Recent Advances and Future Directions in Oncology: Gastrointestinal (GI) Cancer

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Discussion Question

In which settings, if any, would you order a circulating tumor DNA (ctDNA)/minimal residual disease (MRD) assay for your patients with colorectal cancer (CRC) outside of a clinical trial? In general, do you currently use the results of ctDNA/MRD assays to inform treatment decisions for these patients?

Chalk Talk – Tanios Bekaii-Saab, MD

- ctDNA detection and quantification methods have the potential to transform clinical practice through determining the risk for relapse
- (MRD assessment/prognosis)
  - ✓ Tumor-informed vs. tumor-naïve platforms
  - ✓ Residual disease detection at earlier timepoints than standard clinical and/or imaging surveillance
- Will this allow for improved patient selection for :?
  - ✓ Adjuvant chemotherapy (ACT) ? ACT Duration?

DYNAMIC Study Design

ACTRN12615000381583

Stage II Colon Cancer

- R0 resection
- ECOG 0 – 2
- Staging CT within 8 weeks
- Provision of adequate tumor tissue within 4 weeks post-op
- No synchronous colorectal cancer

Plasma Collections
Week 4 + 7 post-op

R
2:1

ctDNA-Guided Management

- **ctDNA-Positive → Adjuvant Chemo** (oxaliplatin-based or single agent FP)
- **ctDNA-Negative → Observation**

ctDNA-Positive = Positive result at week 4 and/or 7

Standard Management

Adjuvant treatment decisions based on conventional clinico-pathologic criteria

Endpoints

Primary
- RFS rate at 2 years

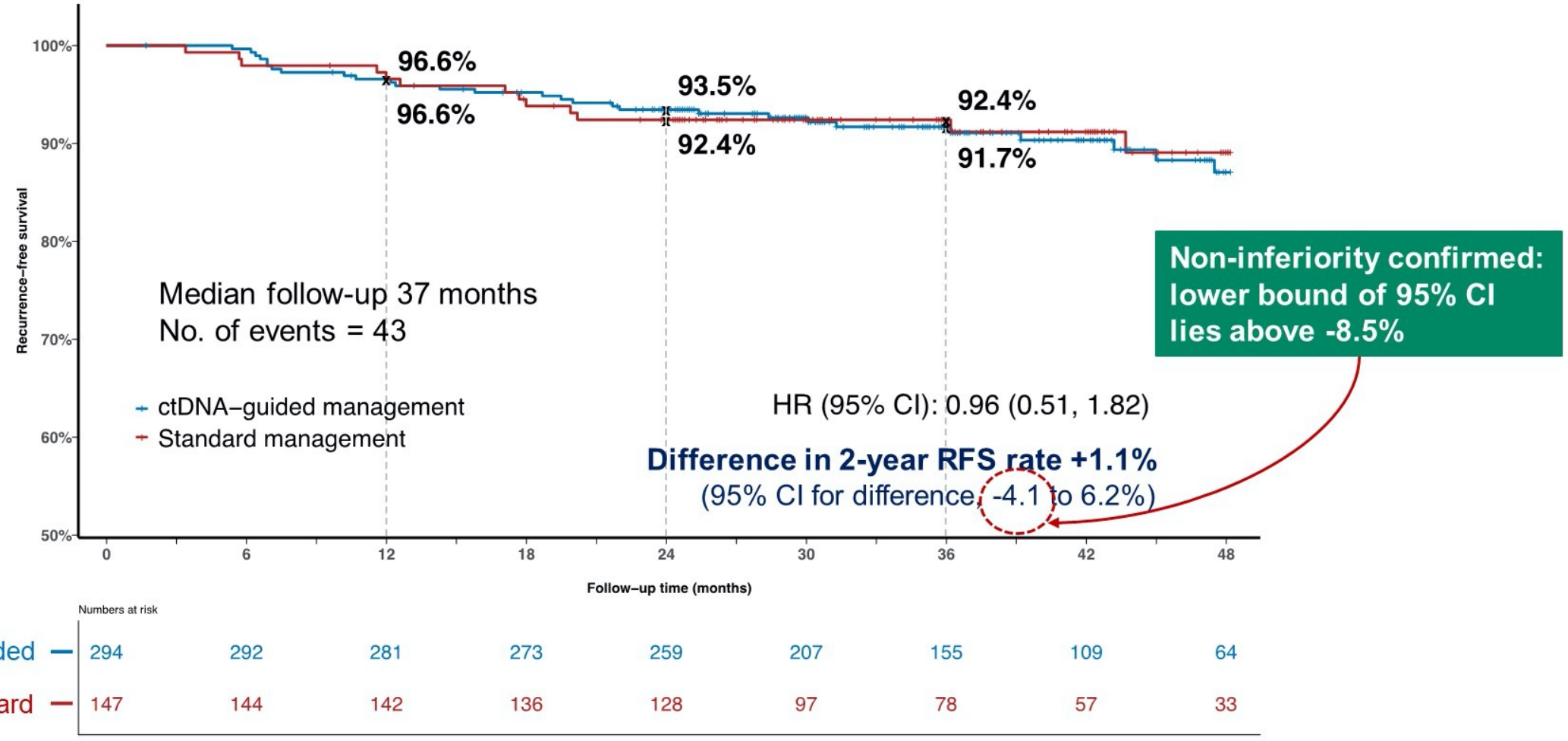
Key Secondary
- Proportion receiving adjuvant chemo

