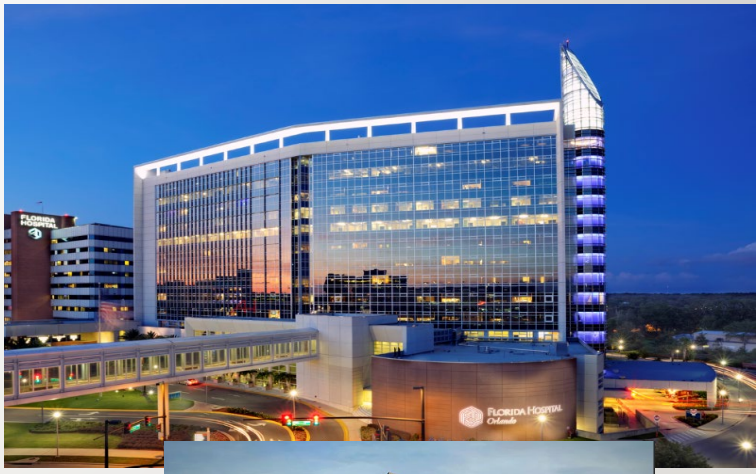
COLON CANCER:

NOVEL THERAPIES AND

FUTURE APPROACHES



Ahmed Zakari. MD
Associate Professor University of Central Florida, College of Medicine
Medical Director, GastroIntestinal Cancer Program
AdventHealth Cancer Institute

DISCLOSURES

BAYER : Speaker Program, Consulting

AMGEN : Speaker Program

LILLY : Speaker Program

INCYTE : speaker

Tumor

Location: Right Vs Left

Disease Burden: Resectable Vs Never resectable

Molecular Profile:

Kras/Nras..

Braf

Heur 2 Neu

MMR → Proficient Vs deficient

NTRK

Patient :

Age

Performance Status

Functionality

Desire

Long term Rx effects

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Colon Cancer

NCCN G[illegible]
Ta[illegible]

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

Patient appropriate for intensive therapy

INITIAL THERAPY[c]

- FOLFOX ± bevacizumab[d] → Progression → See COL-D (2 of 13)
- or CAPEOX ± bevacizumab[d] → Progression → See COL-D (2 of 13)
- or FOLFOX + (cetuximab or panitumumab)[e,f] (*KRAS/NRAS/BRAF* WT and left-sided tumors only) → Progression → See COL-D (2 of 13)
- or FOLFIRI[g] ± bevacizumab[d] → Progression → See COL-D (3 of 13)
- or FOLFIRI[g] + (cetuximab or panitumumab)[e,f] (*KRAS/NRAS/BRAF* WT and left-sided tumors only) → Progression → See COL-D (3 of 13)
- or FOLFOXIRI[g,h] ± bevacizumab[d] → Progression → See COL-D (4 of 13)
- or ([Nivolumab ± ipilimumab] or pembrolizumab [preferred][*])[i,j,k,l] (dMMR/MSI-H only)[e] → Progression → See COL-D (5 of 13)

Patient not appropriate for intensive therapy

- 5-FU ± leucovorin ± bevacizumab[d]
- or Capecitabine ± bevacizumab[d]
- or (Cetuximab or panitumumab)[e,f] (category 2B) (*KRAS/NRAS/BRAF* WT and left-sided tumors only)
- or (Nivolumab or pembrolizumab [preferred])[i,j,k,l] (dMMR/MSI-H only)[e]
- or Nivolumab + ipilimumab[i,j,k,l] (dMMR/MSI-H only)[e] (category 2B)
- or (Trastuzumab[m] + [pertuzumab or lapatinib])[n] or fam-trastuzumab deruxtecan-nxki[o] (HER2-amplified and *RAS and* BRAF WT)[e]

→ Progression

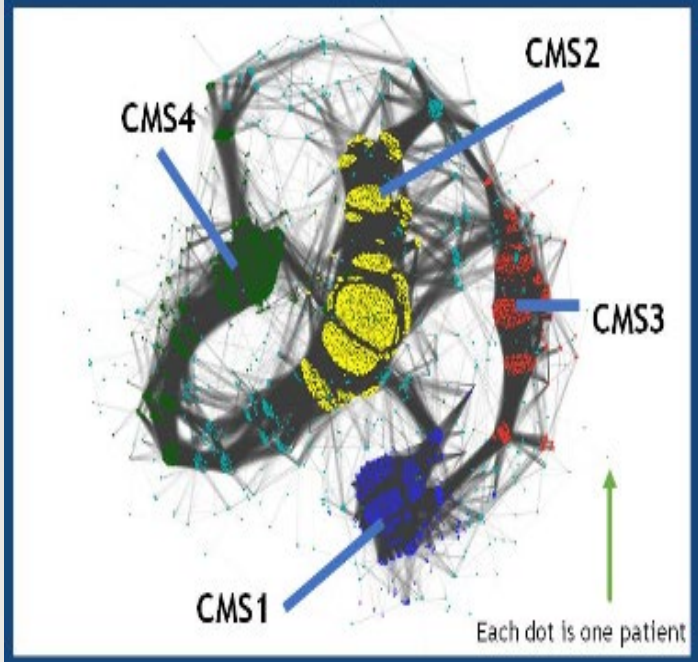
- Improvement in functional status → Consider initial therapy as above[p] or If previous fluoropyrimidine, see COL-D (5 of 13)
- No improvement in functional status → Best supportive care See NCCN Guidelines for Palliative Care

[*] Patients should be followed closely for 10 weeks to assess for response.

See footnotes on COL-D (7 of 13)

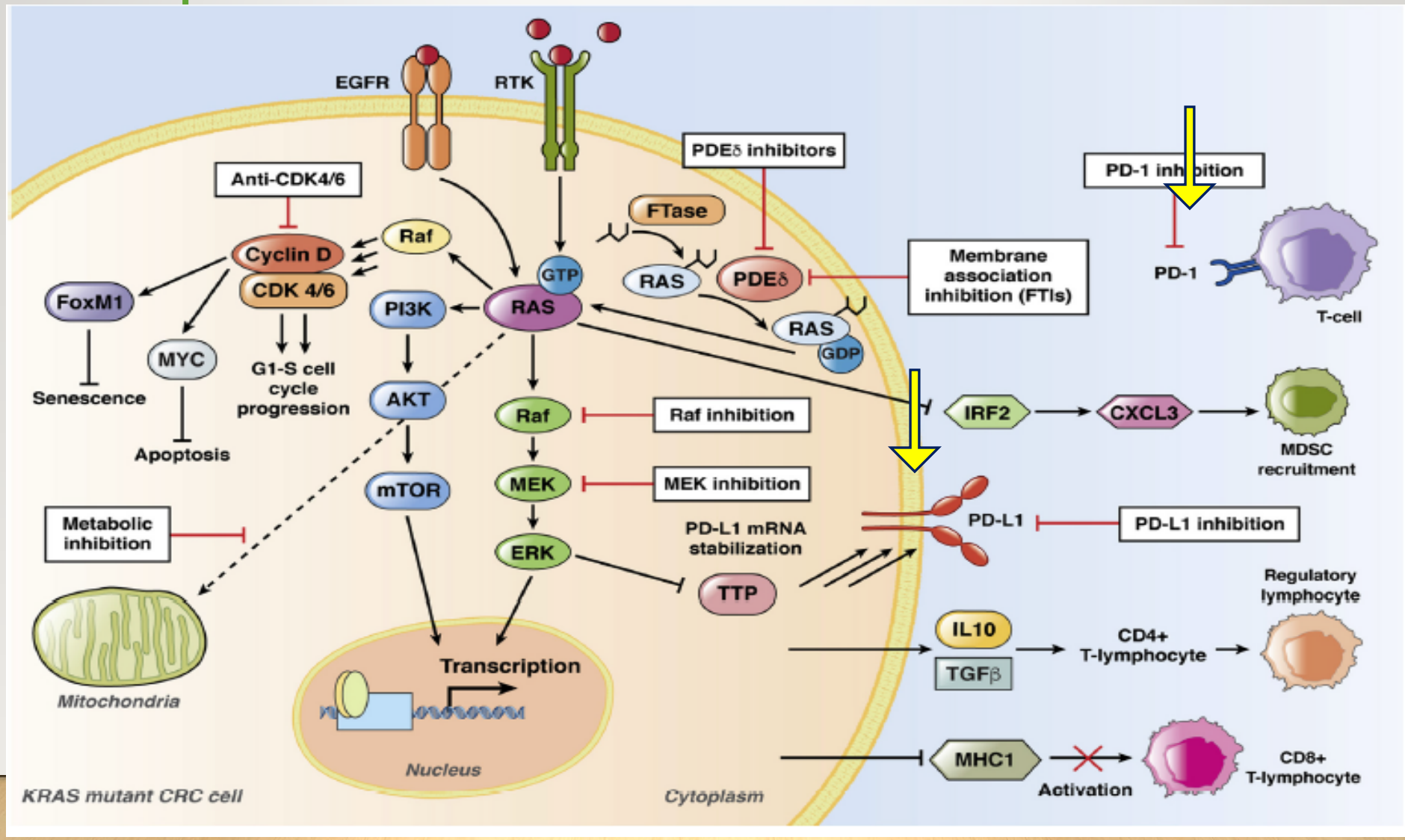
Personalizing Treatment Options in Met CRC

- **Right Sided versus Left Sided Met CRC**
- **Immunotherpay as First Line in dMMR met CRC :**
  - **Pembrolizumab**
  - **Combination Nivolumab / Ipilimumab**
- **Braf Mutant , Ras WT CRC**
- **Triplet Vs Doublet as induction Therapy**
- **Bevacizumab with FOLFOXIRI Vs Anti-EGFR with FOLFOXIRI in the 1stL**
- **FOLFOXIRI with Bilogic in the Braf-Mut met CRC**
- **Molecular markers as Predictors for Resectability**
- **Maintenance Therapy /De-Escalated therapy after induction**
- **Targeting Kras G12C Mutatant Met CRC**

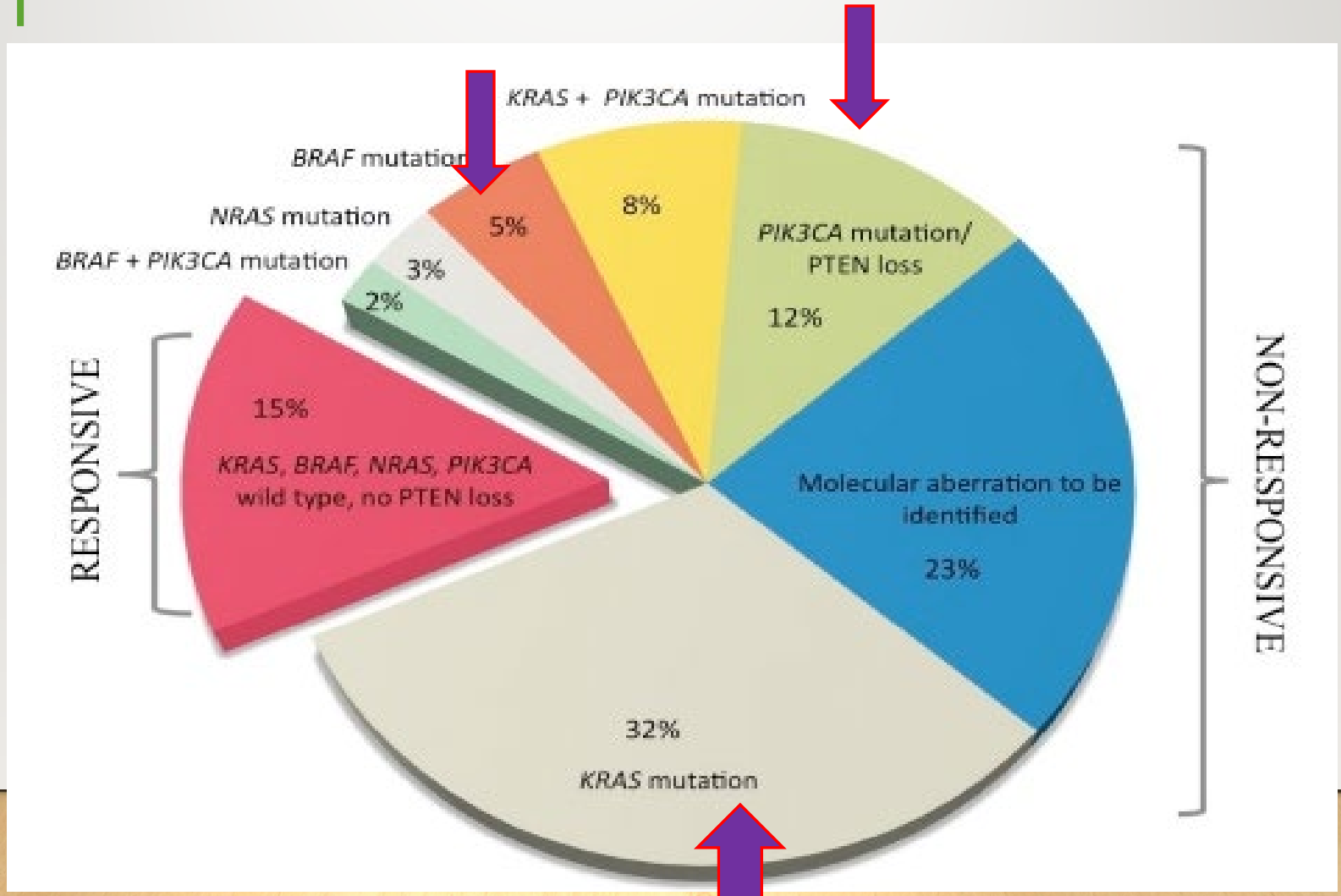


CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high Hypermutation	SCNA high	Mixed MSI status SCNA low, CIMP low	SCN high
BRAF mutations	*KRAS* mutations		
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration TGF beta activation Angiogenesis
Worse survival after relapse	Better survival after relaspe		Worse relapse-free and overall survival

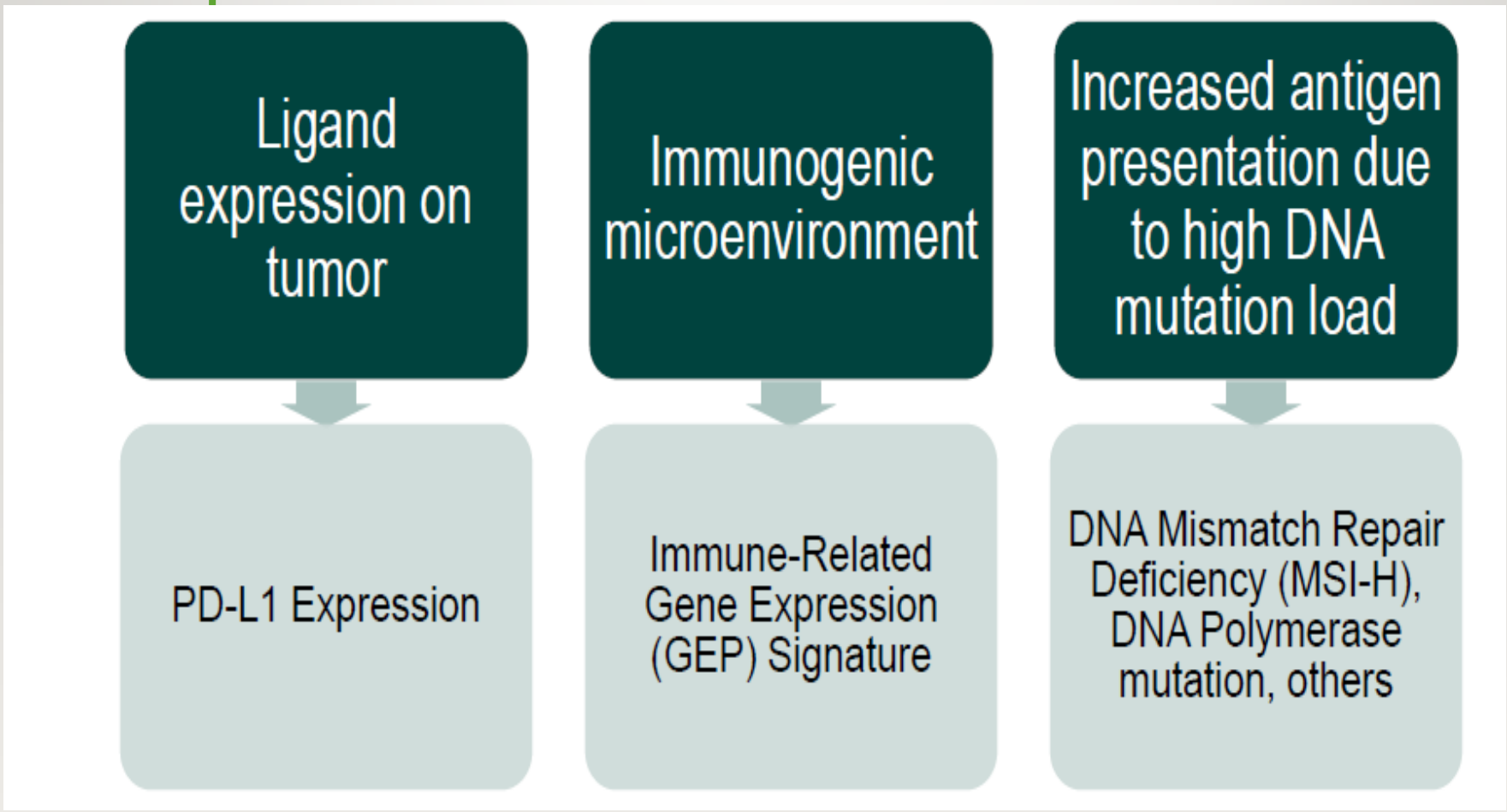
ONCOGENESIS PATHWAYS INVOLVED IN CRC



Potential Targeted Therapy



Biomarkers Identification



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 3, 2020 VOL. 383 NO. 23

Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Punt, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Elez, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Farooqui, P. Marinello, and L.A. Diaz, Jr., for the KEYNOTE-177 Investigators*

