Biliary Cancer

TOPAZ-1 trial set the standard of care

KEYNOTE-966 Study Design
Randomized, Double-Blind, Phase 3 Trial

Presented : Dr. Yoo ASCO 2023

Key Eligibility Criteria
- Histologically confirmed extrahepatic or intrahepatic cholangiocarcinoma or gallbladder cancer
- Unresectable locally advanced or metastatic disease measurable per RECIST v1.1 by investigator review
- No prior systemic therapy[a]
- ECOG PS 0 or 1
- Life expectancy >3 months

R 1:1

Pembrolizumab 200 mg IV Q3W (maximum, 35 cycles)
+
Gemcitabine 1000 mg/m² IV on days 1 and 8 Q3W (no maximum)
+
Cisplatin 25 mg/m² IV on days 1 and 8 Q3W (maximum, 8 cycles)

Placebo IV Q3W for (maximum, 35 cycles)
+
Gemcitabine 1000 mg/m² IV on days 1 and 8 Q3W (no maximum)
+
Cisplatin 25 mg/m² IV on days 1 and 8 Q3W (maximum, 8 cycles)

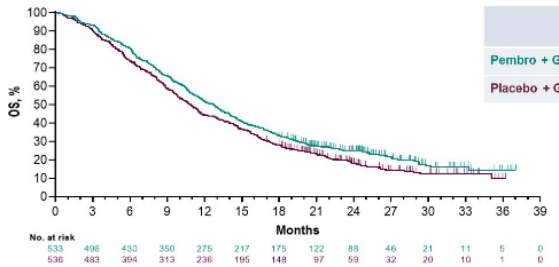
Stratification Factors
- Geographic region (Asia vs not Asia)
- Disease stage (locally advanced vs metastatic)
- Site of origin (extrahepatic vs gallbladder vs intrahepatic)

- **Primary End Point:** OS
- **Secondary End Points:** PFS, ORR, and DOR assessed per RECIST v1.1 by blinded, independent central review and safety
- **Prespecified Exploratory End Points:** PRO end points

Treatment was continued until disease progression, unacceptable toxicity, investigator decision, or, for pembrolizumab and cisplatin, the maximum number of cycles was reached.
[a]Neoadjuvant or adjuvant chemotherapy was permitted if it was completed ≥6 months before the diagnosis of unresectable or metastatic disease.
ClinicalTrials.gov identifier: NCT04003636.

Background

- In KEYNOTE-966, adding the PD-1 inhibitor pembrolizumab to gem/cis provided a statistically significant, clinically meaningful improvement in OS to patients as first-line therapy for biliary tract cancer (BTC)[1]



	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	78%	12.7 (11.5-13.6)
Placebo + Gem/Cis	83%	10.9 (9.9-11.6)

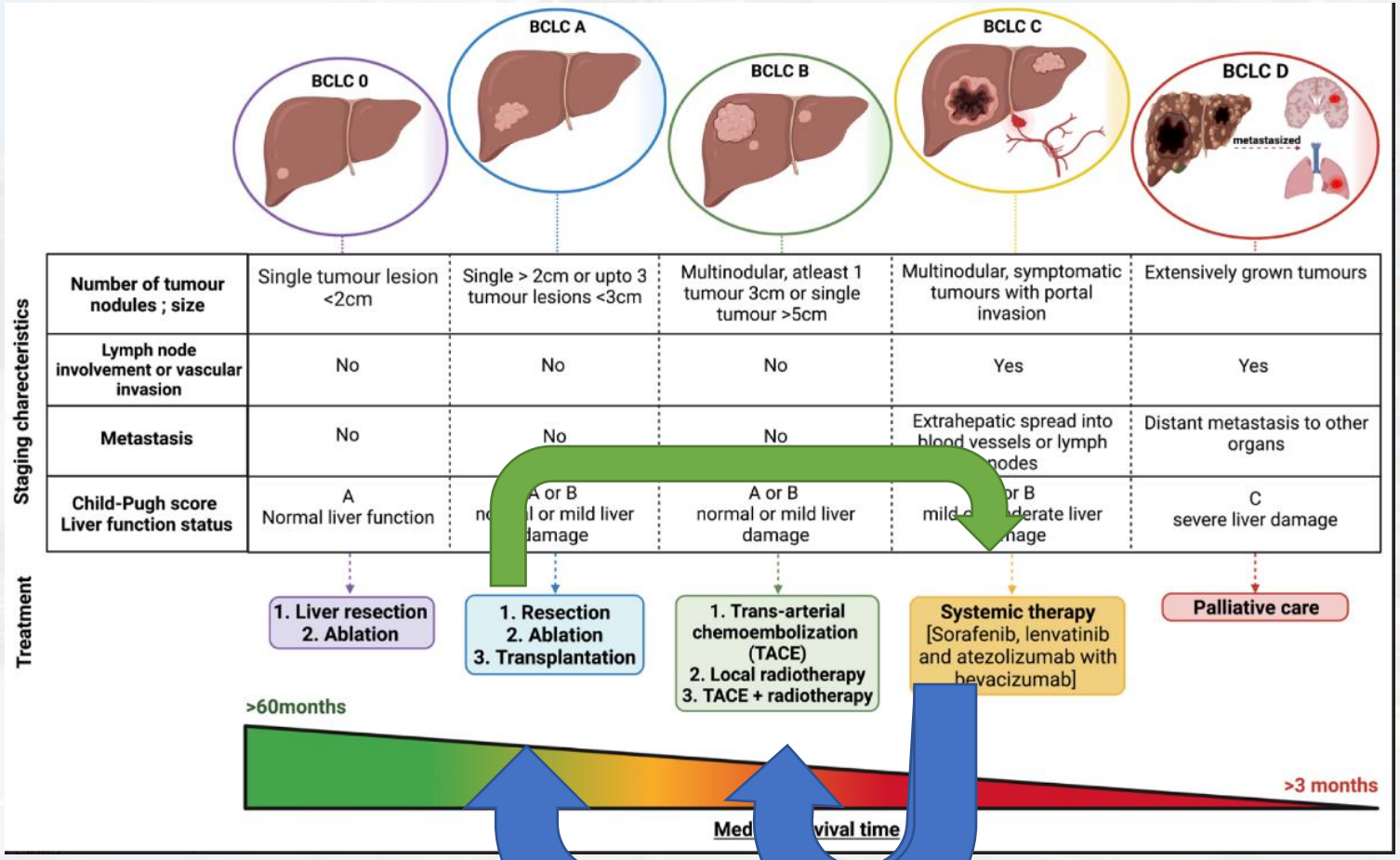
HR 0.83 (95% CI, 0.72-0.95)
***P* = 0.0034**
Below the signficance boundary of *P* = 0.0200

- KEYNOTE-966 showed similar safety profiles between the pembrolizumab and placebo groups[1]
  - 70% of patients treated with pembrolizumab + gem/cis had grade 3 or 4 treatment-related adverse events vs 69% for placebo + gem/cis

[1]Kelley et al. Lancet 2023; 2023;S0140-6736(23)00727-4.

FDA has accepted for review a new supplemental Biologics License Application. The FDA has set a target action date of February 7, 2024.

HCC



Krishnamurthy et al. Cancers 2021, 13, 5180.

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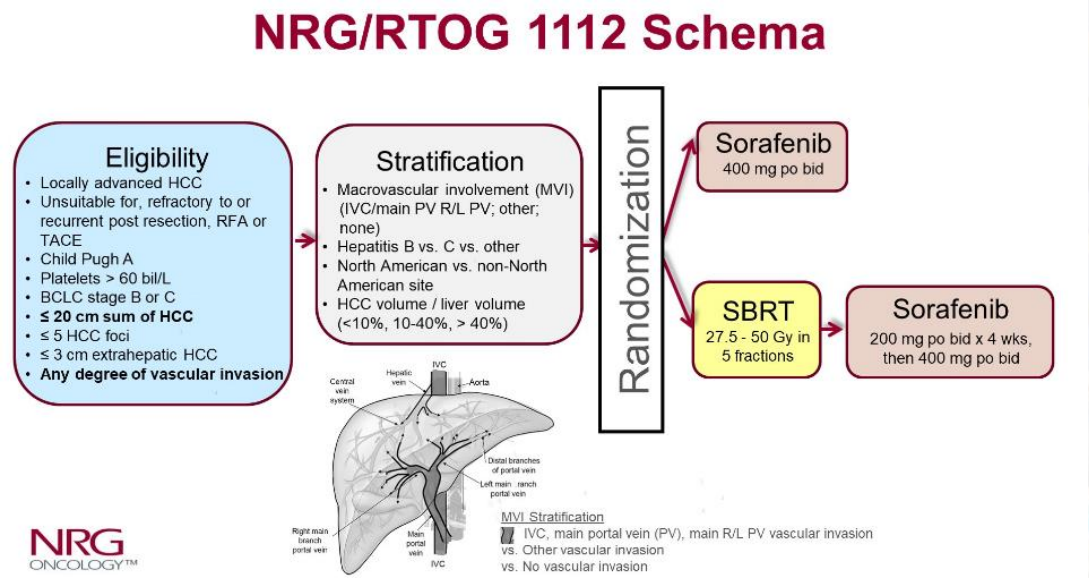
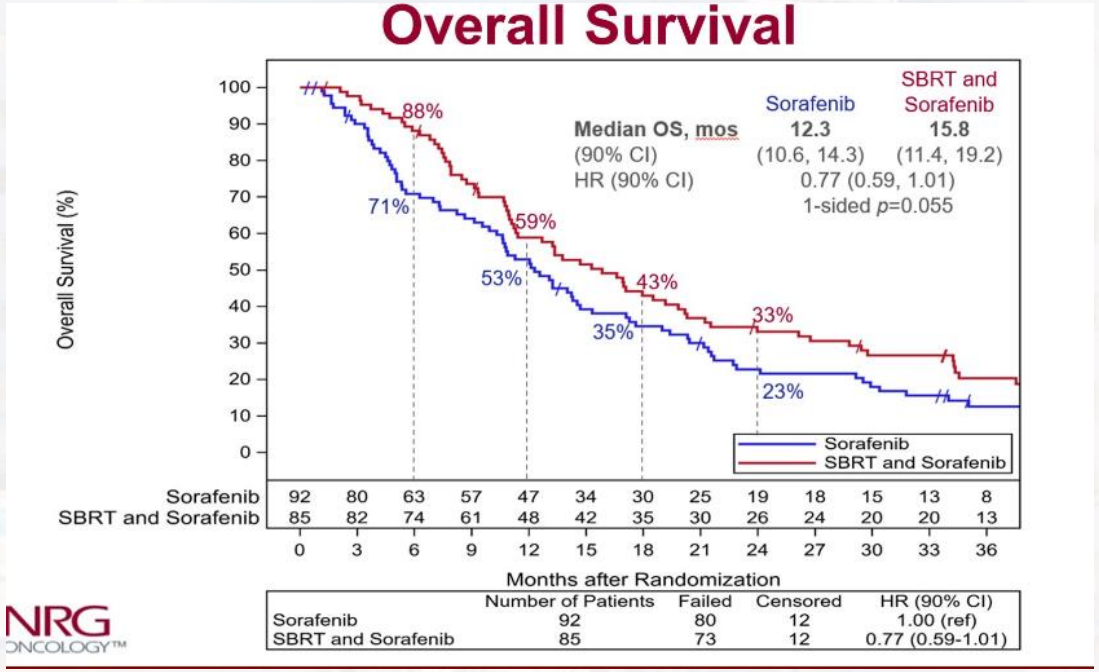