Secondary
- RFS by ctDNA status for ctDNA-guided arm
- TTR
- OS

Stratification Factors
- T stage (T3 vs T4)
- Type of participating center (metropolitan vs regional)

Surveillance:
- CEA → 3-monthly for 24M, then 6-monthly for 36M
- CT C/A/P → 6-monthly for 24M, then at 36M

Recurrence-Free Survival



Adjuvant Treatment Delivery

Treatment Information	ctDNA-Guided N = 294	Standard Management N = 147	P-value
Adjuvant Chemotherapy received, n	45 **(15%)**	41 **(28%)**	0.0017
Chemotherapy regimen received, n			
Oxaliplatin-based doublet	28/45 **(62%)**	4/41 **(10%)**	
Single agent fluoropyrimidine	17/45 **(38%)**	37/41 **(90%)**	<.0001
Time from surgery to commencing chemotherapy, median (IQR), days	83 (76, 89)	53 (49, 61)	<.0001
Treatment duration, median (IQR), weeks	24 (19, 24)	24 (21, 24)	0.9318
Completed planned treatment, n	38 (85%)	32 (78%)	0.7036
Percentage of full dose delivered, median (IQR)	78 (56, 100)	84 (64, 100)	0.6194

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- ctDNA detection and quantification methods have the potential to transform clinical practice through determining the risk for relapse (MRD assessment/prognosis)
  - ✓ Tumor-informed vs. tumor-naïve platforms
  - ✓ Residual disease detection at earlier timepoints than standard clinical and/or imaging surveillance
- Will this allow for improved patient selection for :?
  - ✓ Adjuvant chemotherapy (ACT) ? ACT Duration?
  - ✓ Intensity of radiologic surveillance?
    - ✓ Sensitivity and specificity of ctDNA vs CEA in predicting relapse, indicates that ctDNA significantly outperformed CEA and imaging
  - ✓ Whether ctDNA-based early detection of colon cancer recurrence improved overall survival in patients is unclear and is a subject of future studies.
    - ✓ Until further validation in ongoing RCT → Case by case basis and an indepth discussion with patient re: value of testing

Discussion Question

How do you select between an EGFR inhibitor and bevacizumab as a component of first-line therapy for your patients with RAS wild-type metastatic CRC (mCRC), and how does the left or right location of the primary tumor affect this decision?