KEYNOTE 177 : Pembro vs chemo for CRC MSI-H

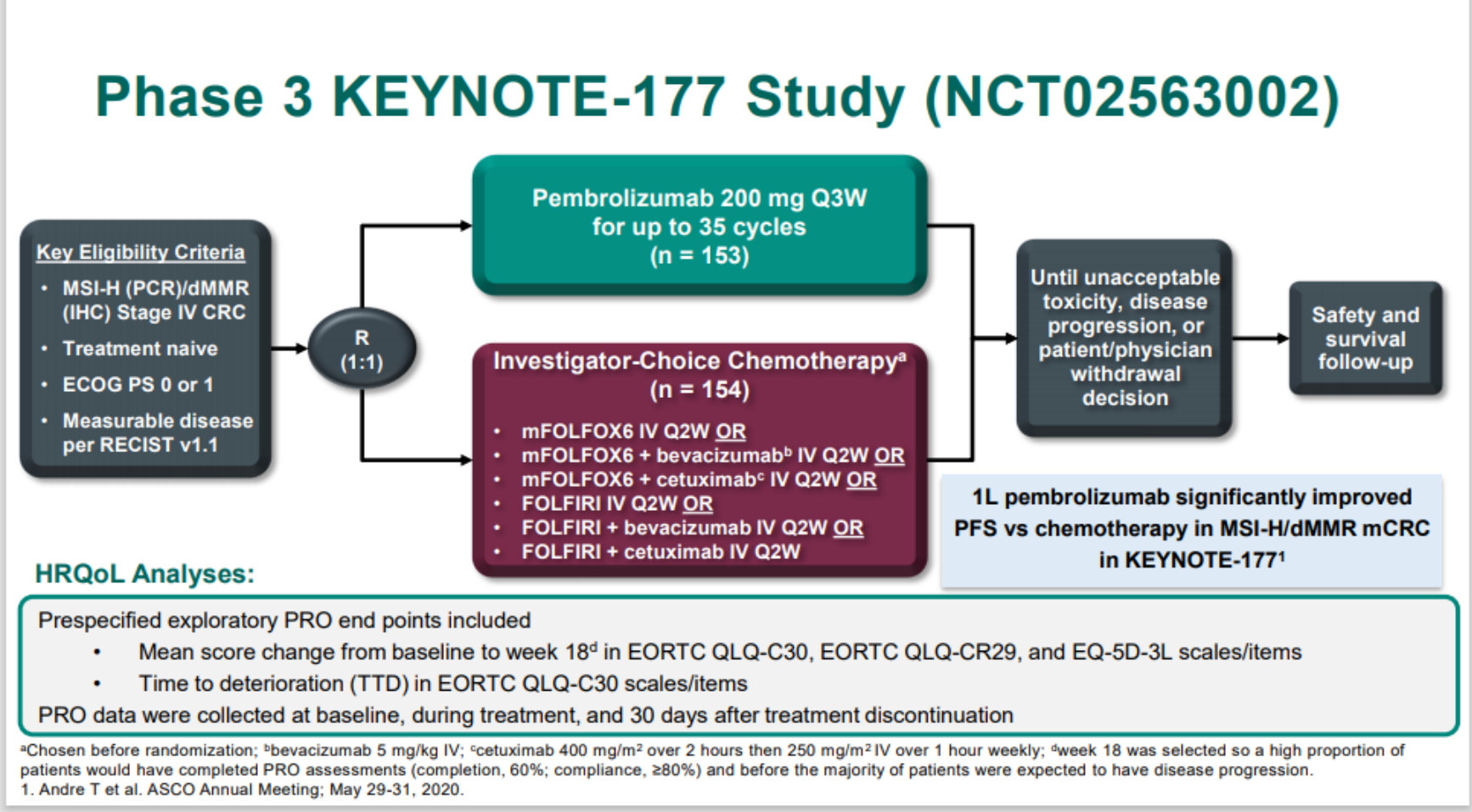
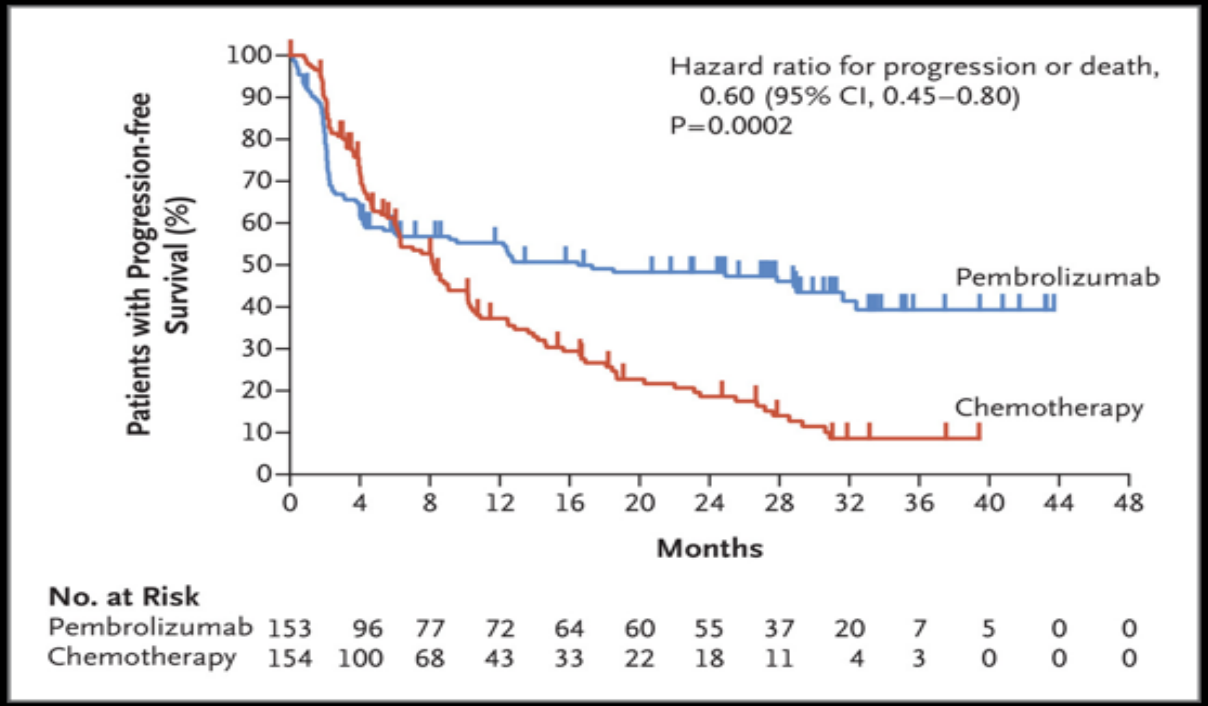


Table 2. Antitumor Activity in the Intention-to-Treat Population.

Variable	Pembrolizumab (N=153)	Chemotherapy (N=154)
Overall response*		
No. of patients	67	51
% (95% CI)	43.8 (35.8 to 52.0)	33.1 (25.8 to 41.1)
Best response — no. (%)†		
Complete response	17 (11.1)	6 (3.9)
Partial response	50 (32.7)	45 (29.2)
Stable disease	32 (20.9)	65 (42.2)
Progressive disease	45 (29.4)	19 (12.3)
Could not be evaluated or no assessment made‡	9 (5.9)	19 (12.3)
Median time to response (range) — mo	2.2 (1.8 to 18.8)	2.1 (1.7 to 24.9)
Median duration of response (range) — mo§	NR (2.3+ to 41.4+)	10.6 (2.8 to 37.5+)
Response duration of ≥24 months — %§	82.6	35.3

KEYNOTE 177 : Pembro vs chemo for CRC MSI-H

Progression-free Survival in Patients with MSI-H–dMMR Metastatic Colorectal Cancer.



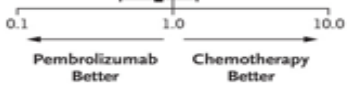
T André et al. N Engl J Med 2020;383:2207-2218.

The NEW ENGLAND JOURNAL of MEDICINE

KEYNOTE 177 :
Pembro vs chemo for CRC MSI-H

Progression-free Survival in Key Subgroups of Patients with MSI-H–dMMR Metastatic Colorectal Cancer.

Subgroup	No. of Events/No. of Patients	Hazard Ratio (95% CI)
All patients	195/307	0.60 (0.45–0.80)
Age		
≤70 yr	132/217	0.52 (0.37–0.75)
>70 yr	63/90	0.77 (0.46–1.27)
Sex		
Male	91/153	0.59 (0.38–0.90)
Female	104/154	0.58 (0.39–0.87)
ECOG performance-status score		
0	90/159	0.37 (0.24–0.59)
1	105/148	0.84 (0.57–1.24)
Geographic region		
Asia	28/48	0.65 (0.30–1.41)
Western Europe or North America	146/222	0.62 (0.44–0.87)
Rest of the world	21/37	0.40 (0.16–0.98)
Stage		
Recurrent metachronous	87/154	0.53 (0.34–0.82)
Newly diagnosed	108/153	0.70 (0.47–1.04)
BRAF		
BRAF wild type	78/131	0.50 (0.31–0.80)
BRAF^{V600E}	51/77	0.48 (0.27–0.86)
KRAS or *NRAS*		
All wild type	95/151	0.44 (0.29–0.67)
KRAS or *NRAS* mutant	51/74	1.19 (0.68–2.07)
Site of primary tumor		
Right	137/209	0.54 (0.38–0.77)
Left	50/88	0.81 (0.46–1.43)



T André et al. N Engl J Med 2020;383:2207-2218.

The NEW ENGLAND JOURNAL of MEDICINE

TARGETING BRAF IN mCRC

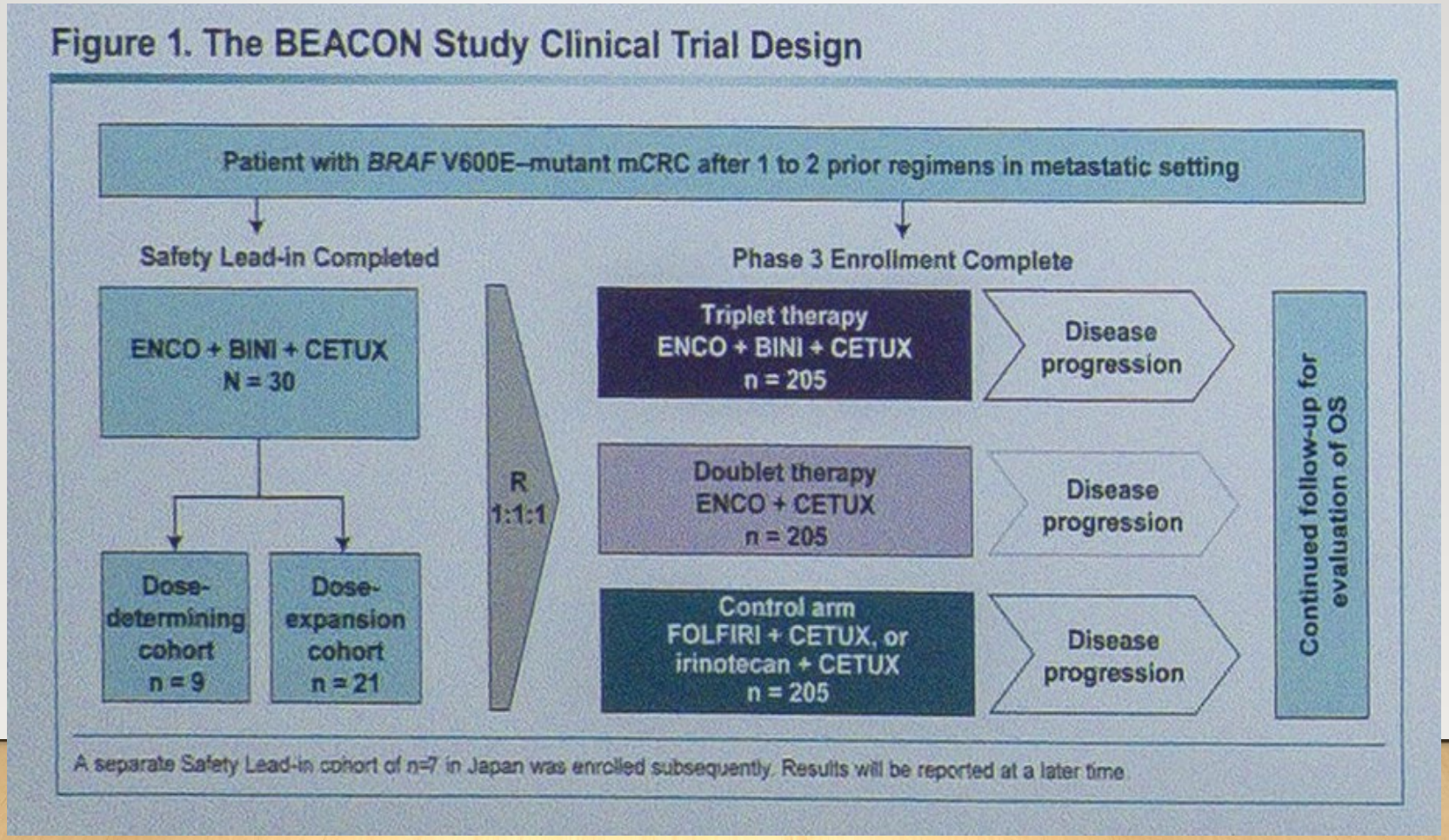
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

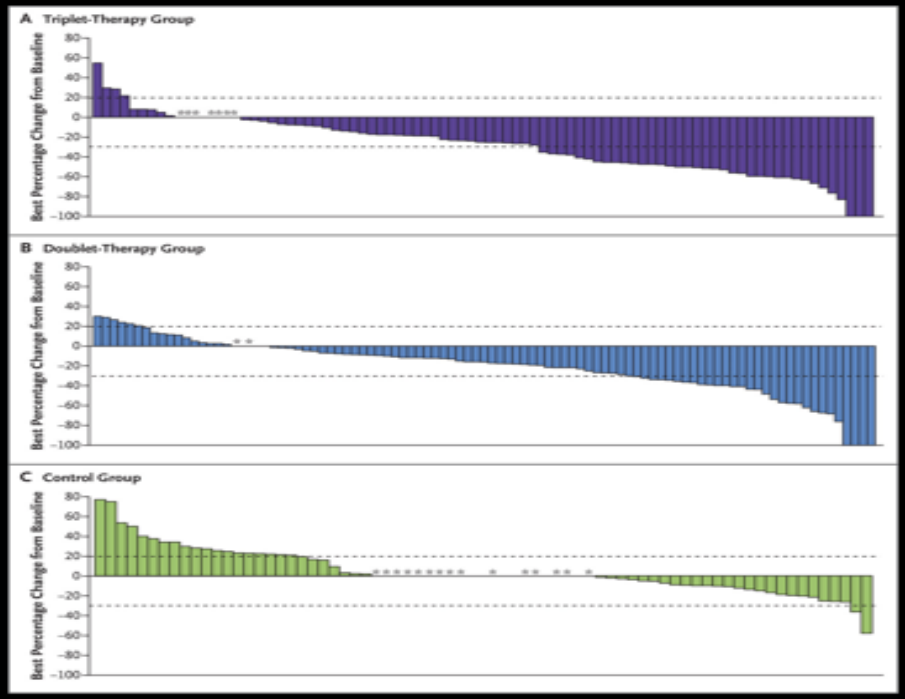
S. Kopetz, A. Grothey, R. Yaeger, E. Van Cutsem, J. Desai, T. Yoshino, H. Wasan, F. Ciardiello, F. Loupakis, Y.S. Hong, N. Steeghs, T.K. Guren, H.-T. Arkenau, P. Garcia-Alfonso, P. Pfeiffer, S. Orlov, S. Lonardi, E. Elez, T.-W. Kim, J.H.M. Schellens, C. Guo, A. Krishnan, J. Dekervel, V. Morris, A. Calvo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

TARGETING BRAF IN mCRC
(BEACON Trial)



TARGETING BRAF IN mCRC (BEACON Trial)

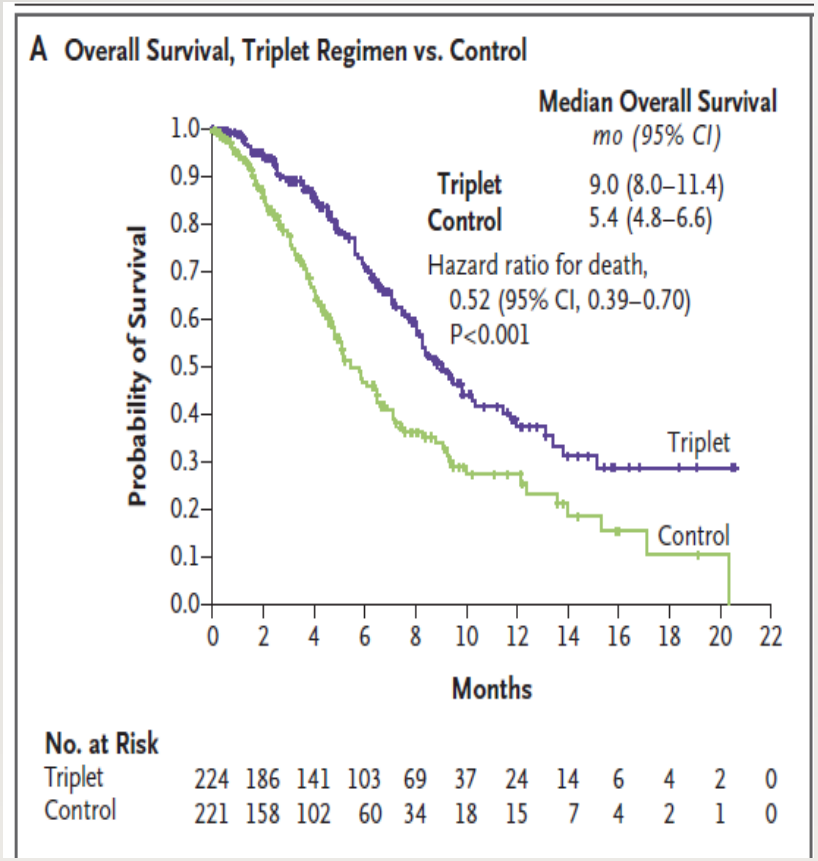
Best Percentage Change in Size of Target Lesions.