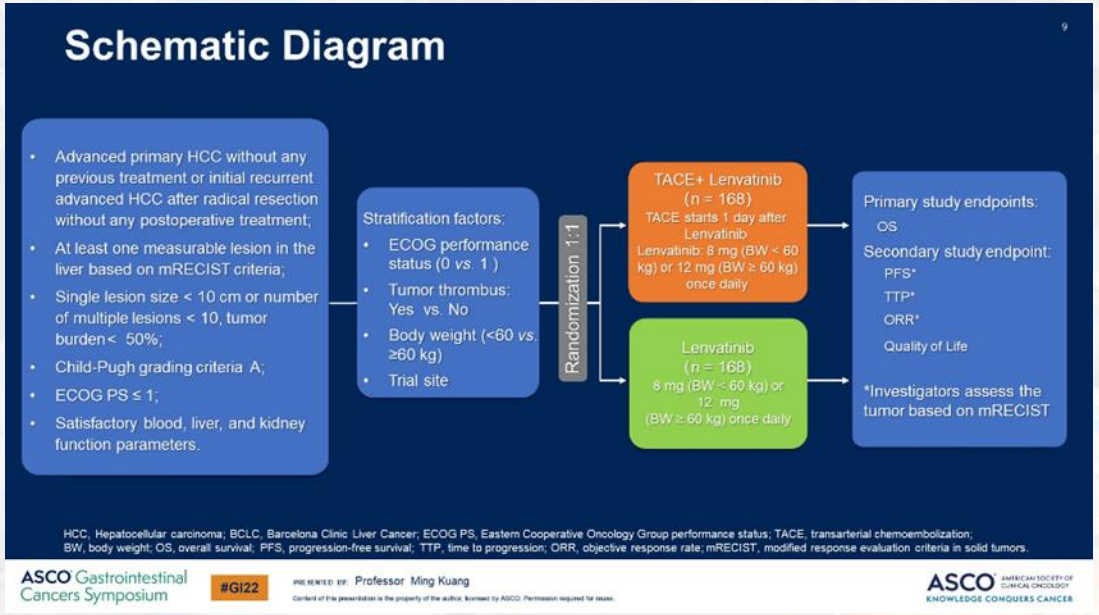


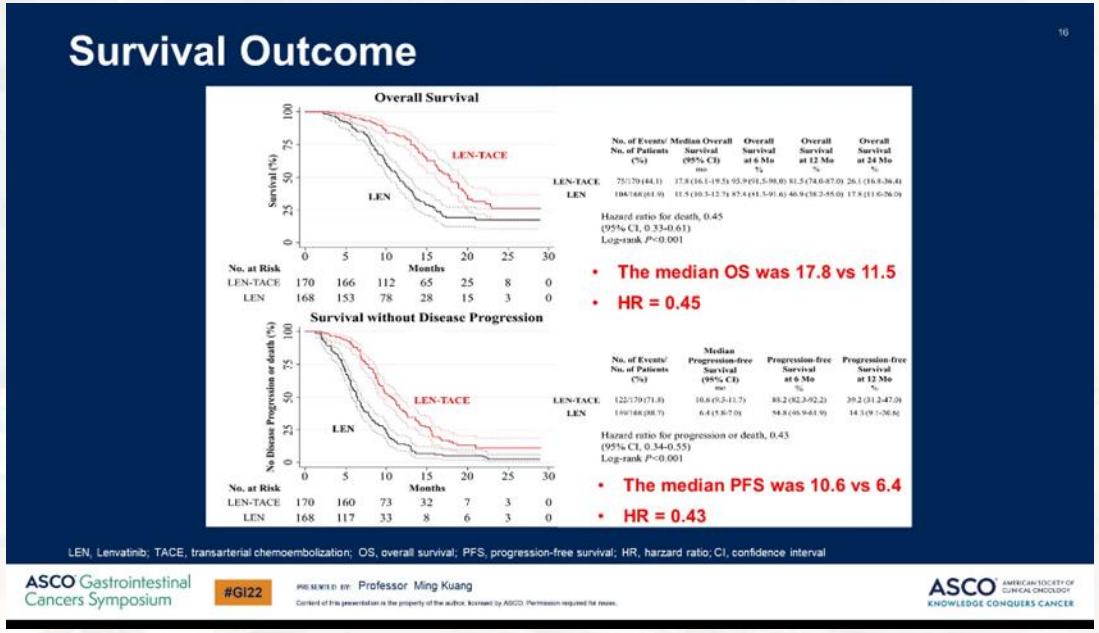
Presented ASCO GI 23 By Dr. Dawson

Dawson et al. J Clin Oncol 41, 2023 (suppl 4; abstr 489)

HCC

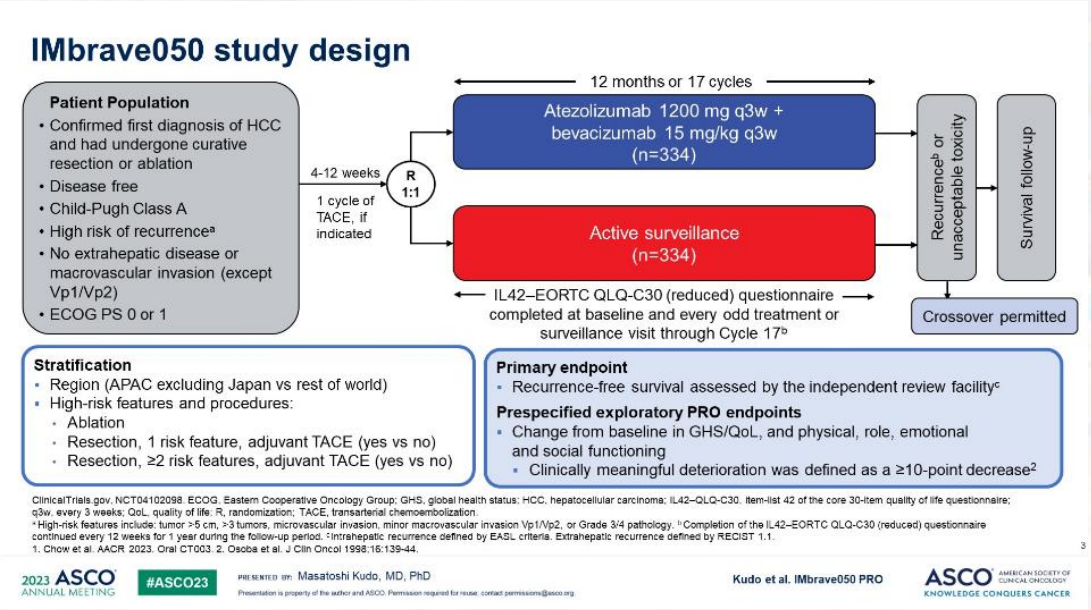
Similar theme from LAUNCH trial

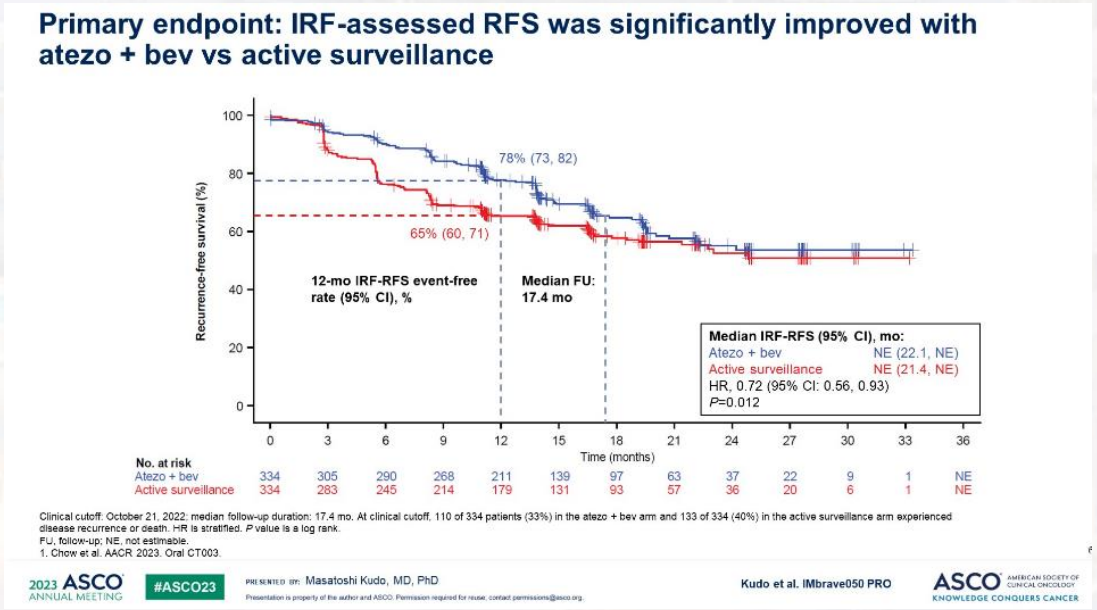




Awaiting SBRT+ ICI combinations
MVI population could benefit significantly
MDC discussions are key

HCC





Kudo et al. J Clin Oncol 41, 2023 (suppl 16; abstr 4002)

Pancreatic Adenocarcinoma

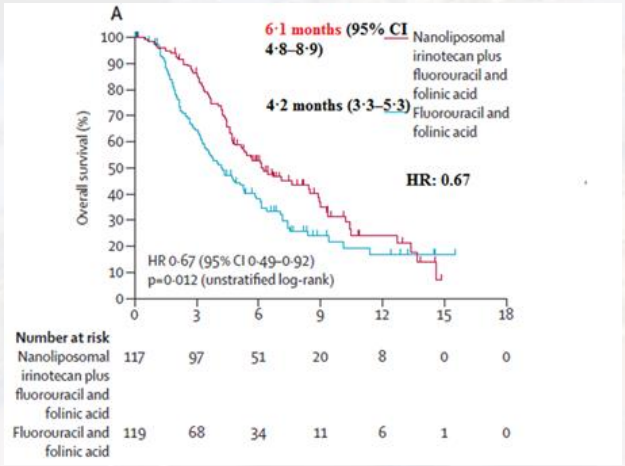
Landmark trials:

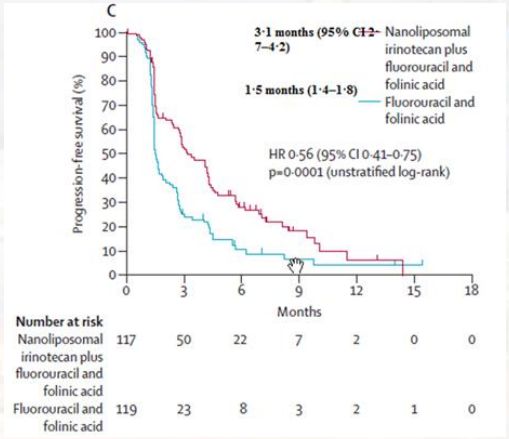
Trial	Standard of Care
Burris et al. J Clin Oncol. **1997** Jun;15(6):2403-13	Gemcitabine
Moore et al. J Clin Oncol. 2007 May 20;25(15):1960-6	Gemcitabine + Erlotinib
Conroy et Al. N Engl J Med **2011**; 364:1817-1825	FOLFIRINOX
Von Hoff et Al. N Engl J Med **2013**; 369:1691-1703	Gemcitabine + nab- paclitaxel
Wang Gillum et al. The lancet. VOLUME 387, ISSUE 10018, P545-557, FEBRUARY 06, **2016**	2nd line NALIRI
Golan et al. N Engl J Med **2019**; 381:317-327	Maintenance Olaparib
Wainberg et al. Journal of Clinical Oncology 41, no. 4_suppl (February 01, **2023**) LBA661-LBA661 ??	NALFIRINOX??