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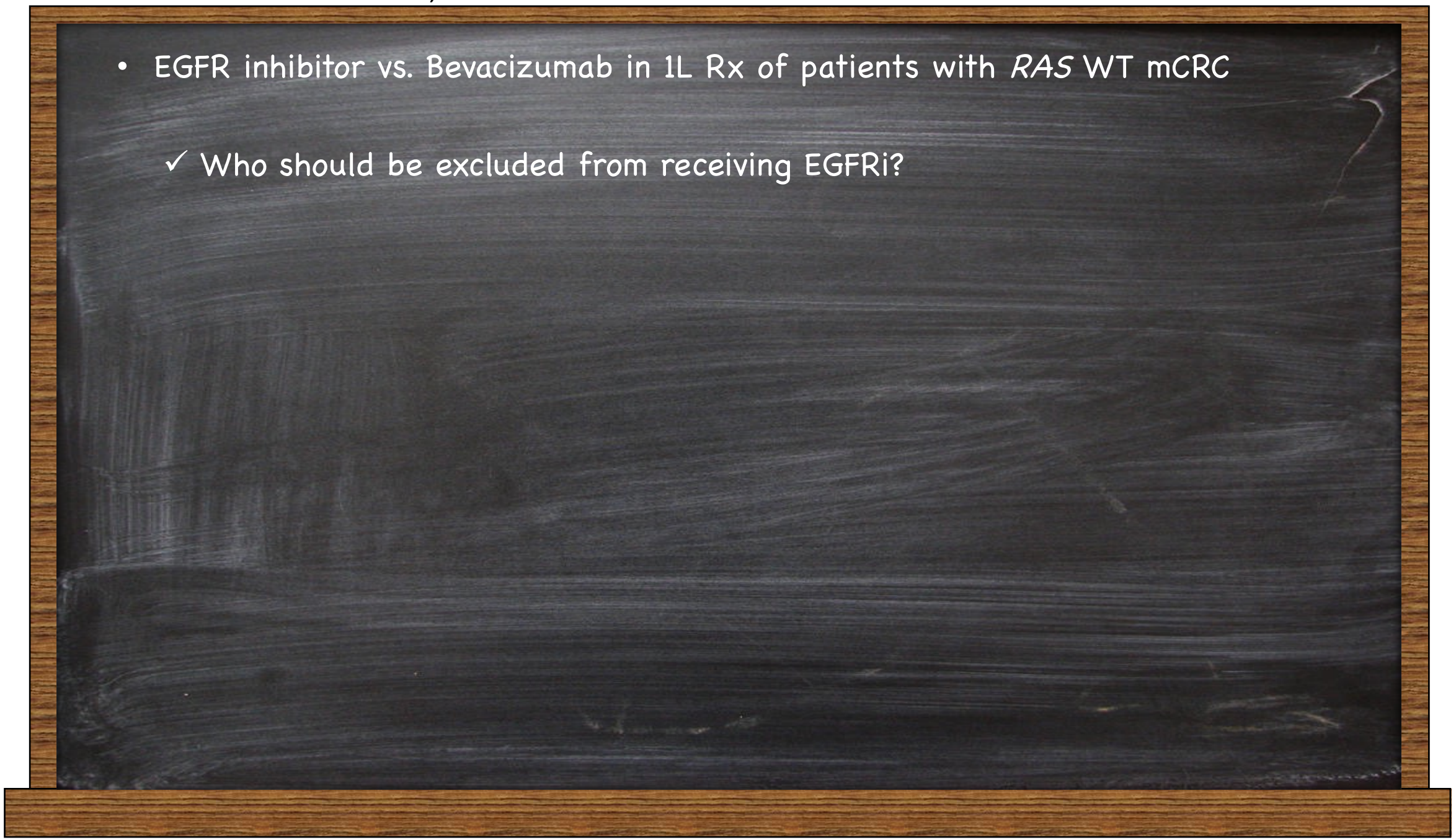
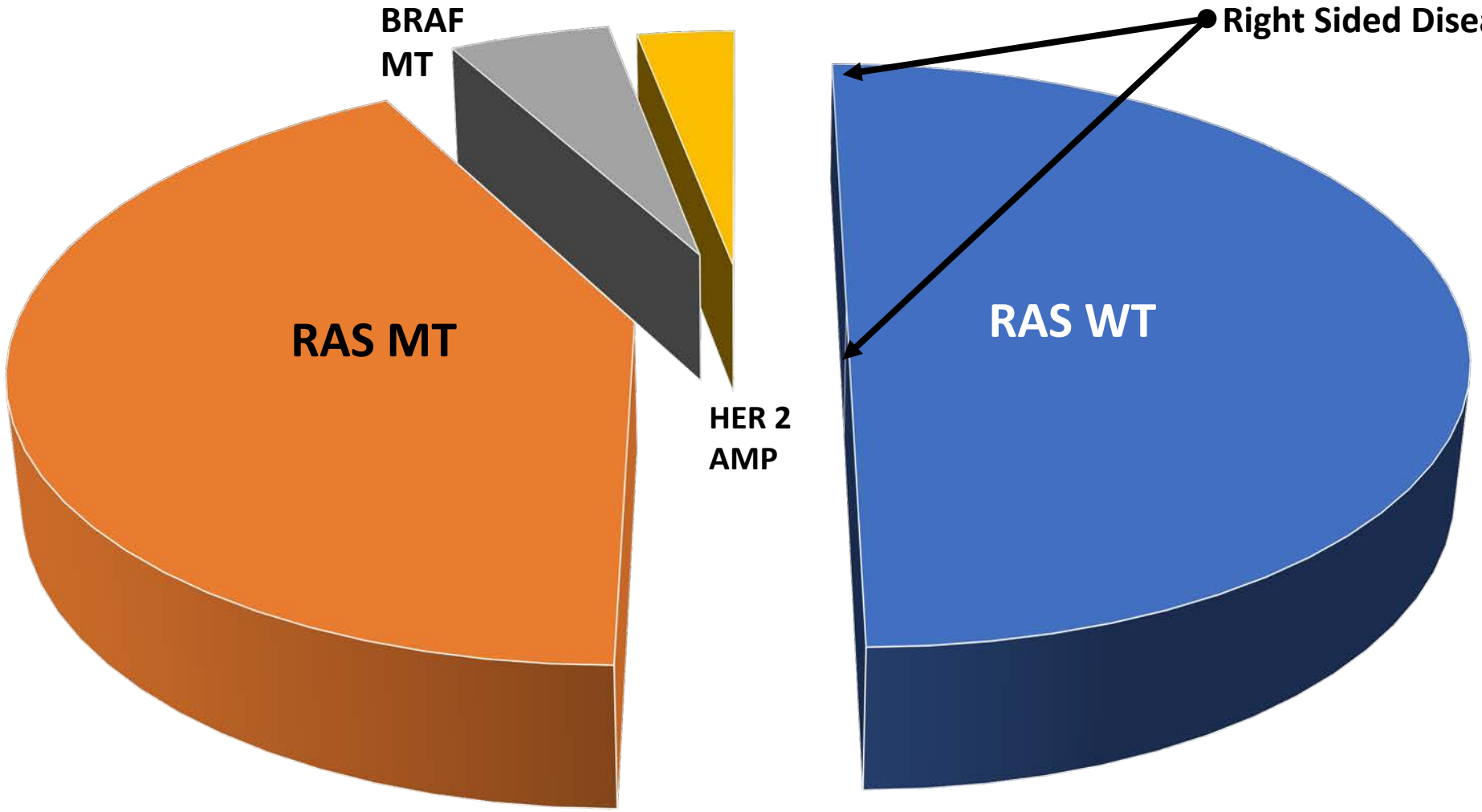
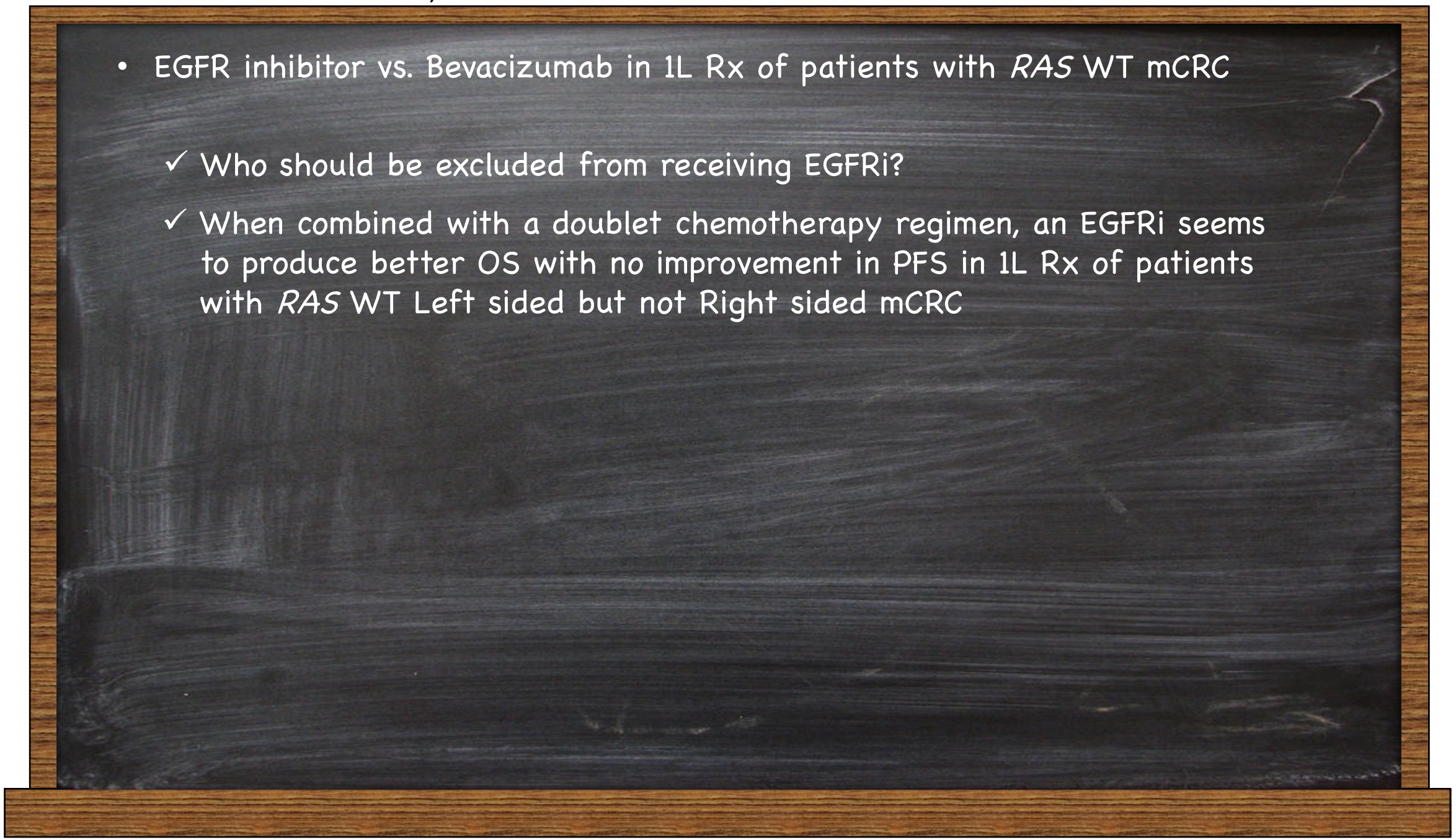