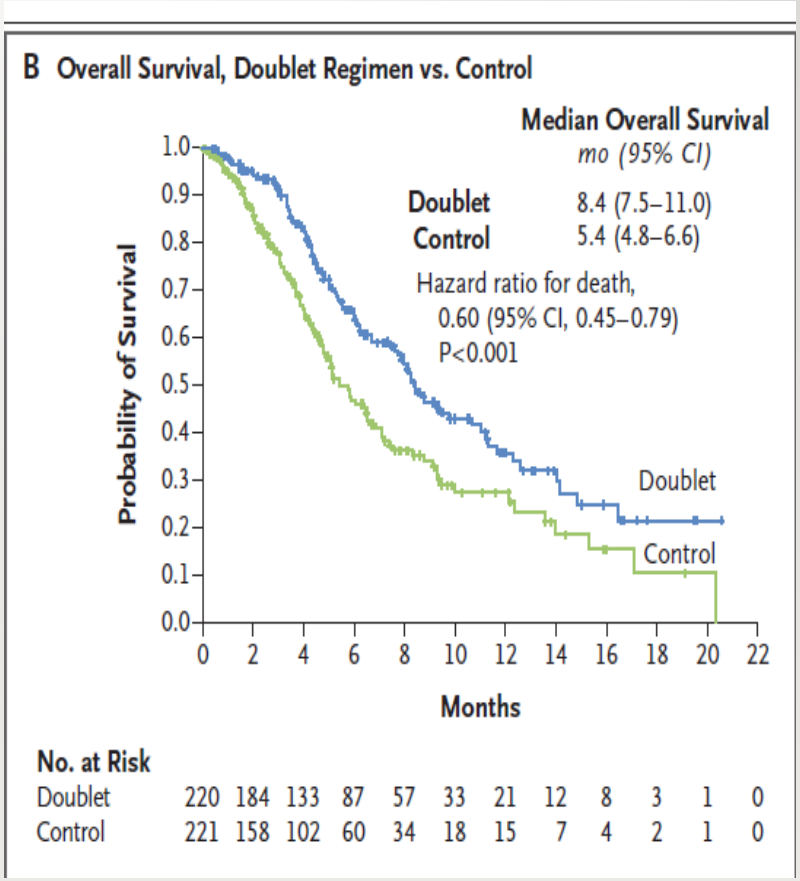


S Kopetz et al. N Engl J Med 2019;381:1632-1643.

The NEW ENGLAND JOURNAL of MEDICINE

TARGETING BRAF IN mCRC (BEACON Trial)





Personalized Treatment Options for mCRC

ASCO 2021

Methods

✓ Study Design

RAS wild-type colorectal cancer
Previously untreated

R

1:1

Stratification factors
- Primary tumor site (right or left)
- History of postoperative adjuvant chemotherapy
- ECOG PS (0, 1)

m-FOLFOXIRI + Cetuximab

m-FOLFOXIRI + Cetuximab combination therapy (up to 12 courses)

- Cetuximab	400 mg/m² (1course Day1)
	250 mg/m² (Day1, 8)
- Irinotecan	150 mg/m² (Day1)
- Oxaliplatin	85 mg/m² (Day1)
- l-Levofolinate	200 mg/m² (Day1)
- 5-FU infusion	2,400 mg/m² (Day1-3)

5-FU + levofolinate + cet combination therapy

- Cetuximab	250 mg/m² (Day1 , 8)
- l-Levofolinate	200 mg/m² (Day1)
- 5-FU infusion	2,400 mg/m² (Day1-3)

m-FOLFOXIRI + Bevacizumab

m-FOLFOXIRI + Bevacizumab combination therapy (up to 12 courses)

- Bevacizumab	5 mg/kg (Day1)
- Irinotecan	150 mg/m² (Day1)
- Oxaliplatin	85 mg/m² (Day1)
- l-Levofolinate	200 mg/m² (Day1)
- 5-FU infusion	2,400 mg/m² (Day1-3)

5-FU + levofolinate + bev combination therapy

- Bevacizumab	5 mg/kg (Day1)
- l-Levofolinate	200 mg/m² (Day1)
- 5-FU infusion	2,400 mg/m² (Day1-3)

Depth of Response <primary endpoint>

✓ By Central Review

	m-FOLFOXIRI + Cetuximab (n=158*)	m-FOLFOXIRI + Bevacizumab (n=162*)
Median (Range)	57.4% (-15.0-100)	46.0% (-0.6-100)
Mean (95%CI)	55.8% (51.9-59.7)	47.3 % (44.1-50.5)
Standard Deviation (95%CI)	25.06 (22.6-28.2)	20.53 (18.5-23.0)
t-test by welch	*p*=0.0010	

*DpR was analyzed in the per-protocol set population.

Depth of Response by tumor location

Tumor location	Left		Right	
	m-FOLFOXIRI + Cetuximab (n=131)	m-FOLFOXIRI + Bevacizumab (n=137)	m-FOLFOXIRI + Cetuximab (n=27)	m-FOLFOXIRI + Bevacizumab (n=25)
Median (Range)	60.3 (-9.8-100)	46.1 (3.2-100)	50.0 (-15.0-100)	41.2 (-0.6-85.6)
Mean (95%CI)	57.5 (53.2-61.7)	48.2 (44.9-51.5)	47.7 (37.3-58.1)	42.5 (32.1-52.9)
Standard Deviation (95%CI)	24.59 (21.93-27.99)	19.55 (17.48-22.18)	26.19 (20.63-35.90)	25.17 (19.65-35.02)
t-test by welch	p=0.0007		p=0.4663	

JACCRO CC-13: Primary Endpoint Met

Depth of Response <primary endpoint>

✓ By Central Review

	m-FOLFOXIRI + Cetuximab (n=158*)	m-FOLFOXIRI + Bevacizumab (n=162*)
Median (Range)	57.4% (-15.0-100)	46.0% (-0.6-100)
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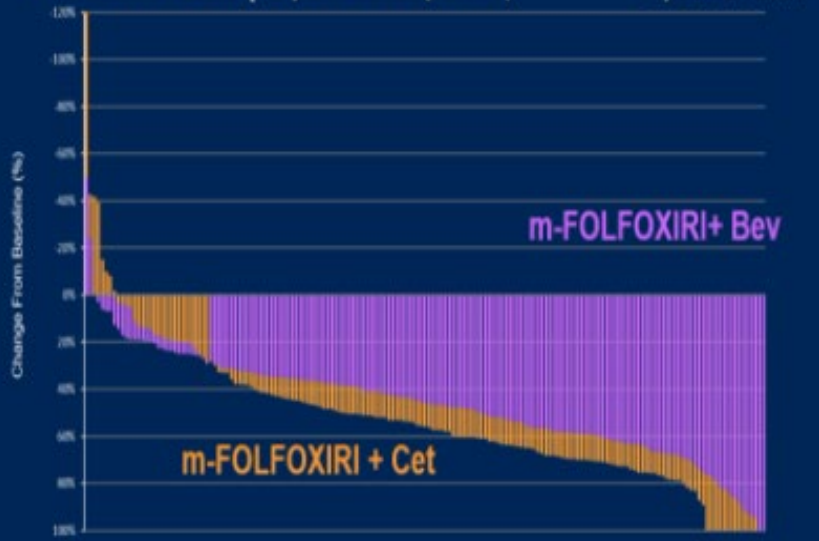
t-test by welch	p=0.0010	

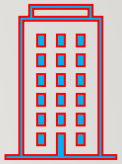
*DpR was analyzed in the per-protocol set population.

Waterfall Plot (Depth of Response)

✓ By Central Review

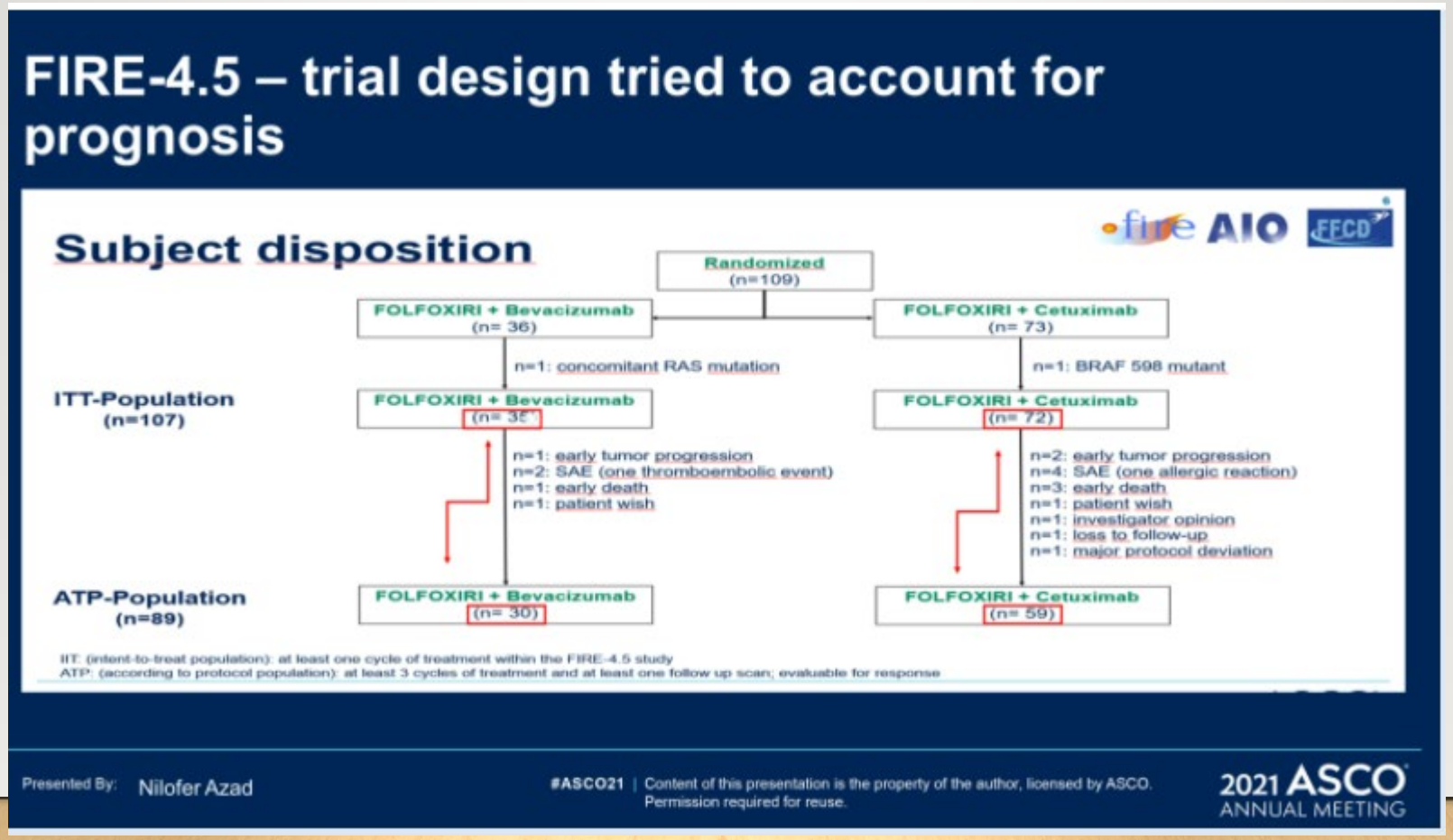


Personalized Treatment Options for mCRC ASCO 2021



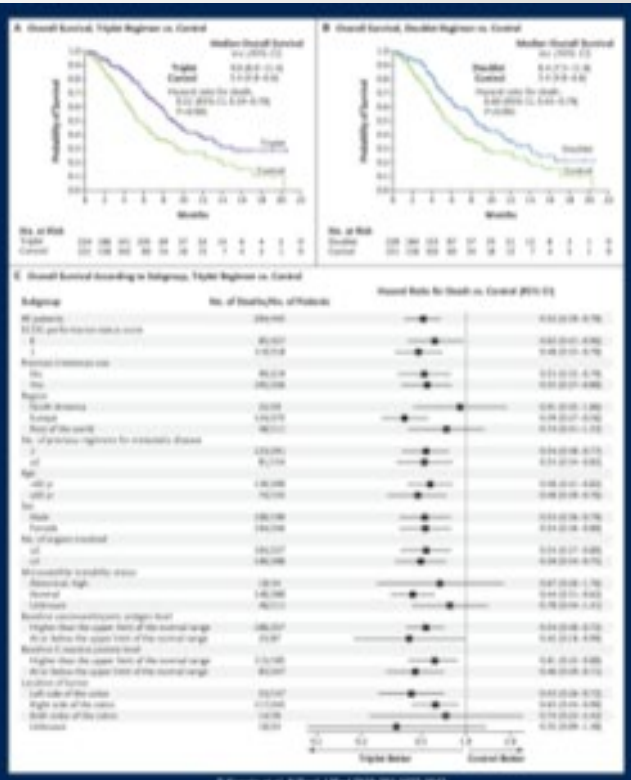
- **FOLFOXIRI / Cetuximab is better tolerated as First Line therapy in the fit population with mCRC**
- **FOLFOXIRI Cetuximab is NO Better than FOLFOXIRI/Bev**
- **Right sided mCRC do better with Bevacizumab/FOLFOXIRI**
- **Pending Final data in terms PFS & OS Bev Vs Cetux and Folfirinox**

Is FOLOFOXIRI / Biologic the best Option for Braf Mutated mCRC



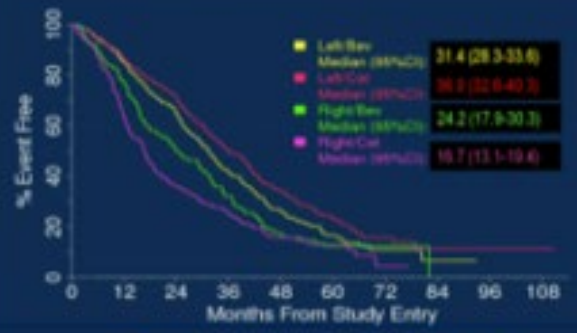
Braf Mutated m CRC Out Comes

- Poor prognosis with OS ~18 months compared to 30-36 months for BRAF WT patients
- Right side predominance
- 1/3+ concordance with MSI instability
- Enriched for CMS1 – poor prognostic phenotype
- EFGR + BRAFi has activity over IRI+EGFRi regimen based on the BEACON study in pretreated CRC



- Poor prognosis with OS ~18-24 months compared to 30-36 months for CRC broadly
- Enriched for CMS1 – poor prognostic phenotype
- EGFRi ineffective as the biological agent for first line therapy for right-sided disease compared to bevacizumab