Pancreatic Adenocarcinoma

NAPOLI 3 Trial- Background

- In Oct 2015, Liposomal irinotecan administered with 5-fluorouracil/leucovorin (5-FU/LV) is approved in the USA for metastatic pancreatic ductal adenocarcinoma (mPDAC) following progression with gemcitabine-based therapy based on NAPOLI-I trial





- Wang-Gillam, Andrea et al. The Lancet , Volume 387 , Issue 10018 , 545 - 557

Pancreatic Adenocarcinom

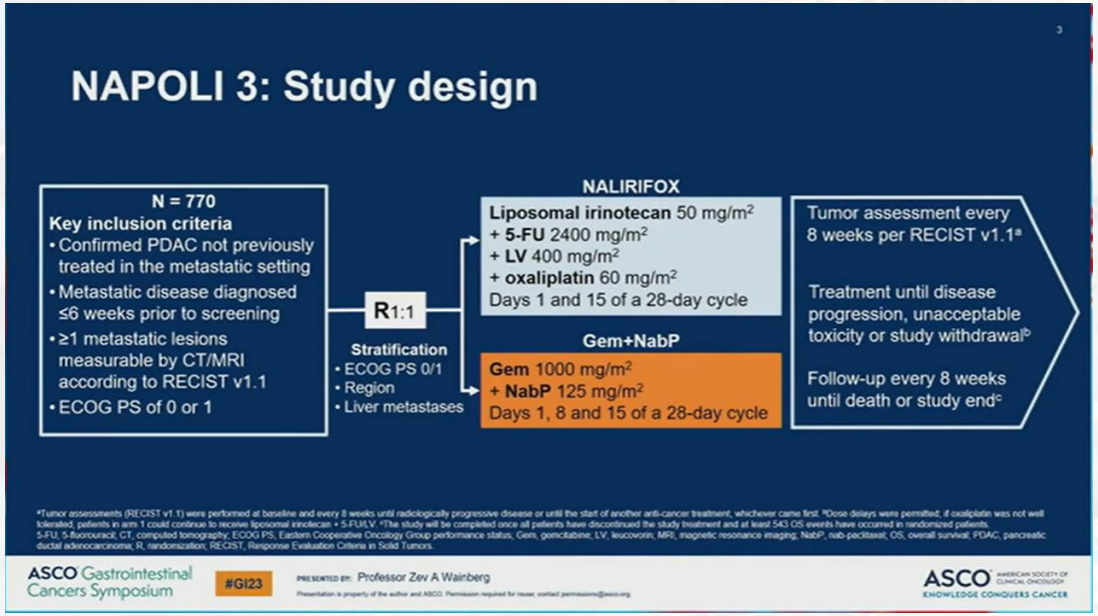
NAPOLI 3 Trial- Genesis

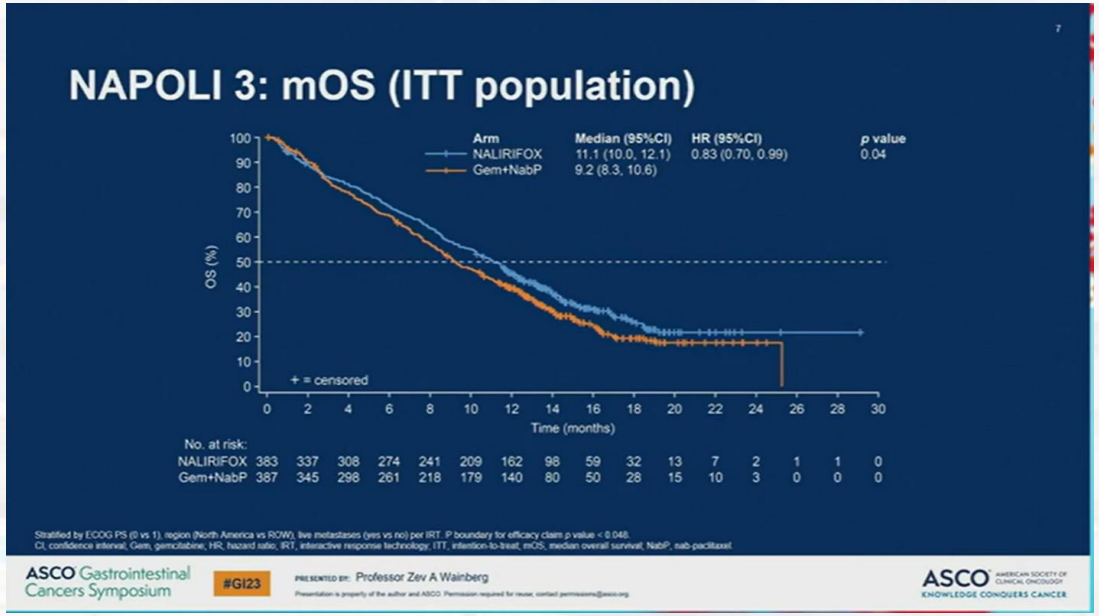
- Phase I/II study of NALFIRINOX in frontline FFX fit patients.
- Presented in 2020 ESMO world congress on GI Cancer.
- Initial dose escalation, Nano liposomal Irinotecan at 50 mg/m2 and Oxaliplatin at 60 mg/m2.

- **Results:**
  - 32 patients.
  - Median PFS 9.2-m (PFS; 95% CI, 7.69-11.96)
  - Median OS 12.6-m (OS; 95% CI, 8.74-18.69).
  - ORR: 34.4% (95% CI, 18.6%-53.3%).

Wainberg et al. Ann Oncol 2019;30 Suppl 4: SO-005

NAPOLI 3 Trial





Is it one disease?

In an unselected population could be SOC

Cost remain significant barrier to adopt the regimen while FOLFIRINOX is available.

CROSS TRIAL comparison is problematic

FDA has set a Prescription Drug User Fee Act action date of February 13, 2024.

	HALO301[4]	RESOLVE[5]	CanStem111P[6]	YOSEMITI[7]
OS	11.5	10.6	11.7	> 13.2
PFS	7.1	6.01	6.1	5.5
ORR	36%	42%	42%	41%

1	NALFIRINOX	GN
OS	11.1 m	9.2
PFS	7.4 m	5.6m
ORR	41%	36%

	FFX Prodige 11[2]	FFX in AVENGER 500[3]
OS	11.1	11.7
PFS	6.4	8.0
ORR	31.6%	34%

1. *Wainberg et al. Lancet. 9/11/23 online*
2. *Conroy T et al. N Engl J Med. 2011 May 12;364(19):1817-25.*
3. *Philip et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4023)*
4. *Van Cutsem et. al. J Clin Oncol. 2020 Sep 20;38(27):3185-3194.*
5. *Tempero M et al. Ann Oncol. 2021 May;32(5):600-608.*
6. *Bekaii-Saab T et al. EClinicalMedicine. 2023 Mar 16;58:101897.*
7. *Cubillo Gracian A et al. Ann Oncol. 2017;28:v209-v268.*

Presented By: Laith Abushahin MBBS
@LAbushahin

TEXAS ONCOLOGY

Pancreatic Adenocarcinoma

- KRAS mutations: 95%[1]
  - G12D: 41%[1]
  - G12V34%1
  - G12R16%1
  - Q61H: 4%1
  - …
  - G12C: 1-2%1

…

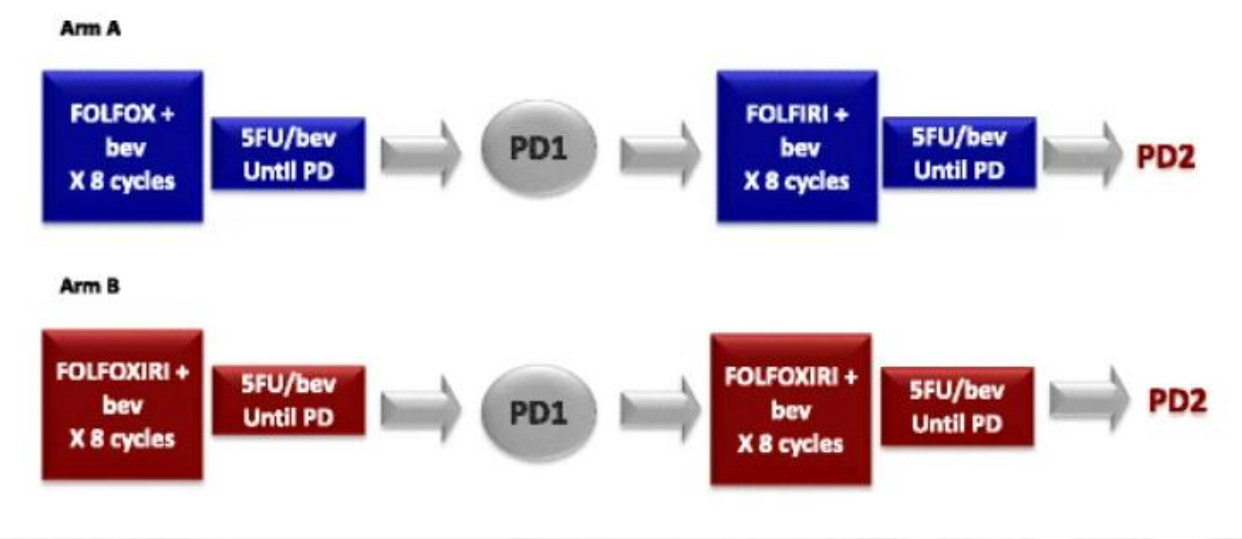
- KRAS wild type: [1,3]
- DDR defects: Platinum, PARPi[4]
- MSI-H : ICI[3]
- Basal like transcriptional phenotype?