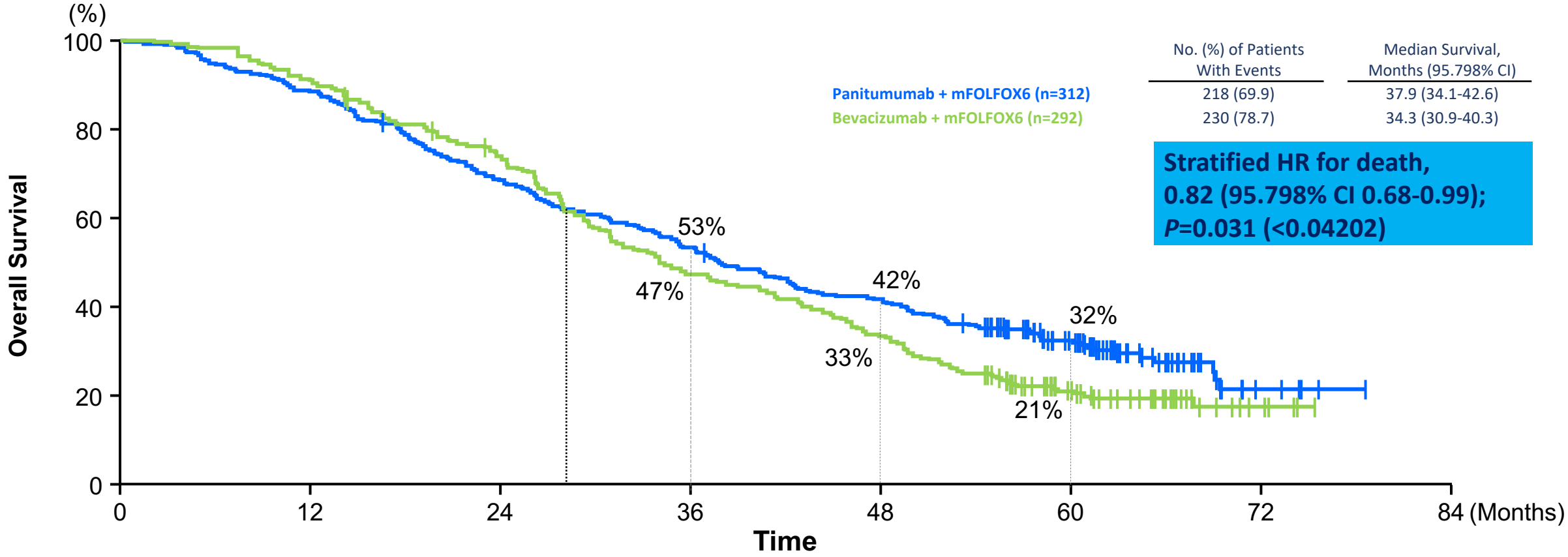
EGFR inhibitors and Metastatic Colorectal Cancer: Negative Predictive Biomarkers