80405 (*KRAS* WT): Overall Survival by Sidedness and Biologic



Sidedness: Prognostic and Predictive

KRAS wt N = 1025	R-sided Median OS (mo)	L-sided Median OS (mo)	HR (95% CI) (adjusted*)	P (adjusted*)
All pts	19.4	33.3	1.55 (1.32,1.82)	P<0.0001
Cet	16.7	30.0	1.87 (1.48, 2.32)	P<0.0001
Bev	24.2	31.4	1.32 (1.08, 1.60)	P=0.01

BIOLOGIC	SIDE OF PRIMARY	HR 95% CI	P (adjusted*)
Any biologic OS and PFS	Cetux + Bev: left Cetux + Bev: right	1.53 (1.13, 2.08)	P_{int}=0.005
Cetux + Bev OS	Left	0.817 (0.65, 0.96)	p=0.018
Cetux + Bev OS	Right	1.259 (0.98, 1.63)	p=0.065

Metastectomy for mCRC and Molecular Biomarkers

Metastasectomy and LAT provides hope in mCRC

RAS and *BRAF* status matters

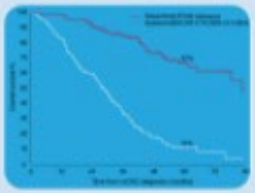
Core message

ASSESS RESECTABILITY REPEATEDLY

Resectable or converted, and fit should have resection or LAT

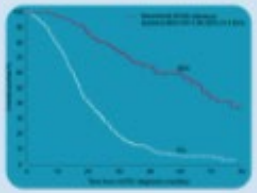
RAS&BRAF wildtype

More males
Most left colon & rectum
More liver mets



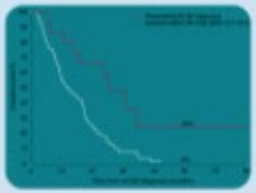
RAS mutant

More males
More left sided & rectum
More lung mets



BRAF mutant

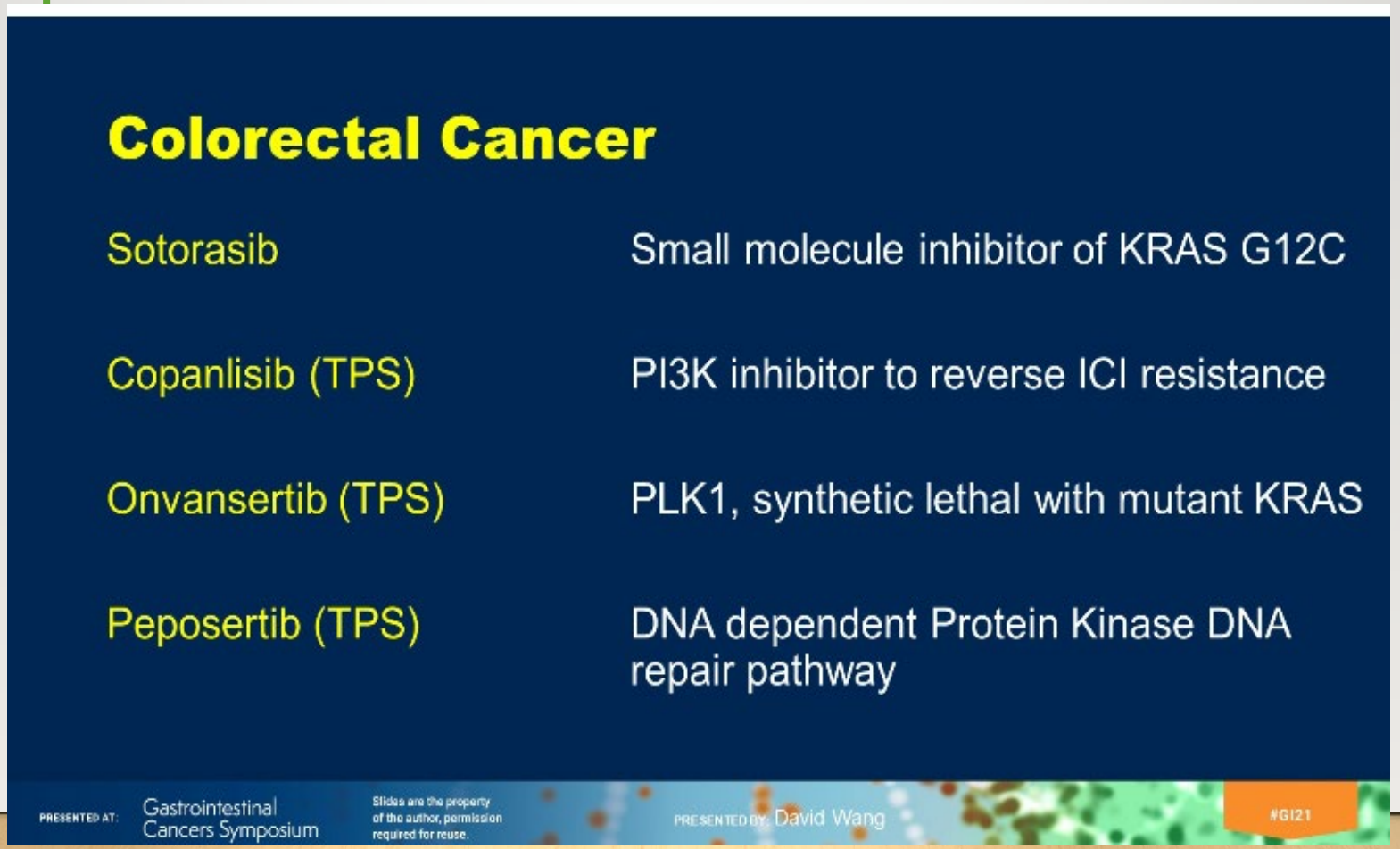
More females
Poorer ECOG PS
Most right colon
Peritoneal mets



Future directions for research

RAS and *BRAF* status should be integrated in baseline demographics of resected and in risk scores

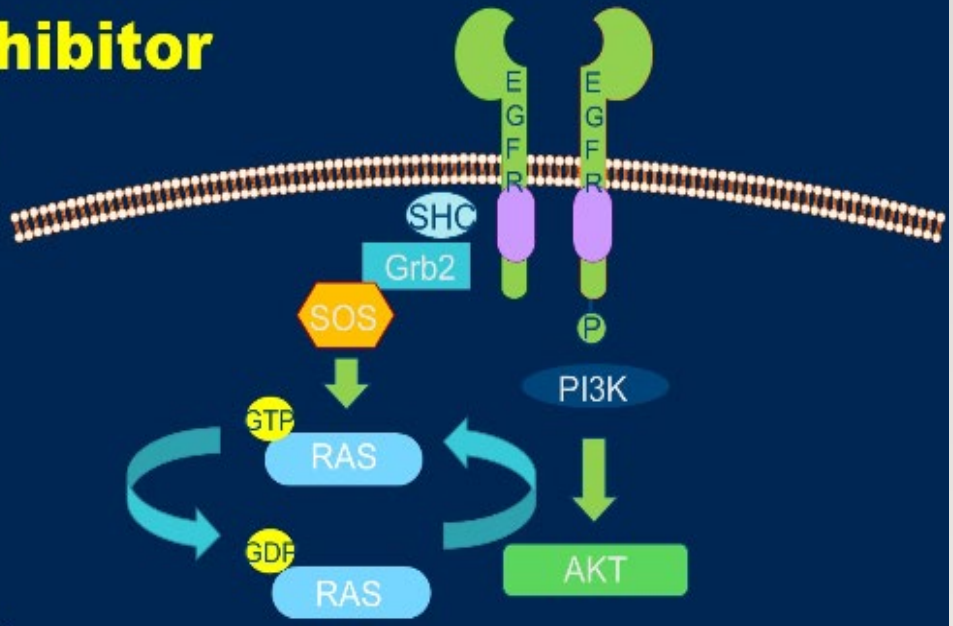
Novel targeted Therapy for CRC



TARGETING KRAS

KRAS G12C Inhibitor

- Sotorasib (AMG510) is oral inhibitor of KRAS G12C mutant
- KRAS G12C favors KRAS in active GTP-bound state
- Sotorasib maintains mutant KRAS in inactive GDP-bound state

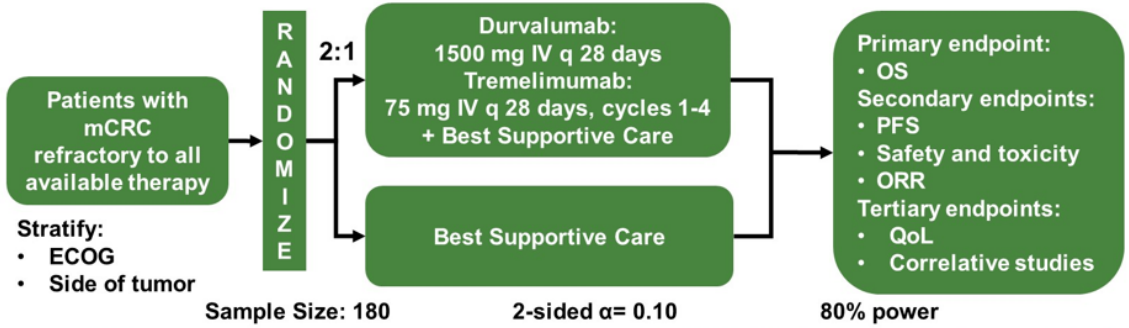


Fakih et al, ASCO 2020 ab4018

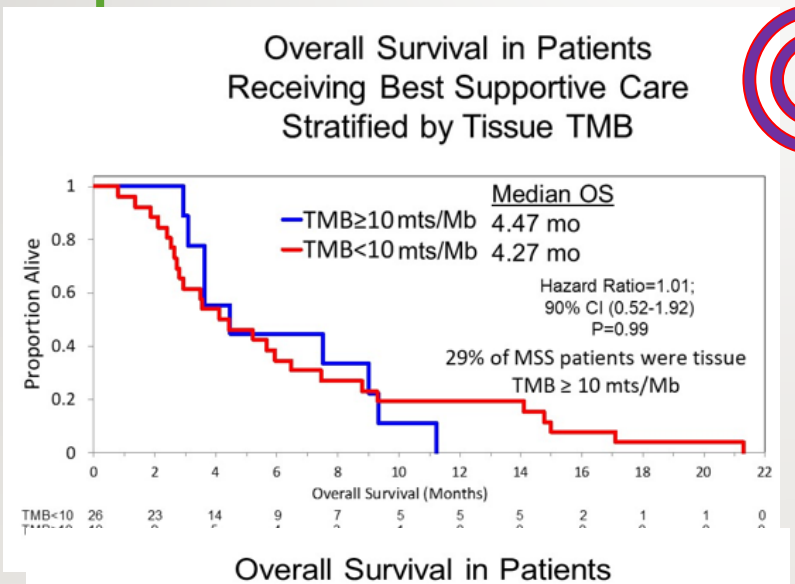
Canadian Cancer Trials Group
A national program of the Canadian Cancer Society

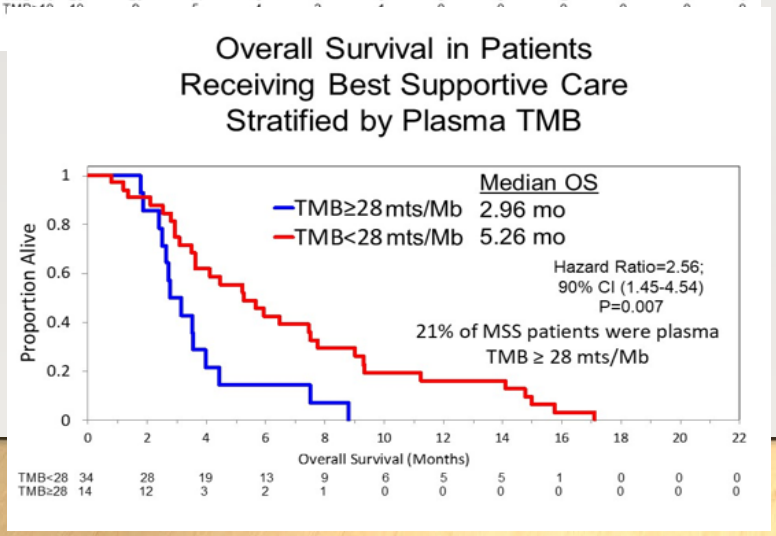
Tissue and plasma tumor mutation burden (TMB) as predictive biomarkers in the CCTG CO.26 trial of durvalumab + tremelimumab versus best supportive care in metastatic colorectal cancer

- We compared tissue and plasma TMB as predictive biomarkers for immunotherapy benefit in patients with MSS mCRC from the CO.26 trial
  - Tissue TMB: derived from exomes (SureSelect All Exon v6) of archival samples and followed TMB Harmonization Project Guidelines with a 32.1 Mb TMB denominator
  - Plasma TMB: utilized the GuardantOMNI™ 500 gene, 2.1 Mb ctDNA panel

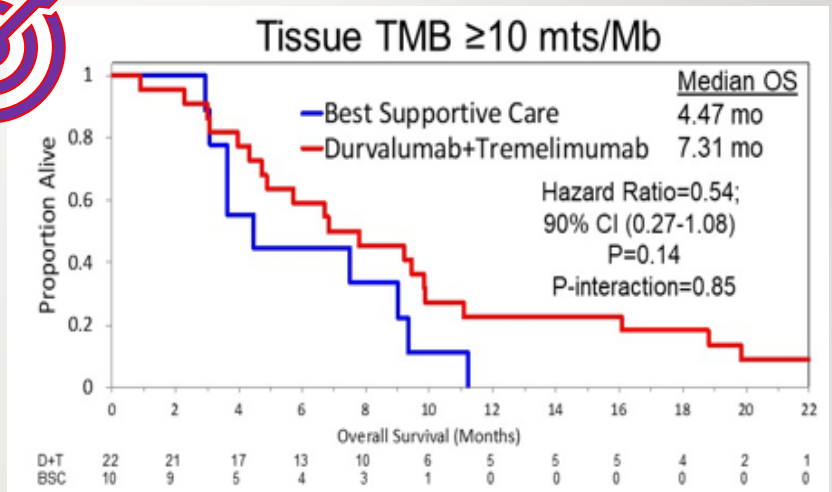


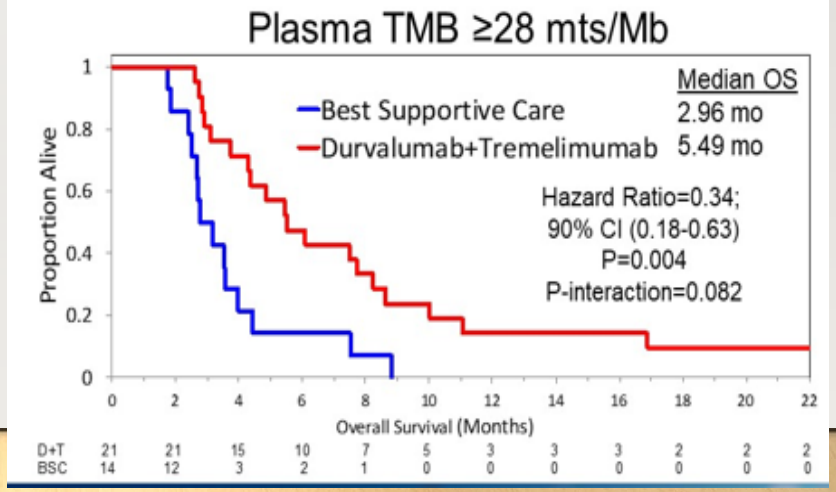
OS : WITH BSC





OS : DURVA/TREME





TRUSTY study design

TRifluridine/tipiracil in Second-line sTudY

Non-inferiority

Prior to randomization, either 5-FU or S-1 was declared by each investigator when allocated FP+IRI+BEV.

mCRC in 2nd-line

- Progression on 1st-line treatment
  - Fluoropyrimidine (5-FU/*l*-LV, Capecitabine, S-1)
  - Oxaliplatin
  - BEV or anti-EGFR antibody
- ECOG PS: 0 or 1
- Age: 20 years or older

R 1:1

n=524

Fluoropyrimidine+Irinotecan+BEV (FP+IRI+BEV)

FOLFIRI + BEV (*q2w*), **S-1 + irinotecan + BEV** (*q3w, q4w*) selected on an individual patient basis

FTD/TPI+BEV

BEV: 5 mg/kg IV d1, d15
FTD/TPI : 35 mg/m^2 bid orally d1-5 and d8-12 *q4w*

Primary endpoint

- Overall survival (OS)

Secondary endpoints

- Progression-free survival (PFS)
- Time to treatment failure (TTF)*
- Response rate (RR)
- Disease control rate (DCR)
- Subsequent treatment
- Time to post-study treatment failure (TTF2)
- Quality of life (QOL)*
- Adverse events (AE)

*not included in this presentation.