1.Bryant KL et al. Trends Biochem Sci. 2014 Feb;39(2):91-100.
2.Luchini Cet al. J Exp Clin Cancer Res. 2020 Oct 28;39(1):227.
3.Yao W et al. EBioMedicine. 2020 Mar;53:102655.
4.O'Reilly EM et al. J Clin Oncol. 2020;38(13):1378-1388

NRG1, FGFR,ALK,ROS,BRAF,HER2,NTRK

Colon Cancer

Not too long ago, Unresectable metastatic colorectal cancer was considered one disease



TRIBE and TRIBE 2:

- 1187 pts
- Right(35%) and left(65%)
- ~55% RAS mutated
- 8% BRAF mutated

Cremolini C et al. Lancet Oncol. 2015 Oct;16(13):1306-15.
Cremolini C et al. BMC Cancer. 2017 Jun 9;17(1):408

Colon Cancer

MSI-H

FDA approval of Pembrolizumab in 1st line 6/29/2020 based on KN177

MSS CRC

- Wild type RAS/ RAF~ 40%
- RAS mutations ~ 50%
- BRAF mutations~5-10%
- HER2 amplifications ~4%(The Cancer Genome Atlas)
  - Mostly in left colon / wild RAS RAF.

Tejpar S. et al Oncologist. 2010;15:390–404.

Colon Cancer

Left Colon MSS CRC Wild type RAS/RAF

The common recent trials question: What is the best 1st line regimen?

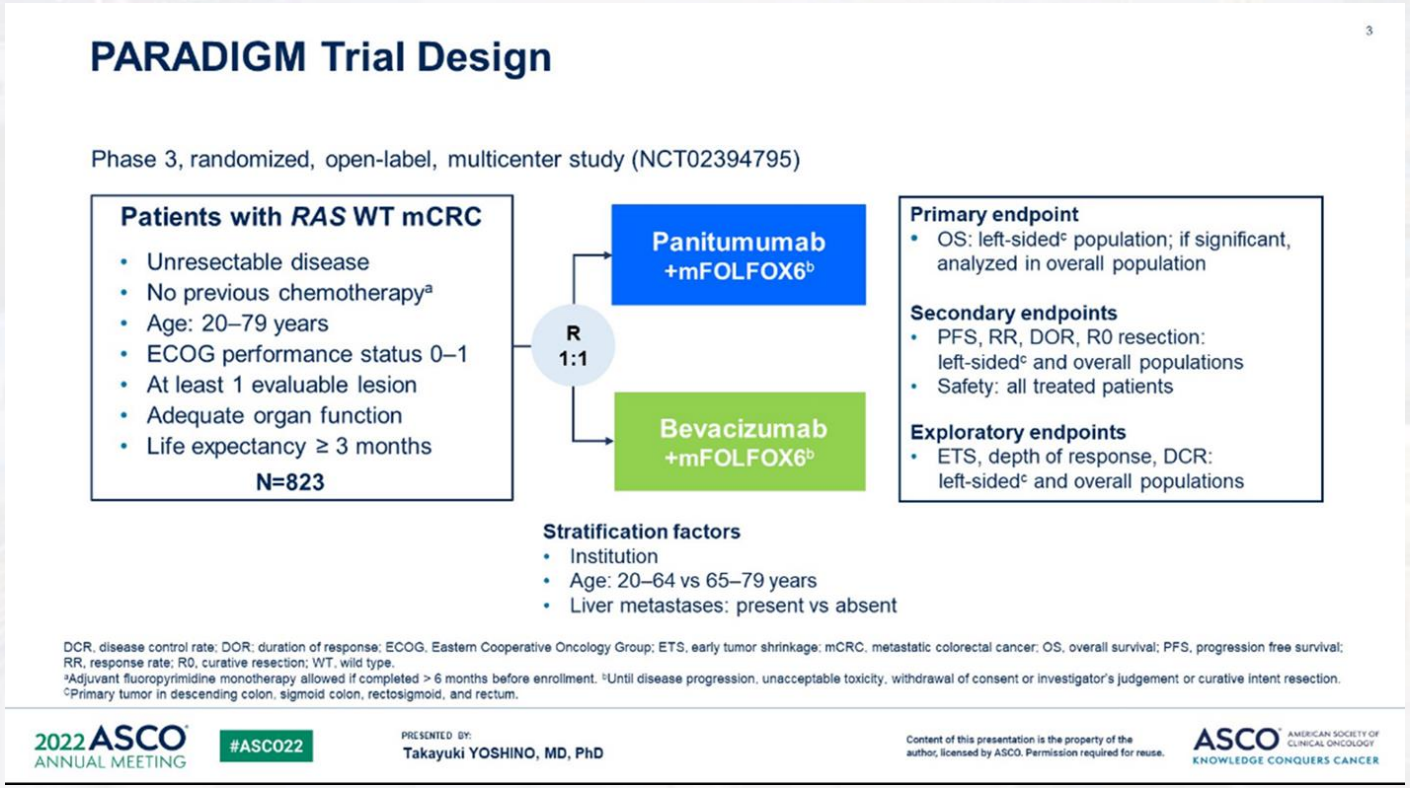
- EGFR vs VGEF targeting ?
- Doublet vs Triplet chemotherapy backbone?

Presented By: Laith Abushahin MBBS
@LAbushahin

TEXAS ONCOLOGY

Colon Cancer

Left Colon MSS CRC Wild type RAS/RAF



PARADIGM Trial Design

3

Phase 3, randomized, open-label, multicenter study (NCT02394795)

Patients with *RAS* WT mCRC
- Unresectable disease
- No previous chemotherapy[a]
- Age: 20–79 years
- ECOG performance status 0–1
- At least 1 evaluable lesion
- Adequate organ function
- Life expectancy ≥ 3 months

N=823

R 1:1

Panitumumab +mFOLFOX6[b]

Bevacizumab +mFOLFOX6[b]

Primary endpoint
- OS: left-sided[c] population; if significant, analyzed in overall population

Secondary endpoints
- PFS, RR, DOR, R0 resection: left-sided[c] and overall populations
- Safety: all treated patients

Exploratory endpoints
- ETS, depth of response, DCR: left-sided[c] and overall populations

Stratification factors
- Institution
- Age: 20–64 vs 65–79 years
- Liver metastases: present vs absent

DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ETS, early tumor shrinkage; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression free survival; RR, response rate; R0, curative resection; WT, wild type.
[a]Adjuvant fluoropyrimidine monotherapy allowed if completed > 6 months before enrollment. [b]Until disease progression, unacceptable toxicity, withdrawal of consent or investigator's judgement or curative intent resection. [c]Primary tumor in descending colon, sigmoid colon, rectosigmoid, and rectum.

2022 ASCO ANNUAL MEETING #ASCO22

PRESENTED BY: Takayuki YOSHINO, MD, PhD

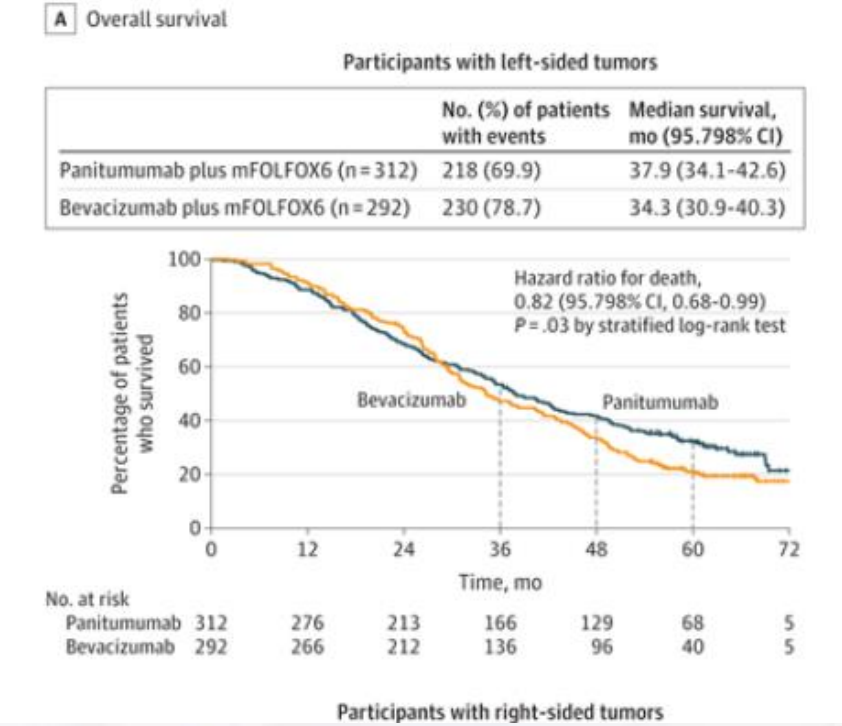
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Presented By: Laith Abushahin MBBS
@LAbushahin

TEXAS ONCOLOGY

Colon Cancer

Left Colon MSS CRC Wild type RAS/RAF



OS: 37.9

PFS: 13.1

ORR: 80%

Watanabe J et al. JAMA. 2023;329(15):1271–1282.

Colon Cancer

Left Colon MSS CRC Wild type RAS/RAF

Q1: is it applicable in a western patient population?
Q2: is it better than FOLFOXIRI + Bev?
No randomized data. **CROSS TRIAL COMPARISION ALERT**

	PARADIAGM (n=312)	Unplanned analysis for TRIBE looking at WT Left side FFX BEV (n=47) [1]
OS	37.9	40.0
PFS	13.1	14.1
ORR	80%	64%

Q3: How about FOLFOXIRI + Panitumumab?
Likely not better based on initial read out of **TRIPLETE** trial

	FOLFOX P (N 217)[2]	FOLFOXIRI P (N 218)[2]
PFS	12.7	12.3
ORR	76%	73%

1. Cremolini et al. Annals of Oncology, Volume 29, Issue 7, 2018, Pages 1528-1534.
2. Cremolini et al. Journal of Clinical Oncology 40, no. 17_suppl (June 10, 2022) LBA3505-LBA3505.

Presented By: Laith Abushahin MBBS
@LAbushahin

Colon Cancer

Left Colon MSS CRC Wild type RAS/RAF

Q4: So can I just give FOLFOX Pmab for any left side wild type CRC???

The Oncologist, 2023, **XX**, 1–9
https://doi.org/10.1093/oncolo/oyad200
Advance access publication 18 July 2023
Original Article

OXFORD

Impact of Anti-EGFR Therapies on HER2-Positive Metastatic Colorectal Cancer: A Systematic Literature Review and Meta-Analysis of Clinical Outcomes

Tanios S. Bekaii-Saab[1], Krzysztof Lach[2], Ling-I Hsu[3], Muriel Siadak[3], Mike Stecher[3], James Ward[3], Rachel Beckerman[2], John H. Strickler[*,4]

[1]Division of Hematology/Oncology, Mayo Clinic, Phoenix, AZ, USA

ORR and PFS lower in HER2 amplified

FOLFOX + Panitumumab appears to be a superior 1st line regimen for CRC if:

- MSS
- Left side
- RAS/ RAF wild Type
- NOT HER2 amplified.