Chalk Talk – Tanios Bekaii-Saab, MD



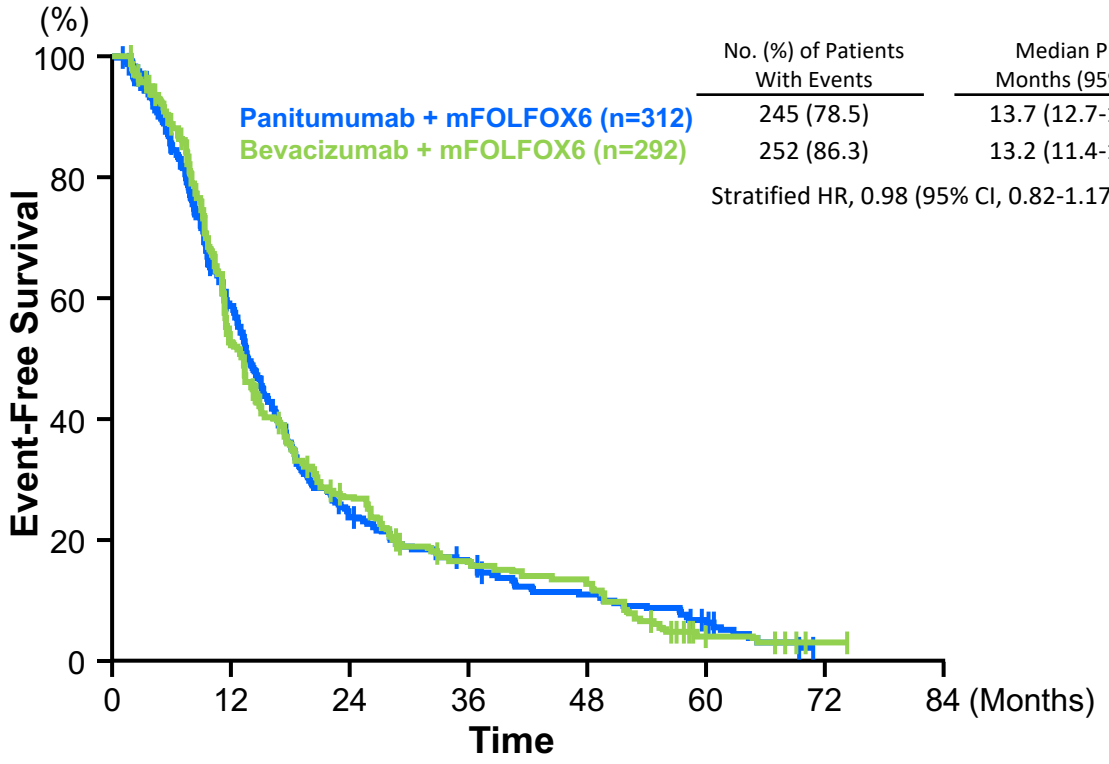
PARADIGM: Panitumumab vs. Bevacizumab: Overall Survival in Left-sided Population