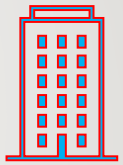
Stratification factors

- *RAS* status (Wild-type vs. Mutant)
- Primary tumor location (Left-sided vs. Right-sided)
- 1st-line treatment with molecularly targeted drug (BEV vs. Anti-EGFR antibody†)

†*RAS* Wild-type only

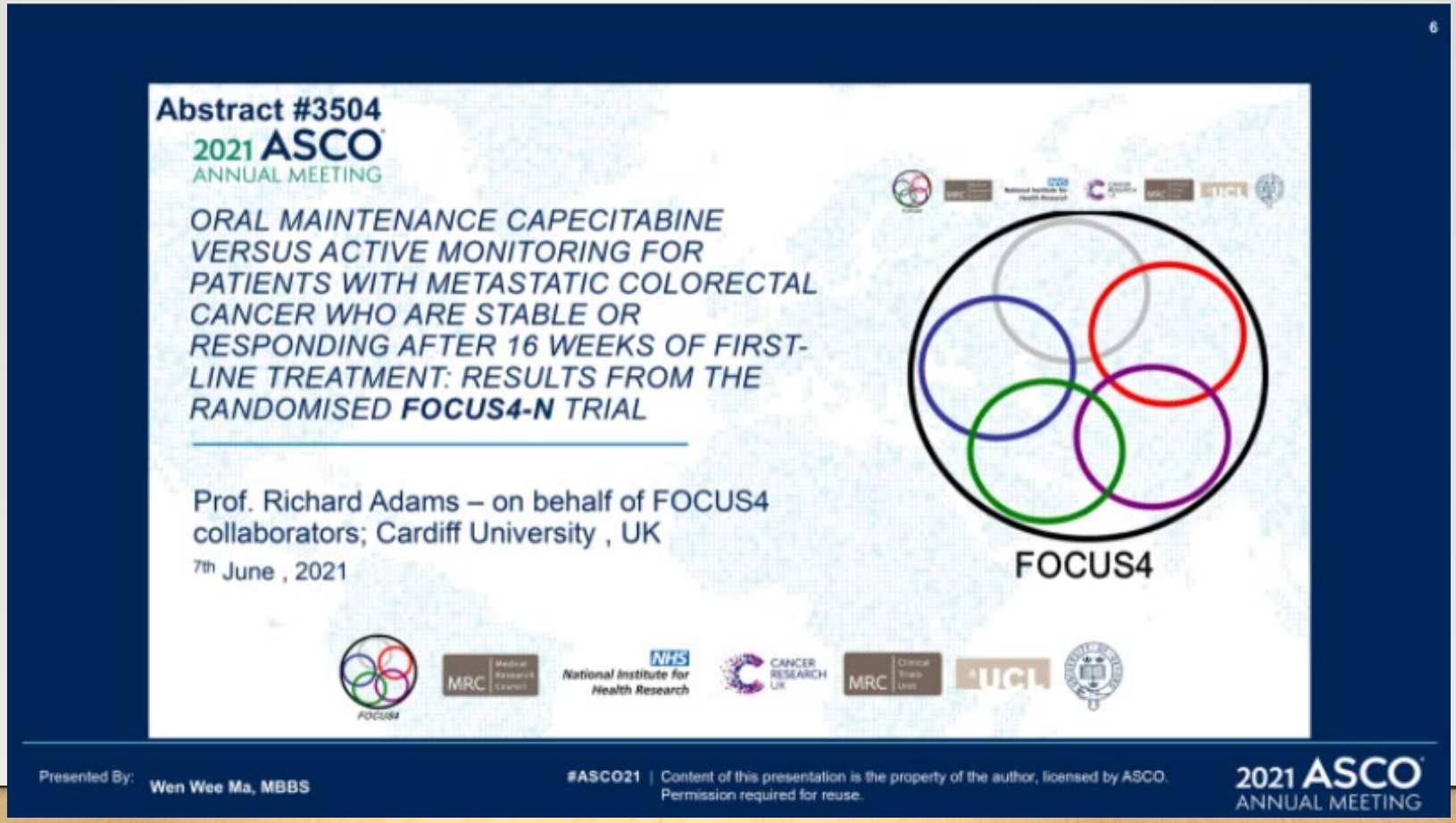
FOLFIRI+BEV irinotecan: 150 mg/m^2 IV d1, BEV: 5 mg/kg IV d1, *l*-LV: 200 mg/m^2 IV d1, 5-FU: 400 mg/m^2 bolus d1, 5-FU: 2400 mg/m^2 46 hr civ d1-2;
S-1+irinotecan+BEV (q3w) irinotecan: 150 mg/m^2 IV d1, BEV: 7.5 mg/kg iv d1, S-1: 40 mg/m^2 bid orally d1-14; **S-1+irinotecan+BEV (q4w)** irinotecan: 100 mg/m^2 VI d1, d15, BEV: 5 mg/kg VI d1,d15, S-1: 40 mg/m^2 bid orally d1-14

The Role of Maintenance Therapy ASCO 2021



- Usually after Induction therapy that should lead to Disease Control Then De-Escalate
- Capecitabine or 5FU along with Bevacizumab is better than No-Bev (Focus-4 Trial)
- Anti-EGFR in Ras/Raf WT along with Capecitabine/ 5FU (Panama Trial)
- Maximum Duration of Induction Therapy?

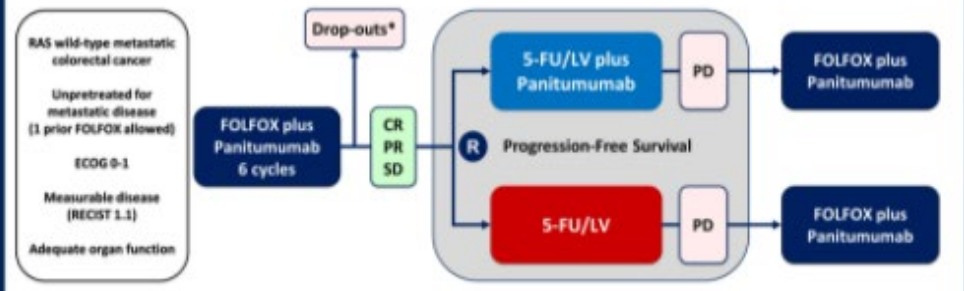
Maintenance Therapy
ASCO 2021



Maintenance Therapy
PANAMA Trial ASCO 2021

PANAMA- AIO KRK 0212- Study Design

AIO



Primary Endpoint

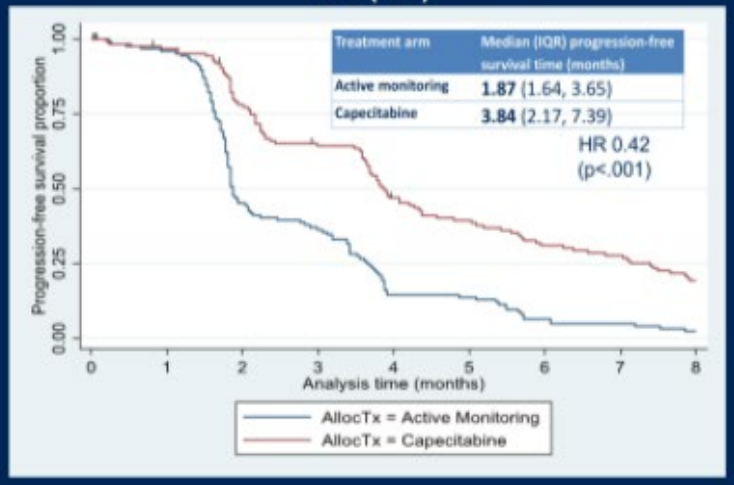
- Progression free survival (from randomization)

Stratification factors

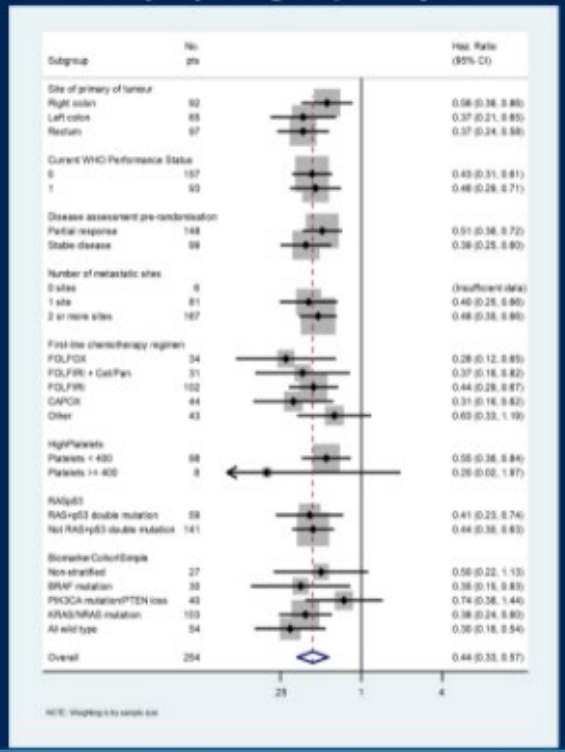
- OR vs SD after induction
- Planned Pmab dosages (full vs reduced)
- Prior oxaliplatin during adjuvant rx

Maintenance Therapy
The FOCUS -4 TRIAL ASCO 2021

PFS (ITT)

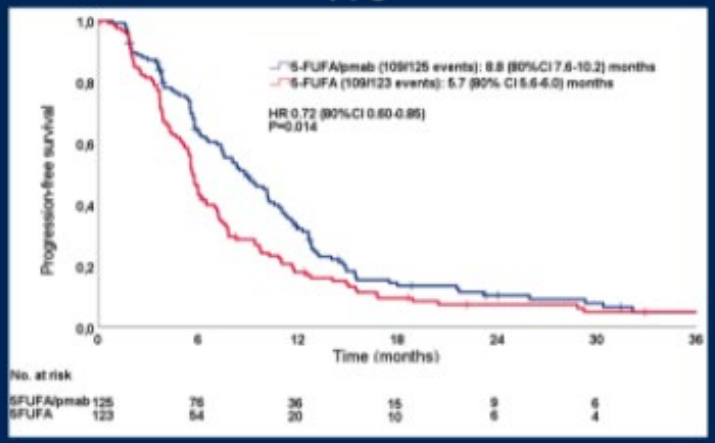


PFS (ITT) Subgroup Analysis



Maintenance Therapy PANAMA Trial ASCO 2021

PFS



Arms	Pmab-5FU-Lv	5FU-Lv
PFS during maintenance	8.8 mo	5.7 mo
PFS during reinduction	3.3 mo	5.8 mo
Total PFS	12.1 mo	11.5 mo

OS: trend favoring pmab-5FU-Lv
- 28.7 vs 25.7 mo; p=0.32

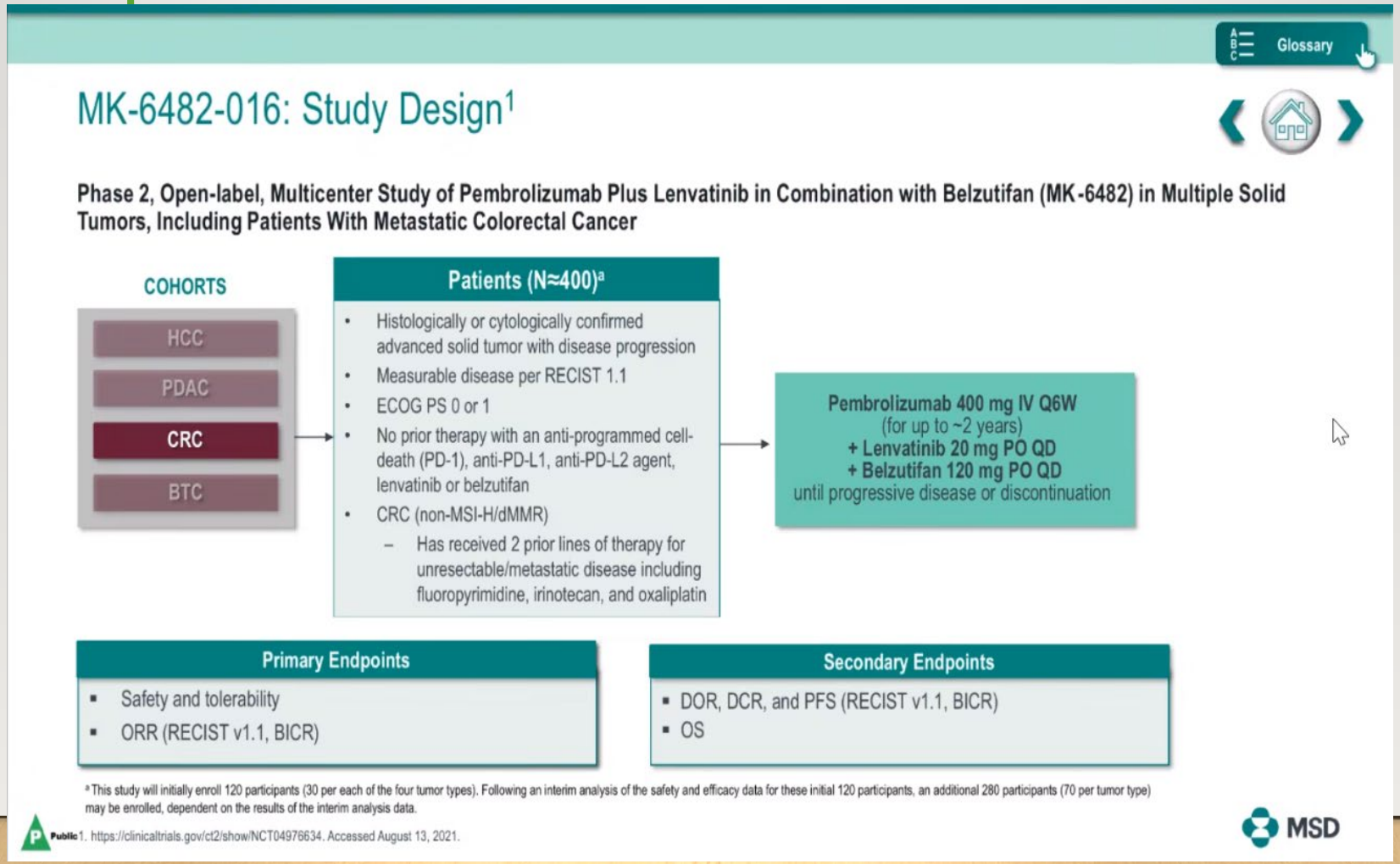
Toxicity profile: more expected Pmab AEs
- skin, electrolytes, diarrhea and stomatitis

Correlative studies on-going

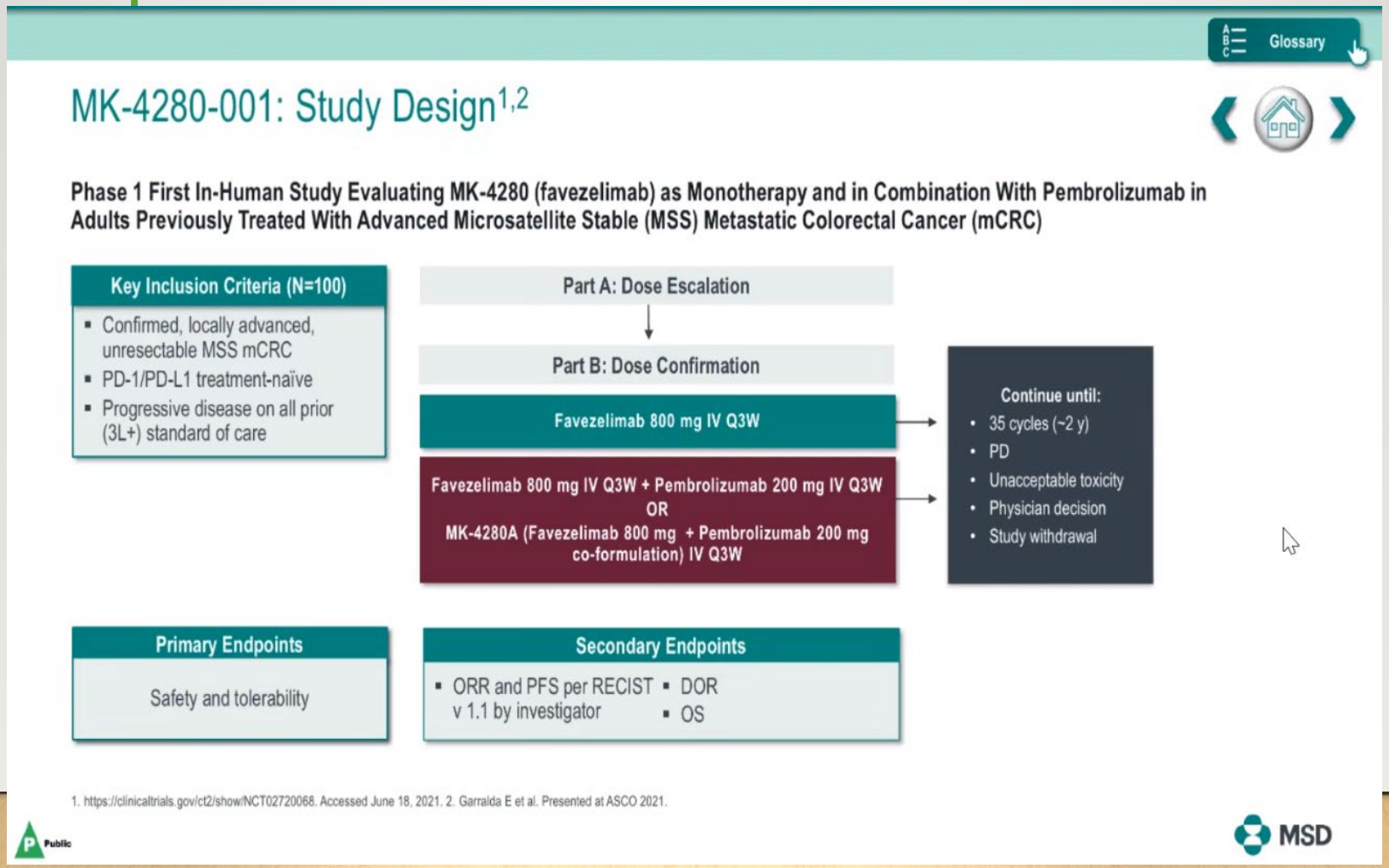
Future Directions for mCRC with Immunotherapy