NCCN CRC Panel recommend at least RAS, RAF, HER2, MSI testing for all patients upfront

Presented By: Laith Abushahin MBBS
@LAbushahin

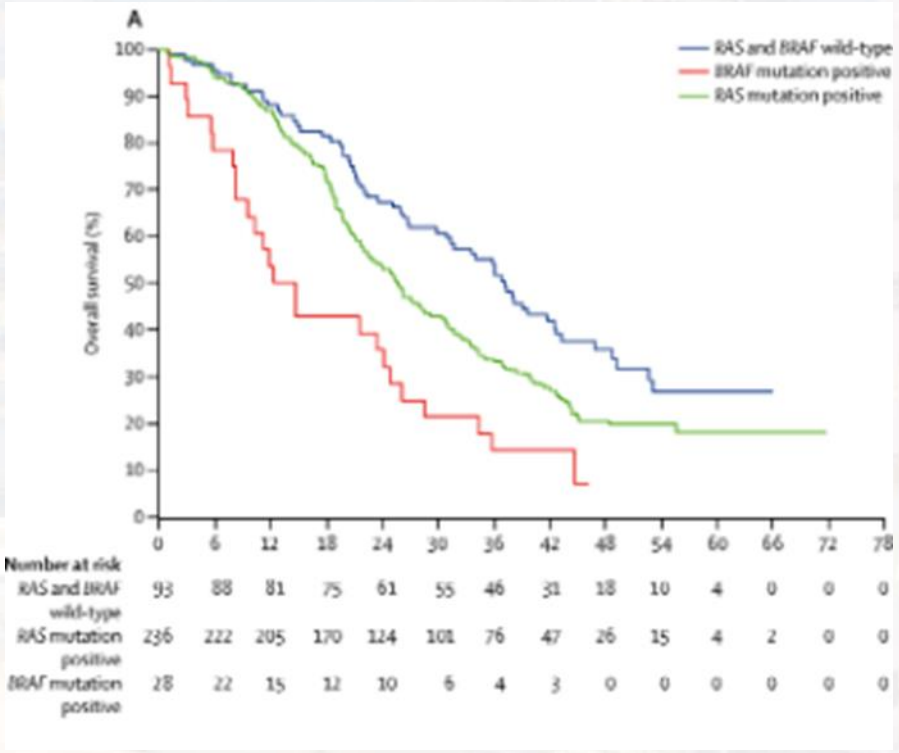
TEXAS ONCOLOGY

Colon Cancer

$BRAF^{V600E}$ mutation:

- 5-10%
- Bad prognosis
- ~25% has MSI-H

Tejpar S. et al Oncologist. 2010;15:390–404.



Cremolini et al. The Lancet Oncology. Volume 16, Issue 13, October 2015, Pages 1306-1315

Colon Cancer

BRAF^{V600E} mutation:

Trial	FIRE-3		CALGB 80405		TRIBE		FIRE-4.5	
Regimen	FOLFIRI+ BEV	FOLFIRI+ CET	FOLFIRI+ BEV	FOLFIRI +CET	FOLFIRI+ BEV	FOLFOXIRI+ BEV	FOLFOXIRI +BEV	FOLFIXIRI+ CET
N	25	23	41	33	12	16	35	72
PFS	6.6	6.6	7.6	6.2	5.5	7.5	8.3	6
OS	13.7	12.3	15	11.7	10.7	19	16.8	14.6

- ❑ Median OS 10.7- 19 months
- ❑ Doublet + Bev > doublet + Cetuximab
- ❑ Triplet + Bev > triplet + cetuximab
- ❑ Triplet + Bev > doublet + Bev

Presented By: Laith Abushahin MBBS
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Colon Cancer

BRAF^{V600E} mutation:

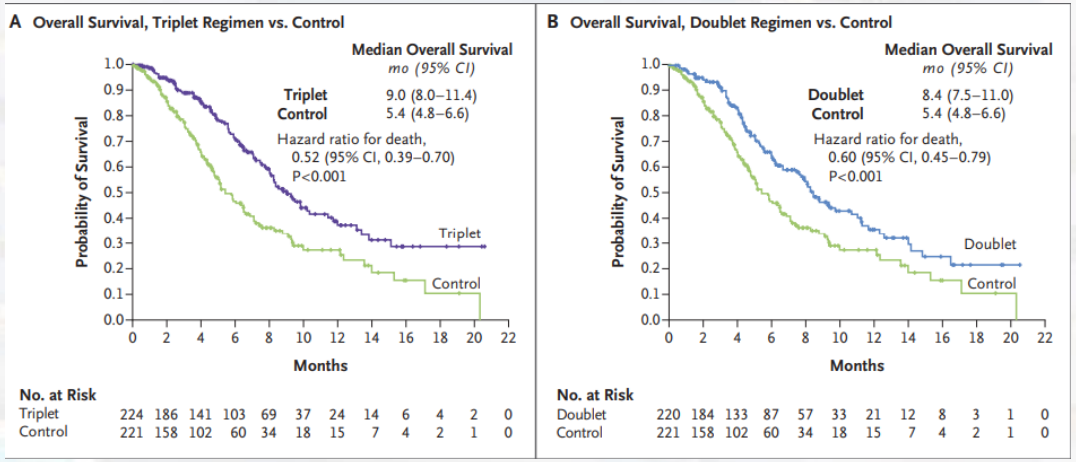
BEACON trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Encorafenib, Binimetinib, and Cetuximab in *BRAF* V600E–Mutated Colorectal Cancer

S. Kopetz, A. Grothey, R. Yaeger, E. Van Cutsem, J. Desai, T. Yoshino, H. Wasan, F. Ciardiello, F. Loupakis, Y.S. Hong, N. Steeghs, T.K. Guren, H.-T. Arkenau, P. Garcia-Alfonso, P. Pfeiffer, S. Orlov, S. Lonardi, E. Elez, T.-W. Kim, J.H.M. Schellens, C. Guo, A. Krishnan, J. Dekervel, V. Morris, A. Calvo Ferrandiz, L.S. Tarpgaard, M. Braun, A. Gollerkeri, C. Keir, K. Maharry, M. Pickard, J. Christy-Bittel, L. Anderson, V. Sandor, and J. Tabernero



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TEXAS ONCOLOGY

Colon Cancer

BRAF^{V600E} mutation:

BEACON trial

Triplet vs Doublet vs Control

- mOS
- 9.3 months for triplet (95% CI, 8.2 to 10.8) (HR 0.60, 95% CI, 0.47 to 0.75)
- 9.3 months for doublet (95% CI, 8.0 to 11.3) (HR 0.61, 95% CI, 0.48 to 0.77)
- 5.9 months for control (95% CI, 5.1 to 7.1)

- ORR
- 26.8% for triplet (95% CI, 21.1% to 33.1%)
- 19.5% for doublet (95% CI, 14.5% to 25.4%)
- 1.8% for control (95% CI, 0.5% to 4.6%)

- Grade ≥ 3 adverse events in 65.8%, 57.4%, and 64.2% for triplet, doublet, and control, respectively.

FDA approves encorafenib in combination with cetuximab for metastatic colorectal cancer with a BRAF V600E mutation

Share Tweet LinkedIn Email Print

On April 8, 2020, the Food and Drug Administration approved encorafenib (BRAFTOVI, Array BioPharma Inc.) in combination with cetuximab for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, detected by an FDA-approved test, after prior therapy.

Presented By: Laith Abushahin MBBS
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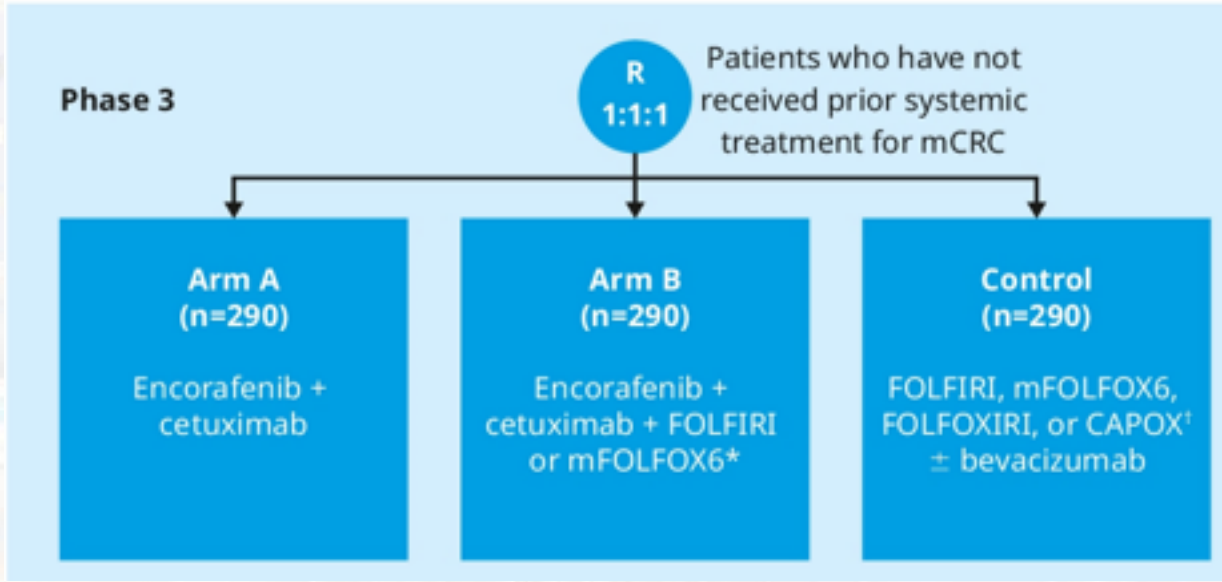
TEXAS ONCOLOGY

Colon Cancer

BRAF^{V600E} mutation:

BREAKWATER trial

870 patients



Kopetz et al. JCO.2022.40.4_suppl.TPS211

Colon Cancer

KRAS Mutated

G12C:

Sotarasib

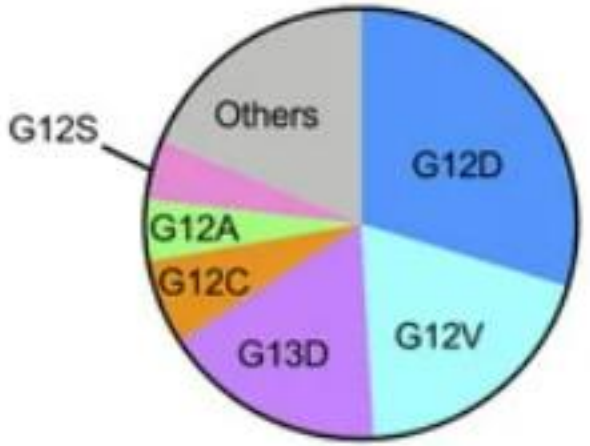
- CodeBreak 100: Modest activity in CRC ORR 9.7% PFS 4m, OS 10.2

Fakih et al. Lancet Oncol. 2022 Jan;23(1):115-124.

- CodeBreak 101: Sotorasib + Pmab: ORR 30% .