No. at risk								
Panitumumab	312	276	213	166	129	68	5	0
Bevacizumab	292	266	212	136	96	40	5	0

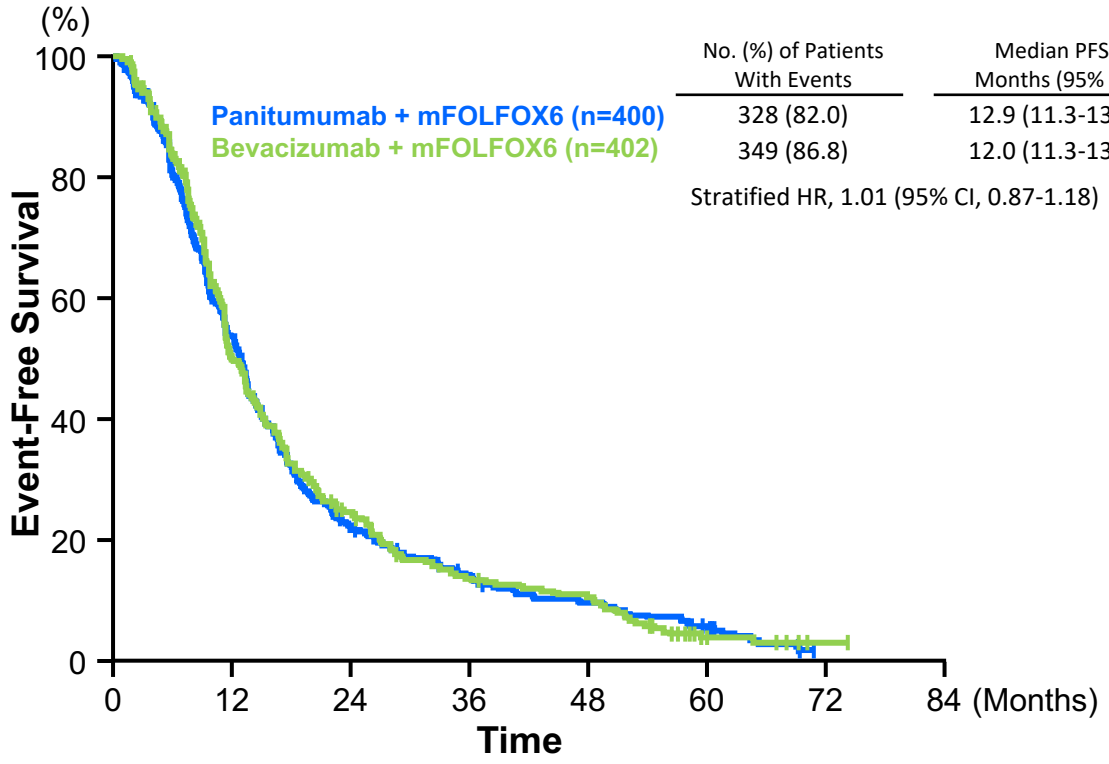
PARADIGM: Panitumumab vs. Bevacizumab: PFS in Left-sided Population

Left-sided Population



No. at risk								
Panitumumab	312	149	59	38	24	13	0	0
Bevacizumab	292	139	67	40	31	5	1	0

Overall Population



No. at risk								
Panitumumab	400	179	71	43	28	15	0	0
Bevacizumab	402	182	83	45	35	6	1	0

*Patients who underwent curative intent resection were censored at the last tumor evaluable assessment date before the resection.