- Beyond Keynote 177 for mCRC MSI-H, should we rechallenge with IO therapy
- Combination of TKI and Pembrolizumab in pMMR (MSS) CRC after 2n Line therapy Vs Approved Targeted therapy
- Dual Blockade with Nivolumab and Ipilimumab in m CRC in MSI-H

Future Directions for mCRC with Immunotherapy



Future Directions for mCRC with Immunotherapy



Future Directions for mCRC with Immunotherapy

Glossary

MK-4280-001 (Part B): Best Response (Investigator Review, RECIST v1.1)

Data cutoff: October 23, 2020[1]

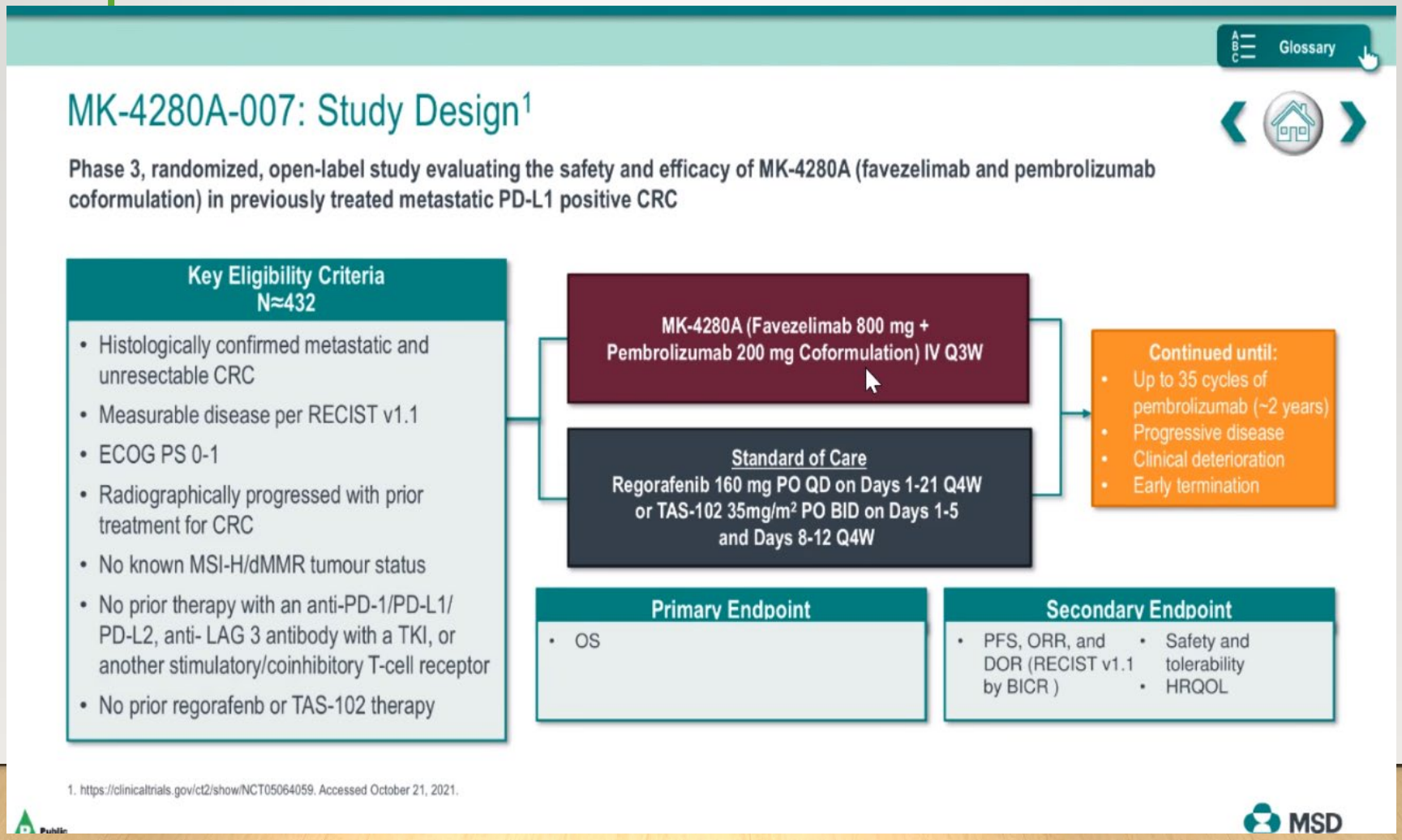
Best Response[a,b]	n	PD-L1 CPS ≥1 n = 36	n	PD-L1 CPS <1 n = 35
ORR, % (95% CI)	4	11 (3.1-26.1)	1	2.9 (0.1-14.9)
Best Overall response, % (95% CI)				
Complete response	1	2.8 (0.1-14.5)	0	0 (0.0-10.0)
Partial response	3	8.3 (1.8-22.5)	1	2.9 (0.1-14.9)
Stable disease	9	25.0 (12.1-42.2)	4	11.4 (3.2-26.7)
Progressive disease	15	41.7 (25.5-59.2)	24	68.6 (50.7-83.1)
DCR (CR+PR+SD)	13	36.1 (20.8-53.8)	5	14.3 (4.8-30.3)
Median duration of response, months (range)	10.6 (5.6-12.5)			

[a]15 patients were nonevaluable or had no assessment. [b]Does not include patients with PD-L1 missing status (n=9).

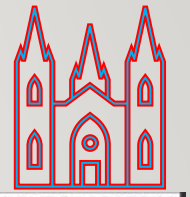
- No patient receiving favezelimab alone responded
- No response occurred in patients with missing PD-L1 status (n=9)

1. Garralda E et al. Presented at ASCO 2021.

Future Directions for mCRC with Immunotherapy



Future Directions for mCRC with Immunotherapy ESMO21



Le MK-3475 KN164 Cohorts A and B ESMO 2021

Pembrolizumab for Previously Treated, Microsatellite Instability–High/ Mismatch Repair–Deficient Advanced Colorectal Cancer: Final Analysis of KEYNOTE-164

D. T. Le[1]; L. A. Diaz[2]; T. W. Kim[3]; E. Van Cutsem[4]; R. Geva[5]; D. Jäger[6]; H. Hara[7]; M. Burge[8]; B. O'Neil[9]; P. Kavan[10]; T. Yoshino[11]; R. Guimbaud[12]; H. Taniguchi[13]; E. Élez[14]; S.-E. Al-Batran[15]; P. M. Boland[16]; Y. Cui[17]; P. Leconte[18]; P. Marinello[19]; T. André[20]

[1]Sidney Kimmel Comprehensive Cancer Center at John Hopkins, Baltimore, MD, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Asan Medical Center, Seoul, South Korea; [4]University Hospitals Gasthuisberg, Leuven and KU Leuven, Leuven, Belgium; [5]Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel; [6]University Medical Center Heidelberg, National Center for Tumor Diseases, Heidelberg, Germany; [7]Saitama Cancer Center, Saitama, Japan; [8]Cancer Care Services, Royal Brisbane Hospital, Brisbane, QLD, Australia; [9]Community North Cancer Center, Indianapolis, IN, USA; [10]McGill University, Montreal, QC, Canada; [11]National Cancer Center Hospital East, Kashiwa, Japan; [12]Centre Hospitalier Universitaire de Toulouse, Toulouse, France; [13]Aichi Cancer Center Hospital, Nagoya, Japan; [14]Vall d'Hebron Barcelona Hospital Campus, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [15]Institut für Klinisch-Onkologische Forschung, Frankfurt am Main, Germany; [16]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [17]MSD China, Shanghai, China; [18]MSD France, Courbevoie, France; [19]Merck & Co., Inc., Kenilworth, NJ, USA; [20]Hôpital Saint-Antoine AP-HP, Paris, France.

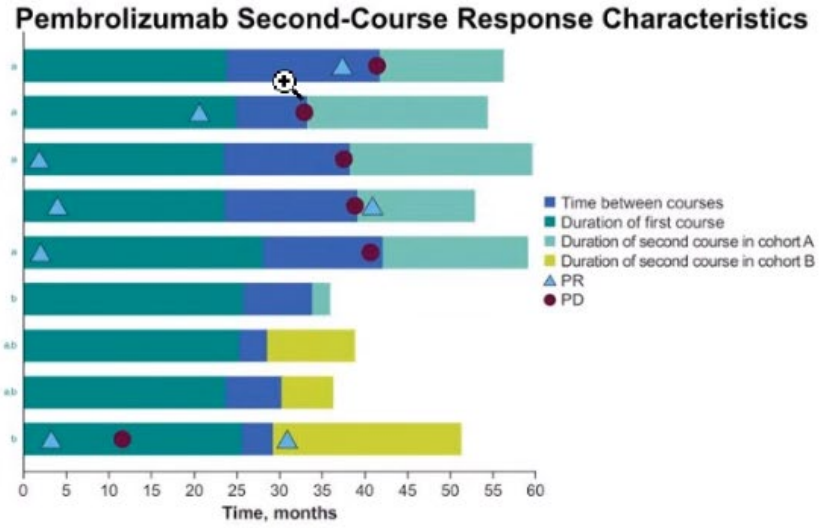
Presented virtually at the European Society for Medical Oncology Virtual Congress 2021 (ESMO)
September 16 – 21, 2021

Future Directions for mCRC with Immunotherapy ESMO21

Le MK-3475 KN164 Cohorts A and B ESMO 2021

Second Course of Pembrolizumab

- 9 patients (6, cohort A; 3, cohort B) who had initial PD and had discontinued pembrolizumab treatment and met second-course eligibility criteria were retreated with pembrolizumab after initial PD and received up to 17 cycles of pembrolizumab during the second course
- 4 patients in cohort A had completed 17 cycles of treatment at data cutoff, and 2 patients had discontinued treatment (1 because of PD, 1 because of grade 3 colitis)
- 2 patients in cohort B had completed treatment at data cutoff, and 1 patient had discontinued treatment because of PD
- 1 patient in each cohort had PR in both the first and second courses, and second-course PR occurred approximately 2 months after the start of the second course (duration of second-course PR: 12.0 [cohort A] and 20.4 [cohort B] months)
- 4 patients in cohort A and 2 patients in cohort B achieved SD during the second course (median duration of second-course SD, 13.7 months [range, 4.1-20.5])



[a]Best response of SD in second course.
[b]PD per investigator after first course of pembrolizumab.

Future Directions for mCRC with Immunotherapy ESMO21

Le MK-3475 KN164 Cohorts A and B ESMO 2021

Conclusions

- Pembrolizumab continued to show durable antitumor activity and prolonged OS in patients with previously treated advanced MSI-H/dMMR CRC at the final analysis of KEYNOTE-164
- Pembrolizumab had a manageable safety profile, as reported previously; no new safety signals were identified[1,2]
- Antitumor activity was again observed in 8 of 9 patients following reexposure to pembrolizumab as part of second-course treatment, thereby demonstrating that some patients derive clinical benefit from retreatment with pembrolizumab upon initial disease progression following a first course of pembrolizumab

1. Le DT et al. *J Clin Oncol*. 2019;38:11-19; **2.** Diaz LA et al. *J Clin Oncol*. 2020;38(15 suppl). Abstract 4032.

Future Directions for mCRC with Immunotherapy ESMO21

LEAP-017: Study Design[1]

Phase 3 Randomized Trial of Pembrolizumab + Lenvatinib Versus Standard of Care in Patients With Metastatic CRC Who Have Received and Progressed on/After or Became Intolerant to Prior Treatment

Patients (N≈434):

- Age ≥18 years
- Histologically/cytologically confirmed diagnosis of unresectable and metastatic colorectal adenocarcinoma (Stage IV A, B and C defined by AJCC 8th edition)
- Previously treated with the following agents:
  - Fluoropyrimidine, irinotecan and oxaliplatin
  - With or without bevacizumab
  - With cetuximab or panitumumab for RAS (KRAS/NRAS) wild-type patients
  - BRAF inhibitor (in combination with cetuximab +/- binimetinib) for BRAF V600E mutated metastatic colon cancer
- Measurable disease per RECIST v1.1
- ECOG PS 0-1
- Tumor sample not previously irradiated
- No MSI-H/dMMR tumors

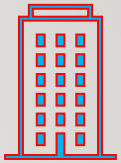
→ Pembrolizumab 400 mg IV on Day 1 Q6W for up to 18 cycles (~2 years) + Lenvatinib 20 mg PO QD until progressive disease

→ Regorafenib 160 mg PO QD on Days 1-21 of each 4-week cycle OR Trifluridine and tipiracil (TAS-102) 35 mg/m² PO BID on Days 1-5 and 8-12 of each 4-week cycle until progressive disease

Primary End Points	Secondary End Points
OS	PFS, ORR, and DOR per RECIST v1.1, safety and tolerability, and HRQOL

1. https://clinicaltrials.gov/ct2/show/NCT04776148. Accessed June 18, 2021.

Future Directions for mCRC with Immunotherapy ASCO 21



ESMO WORLD CONGRESS ON Gastrointestinal Cancer

NIVOLUMAB PLUS LOW-DOSE IPILIMUMAB IN PREVIOUSLY TREATED PATIENTS WITH MICROSATELLITE INSTABILITY-HIGH/ MISMATCH REPAIR-DEFICIENT METASTATIC COLORECTAL CANCER: 4-YEAR FOLLOW-UP FROM CHECKMATE 142

Thierry André,[1] Sara Lonardi,[2] Ka Yeung Mark Wong,[3] Heinz-Josef Lenz,[4] Fabio Gelsomino,[5] Massimo Aglietta,[6] Michael A. Morse,[7] Eric Van Cutsem,[8] Ray McDermott,[9] Andrew Hill,[10] Michael B. Sawyer,[11] Alain Hendlisz,[12] Bart Neyns,[13] Sandzhar Abdullaev,[14] Arteid Memaj,[14] Ming Lei,[14] Scott Kopetz,[15] Michael Overman[15]

[1]Hôpital Saint Antoine, Assistance Publique Hôpitaux de Paris and Sorbonne Université, Paris, France; [2]Istituto Oncologico Veneto IOV-IRCSS, Padova, Italy; [3]Westmead Hospital, Sydney, NSW, Australia; [4]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [5]University Hospital of Modena, Modena, Italy; [6]Candiolo Cancer Institute and University of Torino Medical School, Candiolo, Italy; [7]Duke University Medical Center, Durham, NC, USA; [8]University Hospitals Gasthuisberg/ Leuven and KU Leuven, Leuven, Belgium; [9]St Vincent's University Hospital and Cancer Trials Ireland, Dublin, Ireland; [10]Tasman Oncology Research, Ltd., Southport, QLD, Australia; [11]Cross Cancer Institute and University of Alberta, Edmonton, AB, Canada; [12]Institut Jules Bordet, Brussels, Belgium; [13]Universitair Ziekenhuis Brussel, Brussels, Belgium; [14]Bristol Myers Squibb, Princeton, NJ, USA; [15]MD Anderson Cancer Center, Houston, TX, USA

30 JUNE – 3 JULY 2021

Abstract Number SO-27

Future Directions for mCRC with Immunotherapy ASCO 21

CheckMate 142 NIVO3 + IPI1 2L+ cohort study design

- CheckMate 142 is an ongoing, multicohort, nonrandomized phase 2 trial evaluating the efficacy and safety of NIVO-based therapies in patients with mCRC[a]

- Histologically confirmed metastatic/recurrent CRC
- MSI-H/dMMR per local laboratory
- ≥ 1 prior line of therapy

N = 119 →

NIVO3 + IPI1 Q3W (4 doses, then NIVO3 Q2W)[b]

Primary endpoint:
ORR per investigator assessment (RECIST v1.1)

Other key endpoints:
ORR per BICR, DCR,[c] DOR, PFS, OS, and safety

- At data cutoff (October 2020), the median duration of follow-up was 50.9 months (range, 46.9-62.7)[d]