Annals of Oncology (2022) 33 (suppl_7): S136-S196. 10.1016/annonc/annonc1048

- CodeBreak 300: Phase 3 of the combination vs Lonsurf or Regorafenib. Primary end point is PFS



Sunaga et al. Cancers 2021, 13, 5956

8/3/2023: Amgen announced it met its primary end point

Colon Cancer

KRAS Mutated

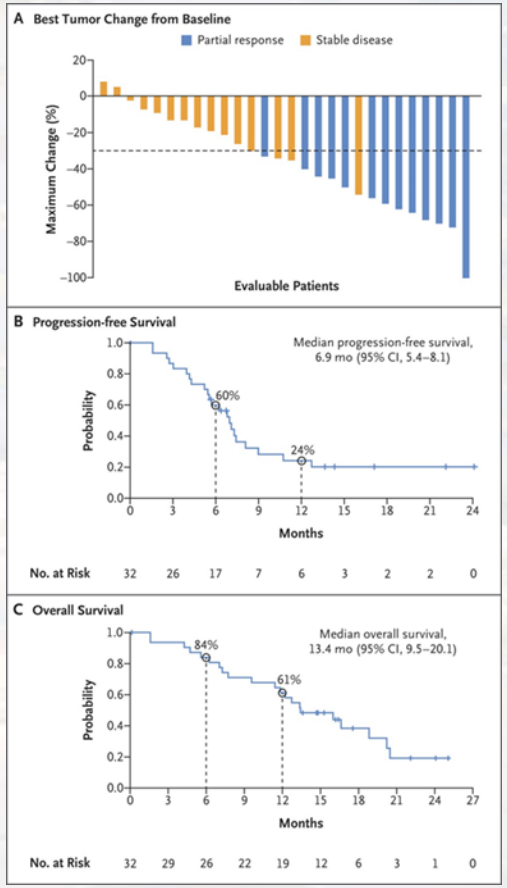
G12C:

Adagarsib

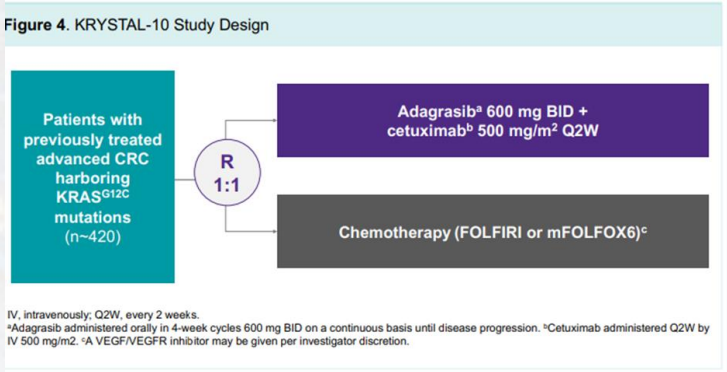
KRYSTAL-1 trial: Monotherapy:

ORR 19%, combination with cetuximab 46%

Yaeger et al. N Engl J Med. 2023 Jan 5;388(1):44-54.



KRYSTAL 10



Colon Cancer

KRAS Mutated

G12C:

Divarasib : more potent and selective than the other 2.

Phase 1 monotherapy in CRC: ORR 31%. Desai et. Al . ESMO 2022

Combination with Cetuximab : ORR 62%.

Ongoing INTRINSIC trial, some arms with combination+/- doublet

Presented By: Laith Abushahin MBBS
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Colon Cancer

KRAS Mutated

G12D:

MRTX 1133 trial nationally started late Macrh 2023.

Presented By: Laith Abushahin MBBS
@LAbushahin

TEXAS ONCOLOGY

Colon Cancer

HER 2 Amplification

- 2-4%. Higher among RAS RAF wild type*
  - RAS/RAF Wild type HER2+

Role for HER2 targeting

  - RAS mutated HER2 +

EGFR targeting?

* • *Djaballah et al. American Society of Clinical Oncology Educational Book 42 (May 17, 2022) 219-232.*

Colon Cancer

HER 2 Amplification

Trial	Population	Agent	N	Outcomes
HERACLES	RAS RAF Wild HER2+	Trastuzumab + lapatinib	27	ORR 28%
HERACLES-B	RAS RAF Wild HER2+	TDM-1+ Pertuzumab	31	ORR 9.7% PFS 4.1
MyPathway	HER2 +	Trastuzumab + Pertuzumab	57	ORR 32% OS 13 Wild vs 8.5 RAS mutated
DESTINY CRC01	RAS RAF Wild HER2+	Fam-Trastuzumab Deruxtecan	78	ORR 45% PFS 6.9 OS 15.5m
MOUNTAINEER	RAS RAF Wild HER2+	Tucatinib+ trastuzumab	54	ORR 38% OS: 24m

Presented By: Laith Abushahin MBBS
@LAbushahin

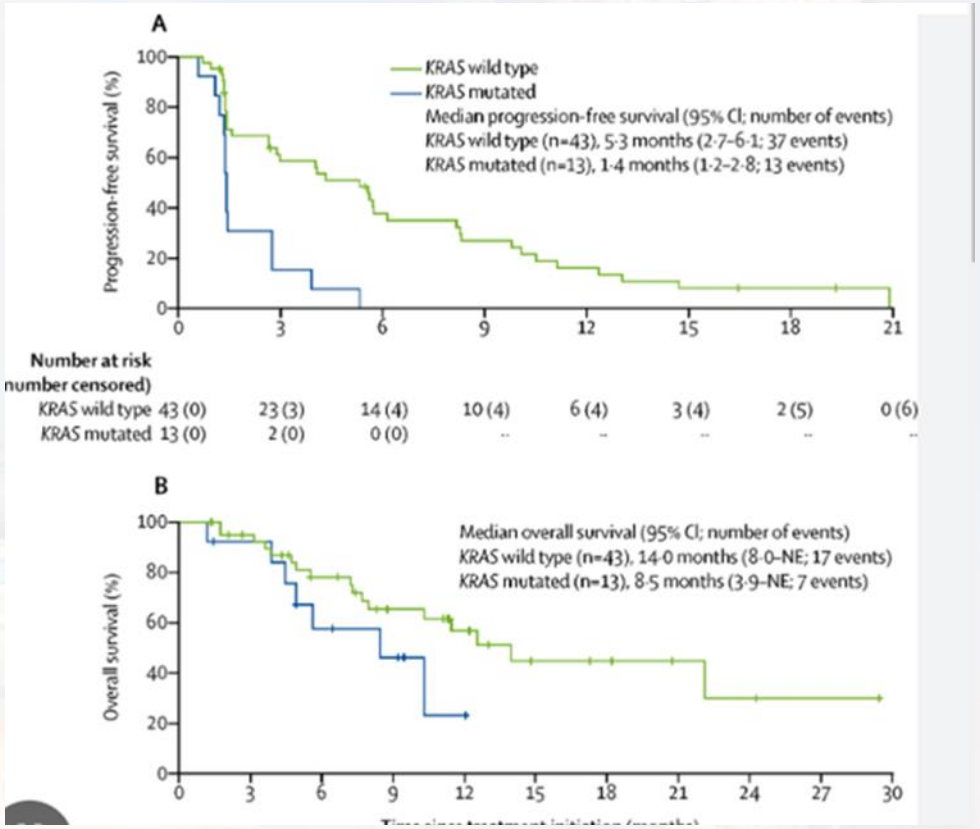
Colon Cancer

HER 2 Amplification

MyPathway trial:

- Phase 2a, multiple basket study.
- Pertuzumab and trastuzumab
- 57 Patients
- ORR (32%, 95% CI 20–45).

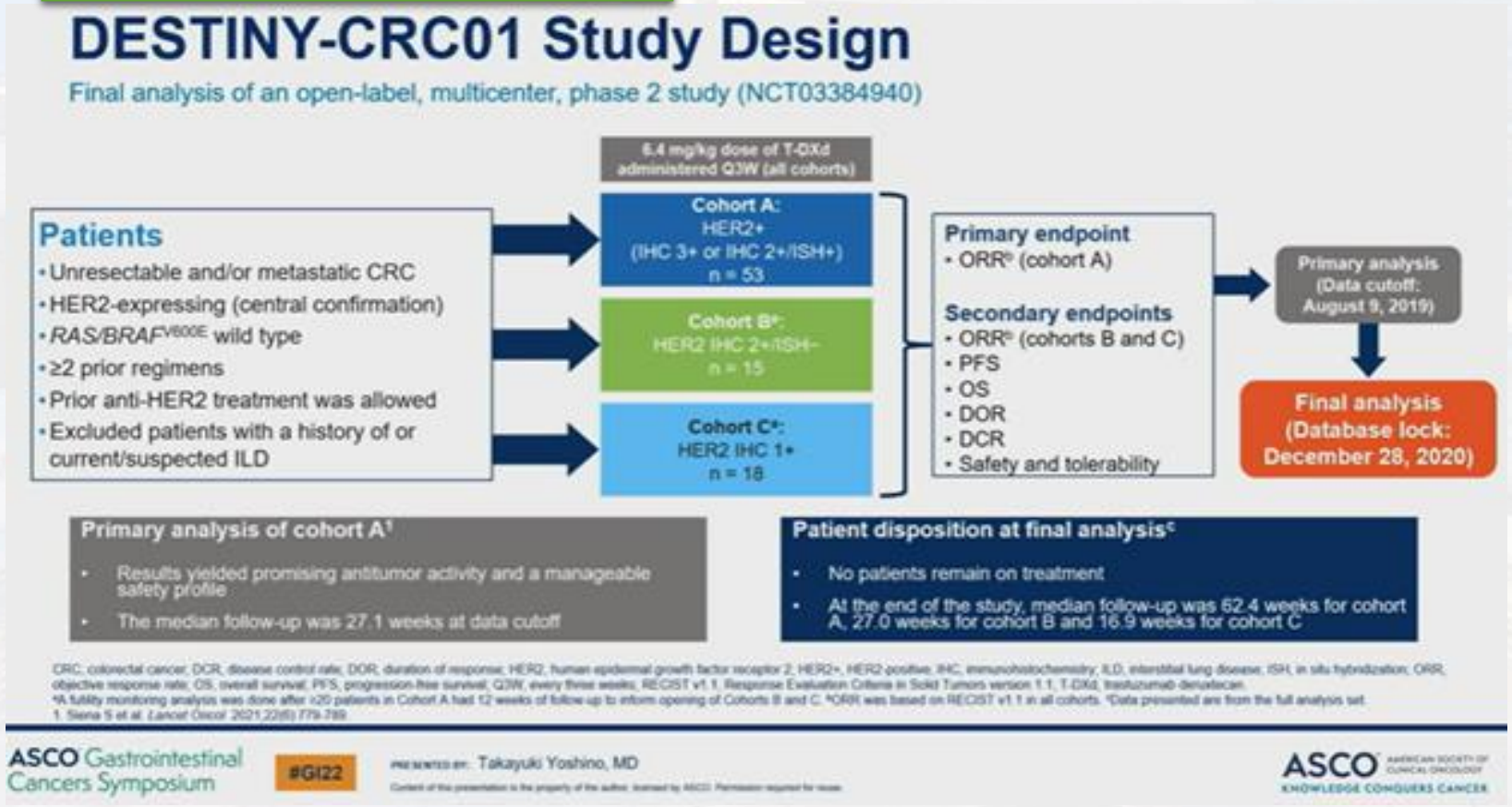
KRAS mutation associated with inferior outcomes