Chalk Talk – Tanios Bekaii-Saab, MD

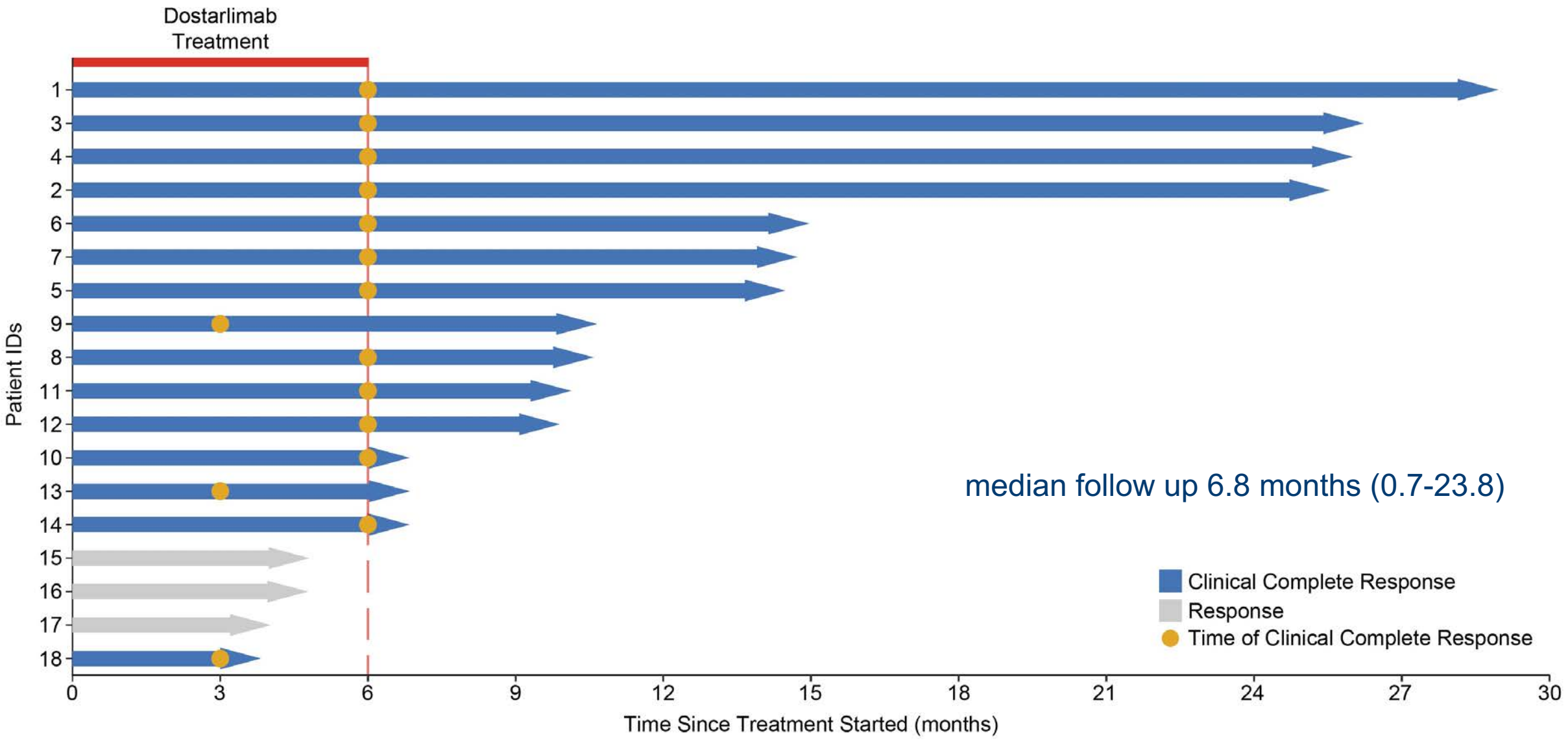
- EGFR inhibitor vs. Bevacizumab in 1L Rx of patients with *RAS* WT mCRC
  - ✓ Who should be excluded from receiving EGFRi ?
  - ✓ When combined with a doublet chemotherapy regimen, an EGFRi seems to produce better OS with no improvement in PFS in 1L Rx of patients with *RAS* WT Left sided but not Right sided mCRC
- Maintenance strategies favor bevacizumab, since EGFRi cumulative toxicities remain challenging
  - ✓ FOLFOXIRI + bevacizumab → Cape/Bev preferred strategy for many

Discussion Question

How do you incorporate immunotherapy in the neoadjuvant/adjuvant and metastatic settings for microsatellite instability-high mCRC? In which line of treatment would you generally recommend HER2-directed therapy to a patient with HER2-positive mCRC, and which specific agents or regimens do you feel are appropriate?