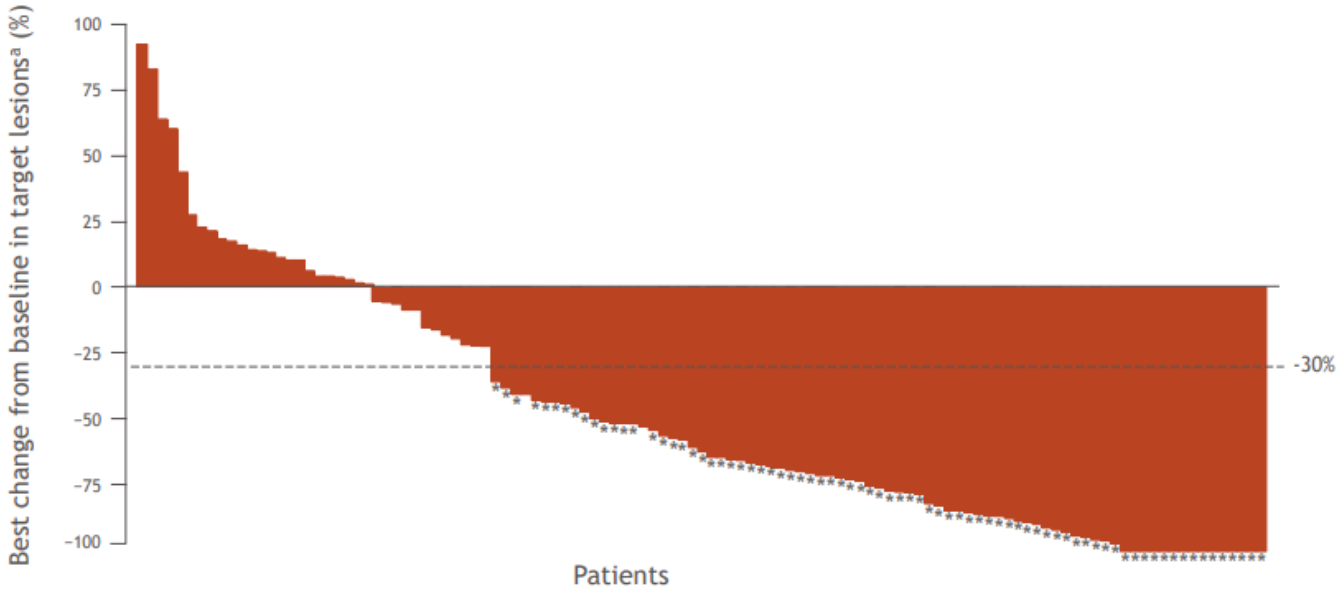
[a]ClinicalTrials.gov number. NCT02060188; [b]Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end; [c]Patients with CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients; [d]Median follow-up was defined as time from first dose to data cutoff.

ESMO World Congress on Gastrointestinal Cancer

Future Directions for mCRC with Immunotherapy ASCO 21

CheckMate 142

Best change in target lesions



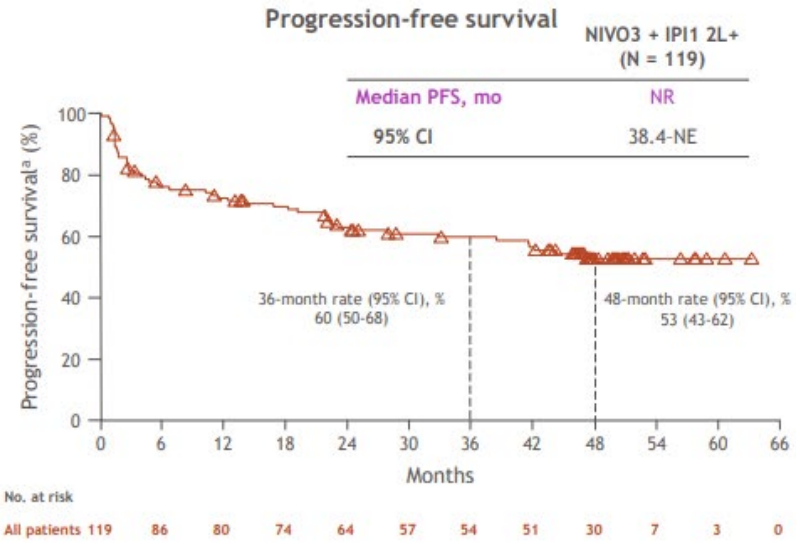
- Most patients (79%) had a reduction in tumor burden from baseline

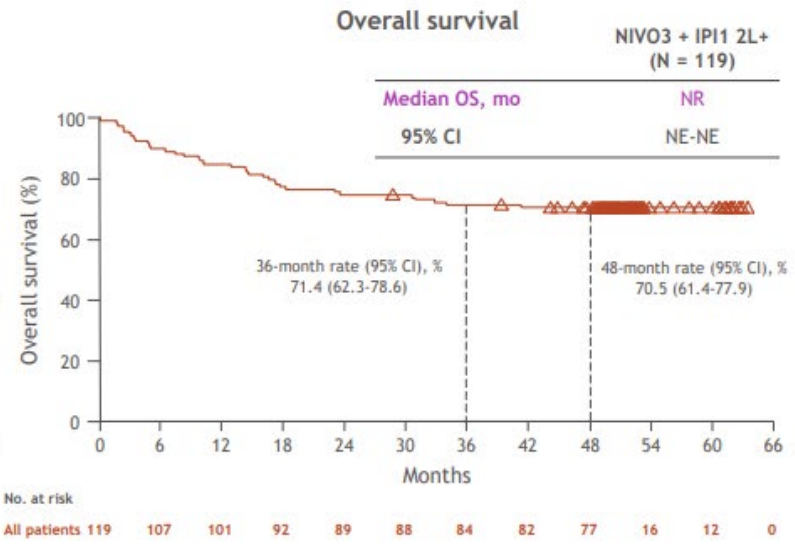
[a]Per investigator assessment. Evaluable patients with a target lesion at baseline and at least 1 on-treatment tumor assessment. Best change is based on evaluable target lesion measurements up to progression or start of subsequent therapy. *Confirmed response per investigator assessment (RECIST v1.1). Horizontal reference line indicates the 30% reduction consistent with a response per RECIST v1.1.

Future Directions for mCRC with Immunotherapy ASCO 2021

CheckMate 142

Progression-free survival and overall survival





- Median PFS was not reached; the 48-month PFS rate was 53%
- Median OS was not reached; the 48-month OS rate was 70.5%

[a]Per investigator assessment.

Future Directions for mCRC with Immunotherapy ASCO 21

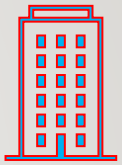
Gastrointestinal Cancers Symposium

Subgroup analyses of patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer treated with nivolumab plus low-dose ipilimumab as first-line therapy: 2-year clinical update

Heinz-Josef Lenz,[1] Sara Lonardi,[2] Vittorina Zagonel,[2] Eric Van Cutsem,[3] Maria Luisa Limon,[4] Ka Yeung Mark Wong,[5] Alain Hendlisz,[6] Massimo Aglietta,[7] Pilar García-Alfonso,[8] Bart Neyns,[9] Gabriele Luppi,[10] Dana B. Cardin,[11] Tomislav Dragovich,[12] Usman Shah,[13] Sandzhar Abdullaev,[14] Arteid Memaj,[14] Michael James Overman[15]

[1]USC Norris Comprehensive Cancer Center, Los Angeles, CA; [2]Istituto Oncologico Veneto IOV-IRCSS, Padova, Italy; [3]University Hospitals Gasthuisberg/Leuven and KU Leuven, Leuven, Belgium; [4]Hospital Universitario Virgen del Rocio, Sevilla, Spain; [5]Westmead Hospital, Sydney, Australia; [6]Institut Jules Bordet, Brussels, Belgium; [7]Department of Oncology, University of Torino and Medical Oncology, Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Italy; [8]Hospital Gral Universitario Gregorio Marañon, Madrid, Spain; [9]Universitair Ziekenhuis Brussel, Brussels, Belgium; [10]University Hospital of Modena, Modena, Italy; [11]Vanderbilt - Ingram Cancer Center, Nashville, TN; [12]Banner MD Anderson Cancer Center, Gilbert, AZ; [13]Lehigh Valley Cancer Institute, Allentown, PA; [14]Bristol Myers Squibb, Princeton, NJ; [15]The University of Texas MD Anderson Cancer Center, Houston, TX

Future Directions for mCRC with Immunotherapy ASCO 21



CheckMate 142 NIVO3 + IPI1 1L cohort study design

- CheckMate 142 is an ongoing, multicohort, nonrandomized phase 2 trial evaluating the efficacy and safety of NIVO-based therapies in patients with mCRC[a]

- Histologically confirmed metastatic or recurrent CRC
- MSI-H/dMMR per local laboratory
- No prior treatment for metastatic disease

→ NIVO3 Q2W + IPI1 Q6W[b]

Primary endpoint:
- ORR per investigator assessment (RECIST v1.1)

Other key endpoints:
- ORR per BICR, DCR,[c] DOR, PFS, OS, and safety

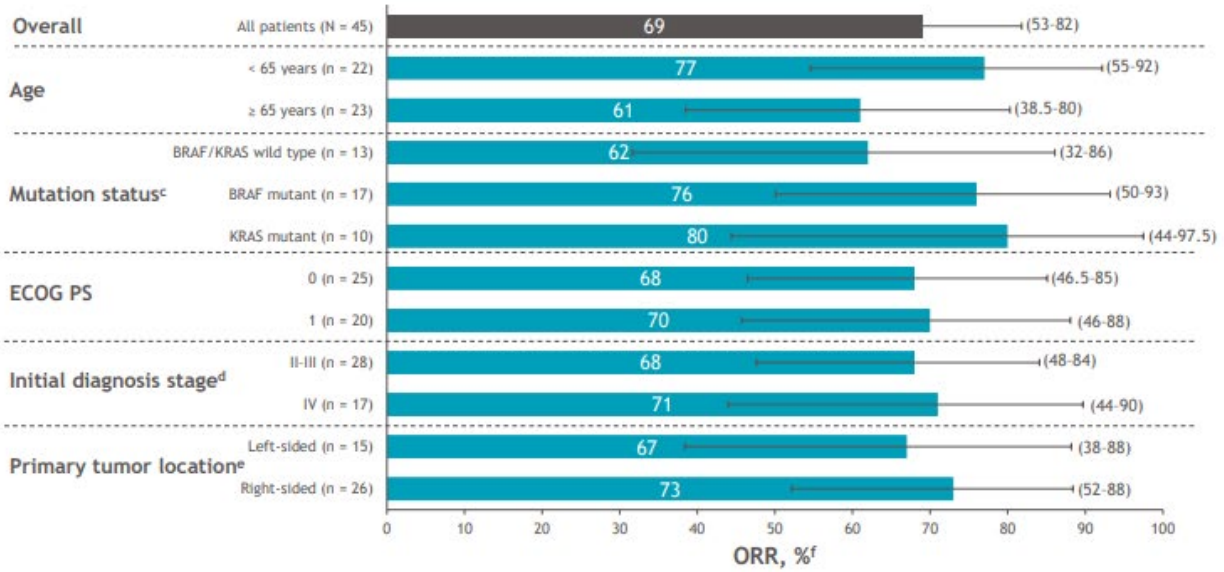
- At data cutoff (October 2019), the median duration of follow-up was 29.0 months (range, 24.2–33.7)[d]

[a]ClinicalTrials.gov number, NCT02060188. [b]Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end. [c]Patients with CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients. [d]Median follow-up was defined as time from first dose to data cutoff. BICR, blinded independent central review; CR, complete response; CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; NIVO3, nivolumab 3 mg/kg; IPI1, ipilimumab 1 mg/kg; PR, partial response; SD, stable disease.

Future Directions for mCRC with Immunotherapy ASCO 21

CheckMate 142

Objective response rate by subgroup[a,b]



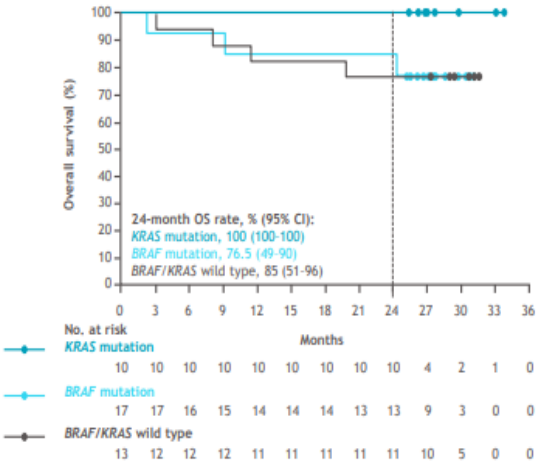
- ORR was generally similar across evaluated subgroups and consistent with that of the overall study population

[a]Median follow-up, 29.0 months. [b]Per investigator assessment. [c]Excluded 5 patients with unknown mutation status. [d]All patients had stage IV disease at study entry. [e]Excluded 4 patients with uncategorized primary tumor location. [f]Error bars and numbers in parentheses indicate 95% CIs; evaluated subgroups had overlapping 95% CIs for ORR.

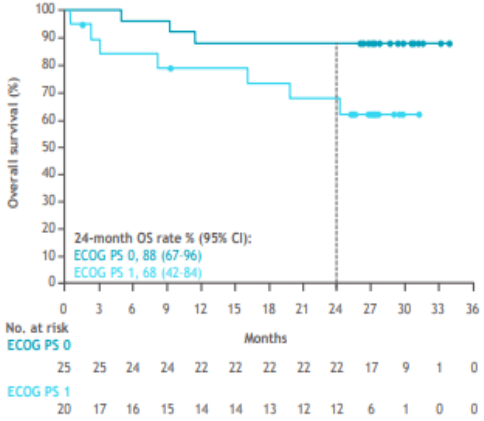
Overall survival by subgroup[a]

- In the overall population, median OS was not reached (95% CI, NE) and the 24-month OS rate was 79% (95% CI, 64.1-88.7)

Mutation status[b]



ECOG PS



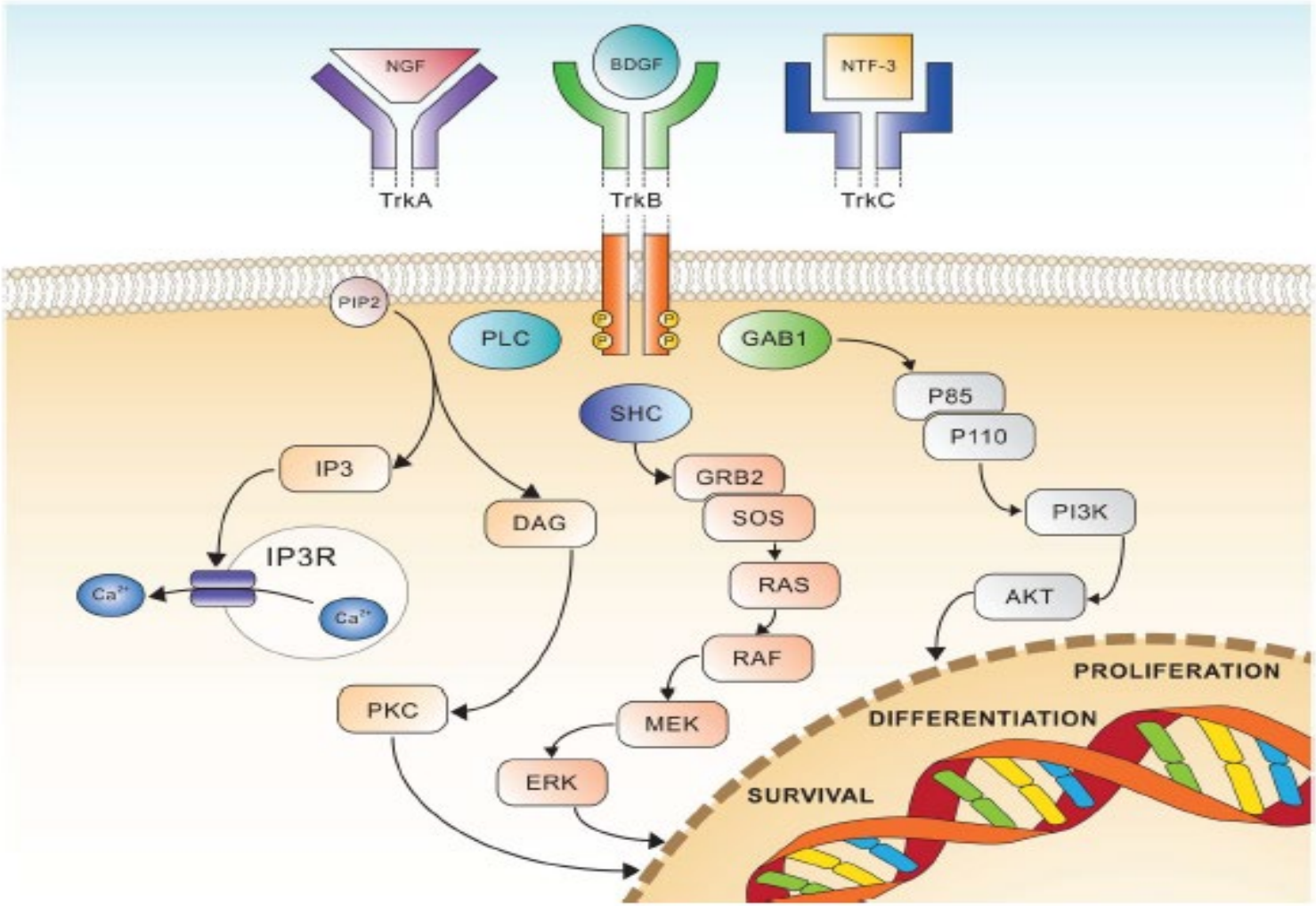
OS in other key subgroups

	24-mo rate, % (95% CI)
Age, years	
< 65 (n = 22)	85 (61-95)
≥ 65 (n = 23)	74 (51-87)
Initial diagnosis stage[c]	
II-III (n = 28)	77 (56.5-89)
IV (n = 17)	82 (55-94)
Primary tumor location[d]	
Left-sided (n = 15)	67 (37.5-85)
Right-sided (n = 26)	84 (63-94)