Meric-Bernstan et al. the lancet. VOLUME 20, ISSUE 4, P518-530, APRIL 2019

Colon Cancer

HER 2 Amplification



Texas Society of Clinical Oncology Annual Conference 2023

Presented By: Laith Abushahin MBBS
@LAbushahin

TEXAS ONCOLOGY

Colon Cancer

HER 2 Amplification

DESTINY CRC01

Efficacy Results

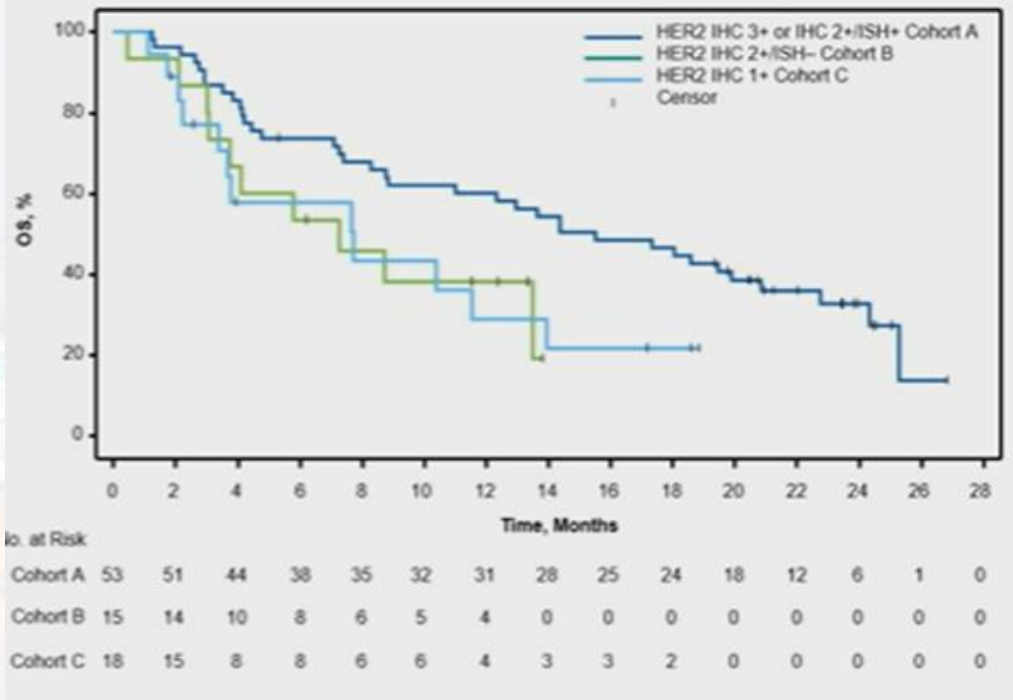
	HER2 IHC 3+ or IHC 2+/ISH+ Cohort A n = 53	HER2 IHC 2+/ISH– Cohort B n = 15	HER2 IHC 1+ Cohort C n = 18
Confirmed ORR by ICR, n (%)	24 (45.3) [95% CI, 31.6-59.6]	0 [95% CI, 0.0-21.8]	0 [95% CI, 0.0-18.5]
CR	0	0	0
PR	24 (45.3)	0	0
SD	20 (37.7)	9 (60.0)	4 (22.2)
PD	5 (9.4)	5 (33.3)	10 (55.6)
NE[a]	4 (7.5)	1 (6.7)	4 (22.2)
DCR, % (95% CI)	83.0 (70.2-91.9)	60.0 (32.3-83.7)	22.2 (6.4-47.6)
Median DOR (95% CI), months	7.0 (5.8-9.5)	NE (NE-NE)	NE (NE-NE)
Median treatment duration (95% CI), months	5.1 (3.9-7.6)	2.1 (1.4-2.6)	1.4 (1.3-1.5)
Median PFS (95% CI), months	6.9 (4.1-8.7)	2.1 (1.4-4.1)	1.4 (1.3-2.1)
Median OS (95% CI), months	15.5 (8.8-20.8)	7.3 (3.0-NE)	7.7 (2.2-13.9)

CR, complete response; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; NE, non-evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a]Patients were missing post-baseline scans.

ASCO Gastrointestinal Cancers Symposium #GI22 Presented by: Takayuki Yoshino, MD

ASCO KNOWLEDGE CONQUERS CANCER

Overall Survival



Presented By: Laith Abushahin MBBS
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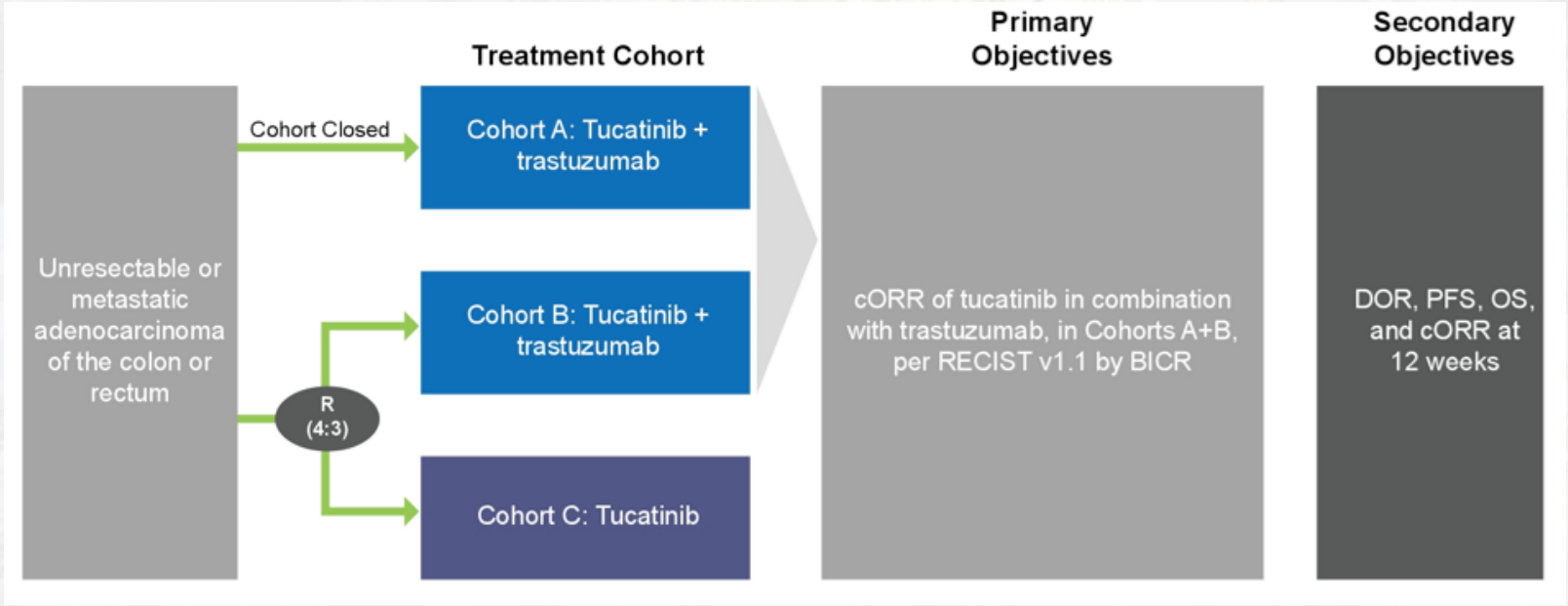
TEXAS ONCOLOGY

Colon Cancer

HER 2 Amplification

MOUNTINEER01



85 on combination
30 monotherapy

Strickler et al. J Clin Oncol 39, 2021 (suppl 3; abstr TPS153)

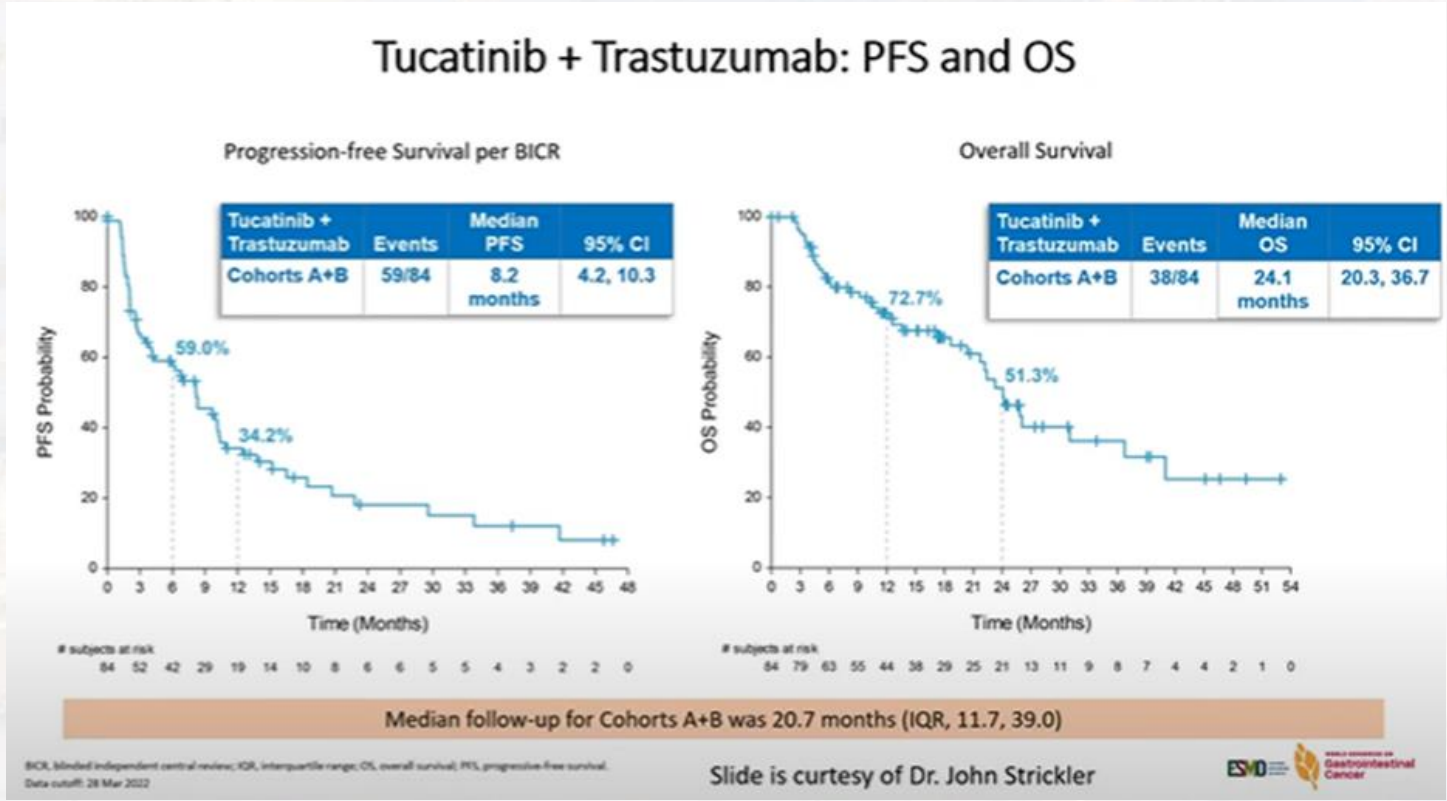
Colon Cancer

HER 2 Amplification

MOUNTINEER01

Primary endpoint:

ORR 38%



Colon Cancer

HER 2 Amplification

FDA grants accelerated approval to tucatinib with trastuzumab for colorectal cancer

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On January 19, 2023, the Food and Drug Administration (FDA) granted accelerated approval to tucatinib (Tukysa, Seagen Inc.) in combination with trastuzumab for RAS wild-type HER2-positive unresectable or metastatic colorectal cancer that has progressed following fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

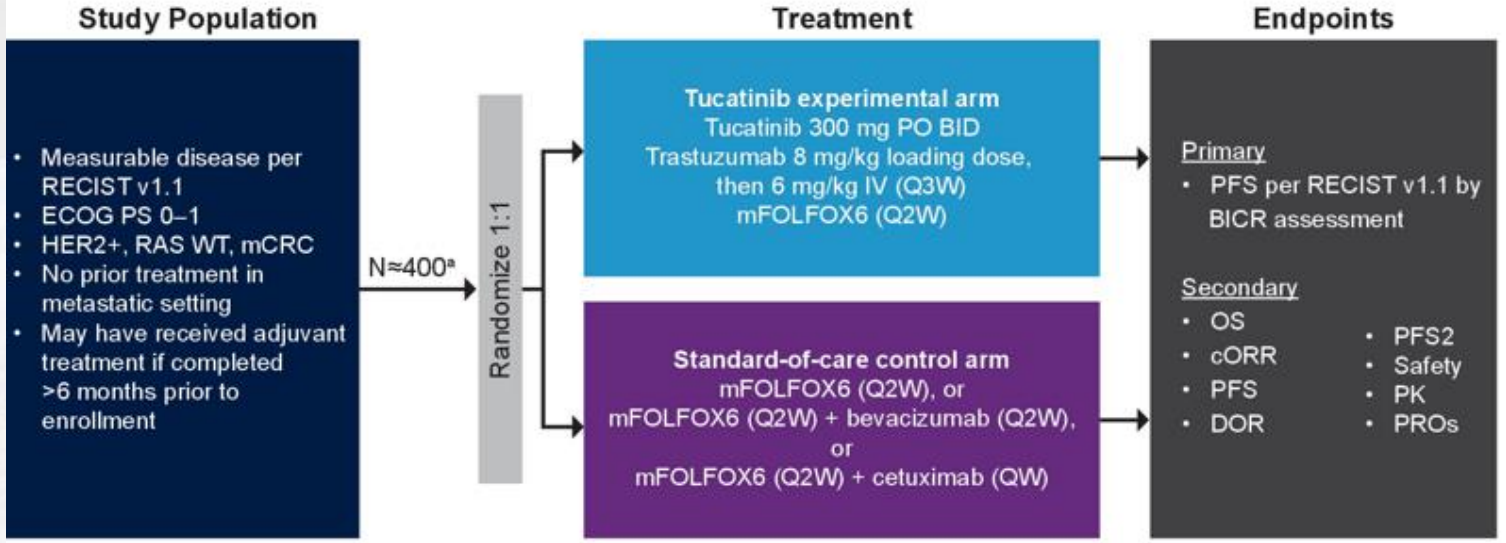
Presented By: Laith Abushahin MBBS
@LAbushahin

TEXAS ONCOLOGY

MOUNTINEER03

Study Design

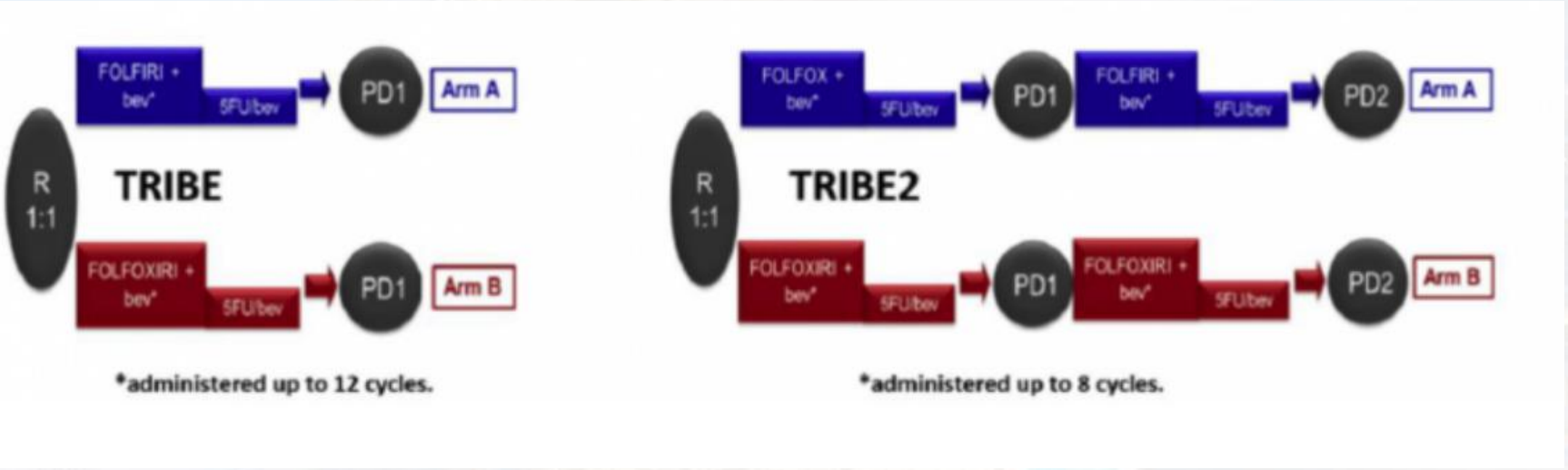
- MOUNTAINEER-03 (NCT05253651) is a global, open-label, randomized, phase 3 study of tucatinib with trastuzumab and mFOLFOX6 versus standard of care for the first-line treatment of HER2+ and RAS wild-type mCRC



a Stratification by both primary tumor location (left-sided versus all other) and liver metastases (presence or absence)

Bekaii-Saab et al. J Clin Oncol 41, 2023 (suppl 4; abstr TPS261)

Colon Cancer



- 1187 pts
- Right(35%) and left(65%)
- ~55% RAS mutated
- 8% BRAF mutated

MSI-H: Preferred 1st line Immunotherapy

Right colon+ Left colon RAS mutated MSS: Preferred 1st line FOLFOXIRI+ Bev or doublet + Bev

BRAF mutated: Preferred FOLFOXIRI + Bev or BREAKWATER trial

Left side wild type HER2 amplified: Doublet / triplet + Bev or MOUNTINEER 3 trial

Left side Wild type HER2 non amplified: FOLFOX + EGFRi

Presented By: Laith Abushahin MBBS
@LAbushahin

TEXAS ONCOLOGY

Possible new approval for refractory disease

Patient Eligibility

- Prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if *RAS* wild type, an anti-EGFR therapy
- Progression on, or intolerance to, TAS-102 and/or regorafenib
- Prior treatment with an immune checkpoint inhibitor or BRAF inhibitor if indicated

R 2:1

N=687

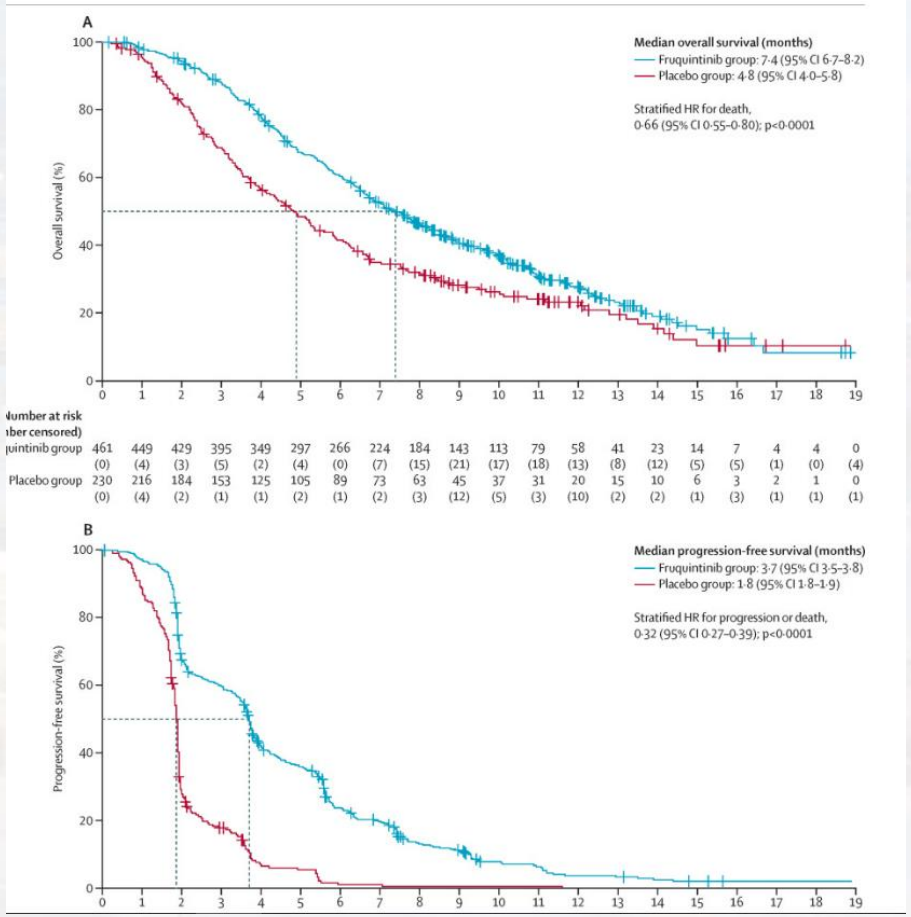
Fruquintinib 5 mg PO, QD (3 weeks on, 1 week off) + BSC (N=458)

Placebo 5 mg PO, QD (3 weeks on, 1 week off) + BSC (N=229)

Treatment until progression or unacceptable toxicity

Stratification Factors

- Prior therapy (TAS-102 vs regorafenib vs TAS-102 and regorafenib)
- *RAS* mutational status (wild-type vs mutant)
- Duration of metastatic disease (≤18 months vs >18 months)



The FDA has accepted and granted priority review to a new drug application (NDA) for fruquintinib with anticipated action date of 11/15/2023.

Thank you

Thank you