- OS benefit was observed with NIVO3 + IPI1 across all evaluated subgroups and consistent with that of the overall population
- Median OS was not reached in any evaluated subgroup

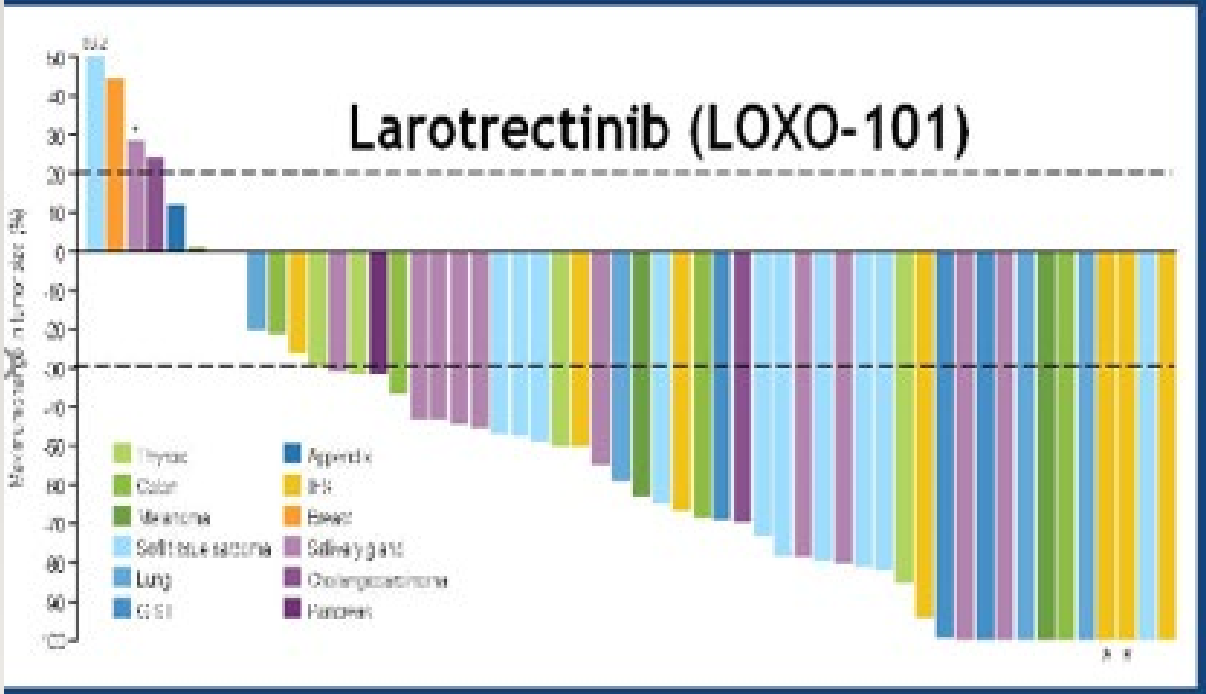
[a]Median follow-up, 29.0 months. [b]Excluded 5 pts with unknown mutation status. [c]All patients had stage IV disease at study entry. [d]Excluded 4 patients with uncategorized primary tumor location. mo, months; NE, not estimable.

Signaling Pathways for NTRK in Cancers with MSI-H



Data of NTRK Fusion in MSI-H Cancers

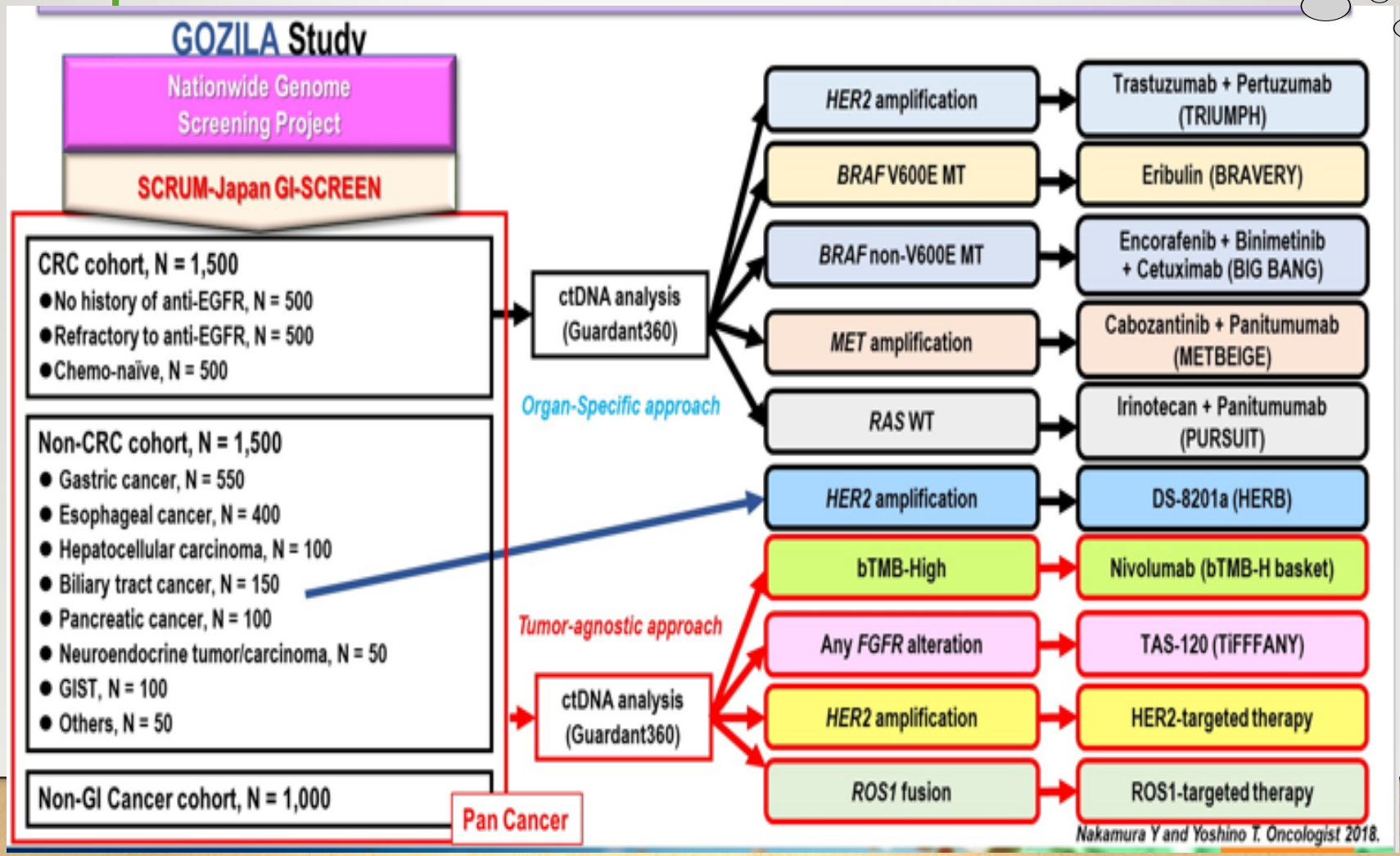
Targeting Tropomyosin receptor kinase (TRK) fusions (High Rate in MSI-high CRC)



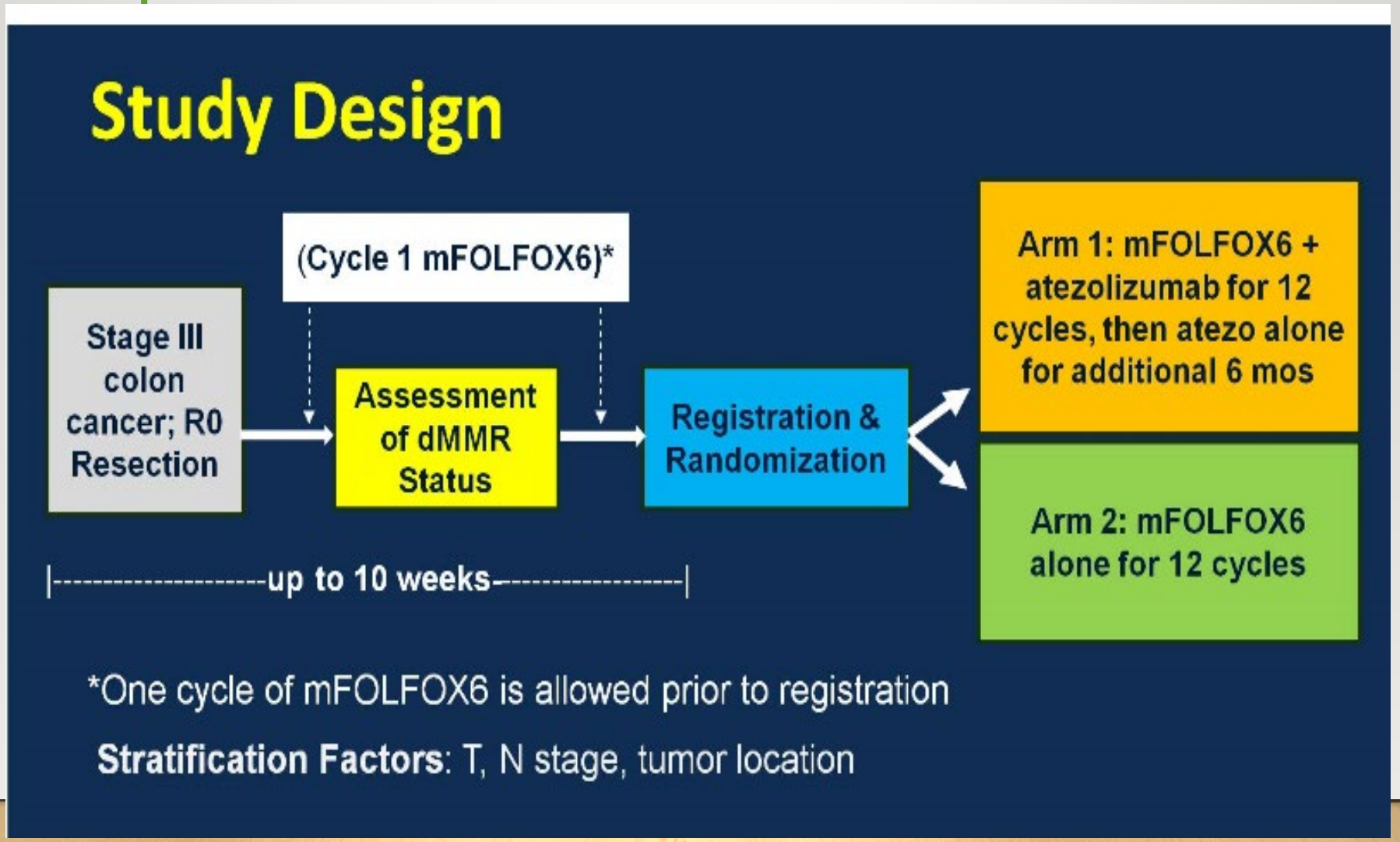
Characteristics	NTRK rearranged (n = 13) No. (%)
MSI status	
MSS (n=162)	3 (23.1)
MSI-high (n=26)	10 (76.9)
NA	0

38% of MSI-high CRC
1.9% of MSS CRC

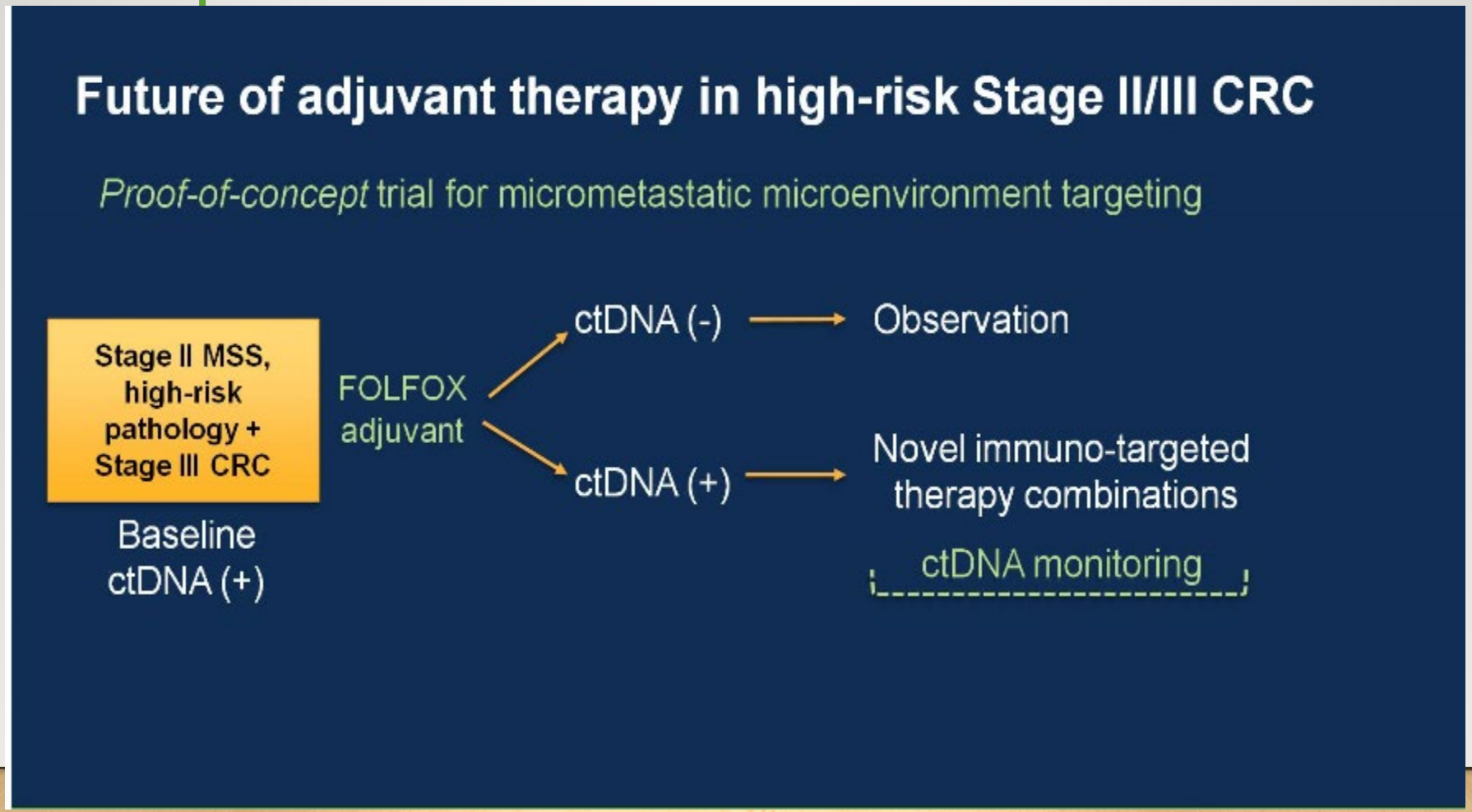
NGS AGNOSTIC TARGTED THERAPY



The ATOMIC Trial stage III CRC MSI-H



Future Immunotherapy du CRC MMR-Deficient (MSI-H)



CONCLUSION

- Personalized Treatment Options for mCRC is still ongoing Process
- Immunotherapy upfront for MSI-H m CRC is leading the role in terms of PFS and OS
- Triplet Vs Doublet along with Bev Vs Anti-EGFR remains major question.
  - Rt Sided mCRC FOLOXIRI/BEV is a better option
  - Left Sided Ras/Raf WT do better FOLFOX/ AntiEGFR
  - Ras WT/Braf Mutatted : Ecorafenib/Cetuximab (BEACON trial)
- IO with TKI or other agents for mCRC NON-MSI-H
- Targeting Kras G12C (Sotorasib) Pending Result