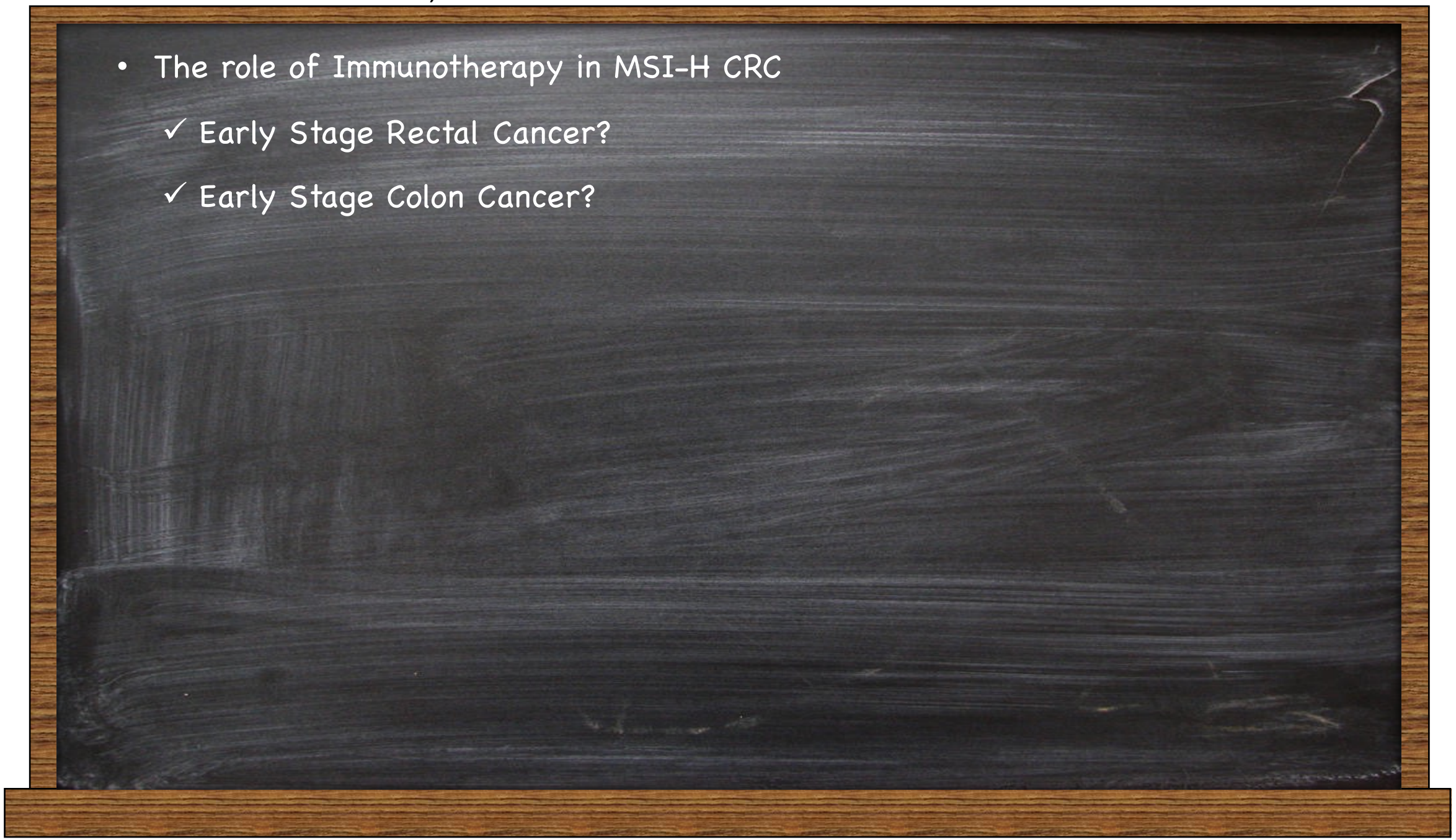
Chalk Talk – Tanios Bekaii-Saab, MD

Dostarlimab in Stage II and III mismatch repair deficient rectal cancer



Cercek, ASCO 2022

Chalk Talk – Tanios Bekaii-Saab, MD



Nivo (3) + Ipi (1) in Early-Stage Colon Cancer

Major pathologic response in 95% of patients; 67% pCR

Pathologic response (RVT)		Patients *n*= 107
Yes	**(≤ 50%)**	**106 (99%)**
Major	(≤10%)	**102 (95%)**
Complete	(0%)	**72 (67%)**
Partial	(10% - 50%)	4 (4%)
No	**(≥50%)**	**1 (1%)**

RVT = residual viable tumor

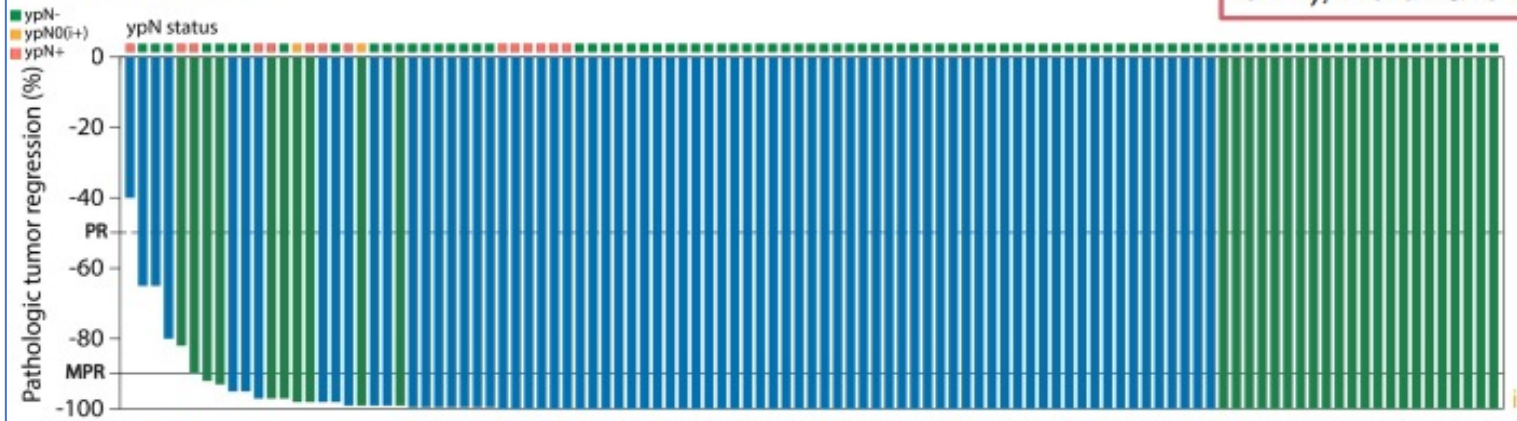
Adjuvant chemotherapy (CTx)

14 patients with ypN+ disease
- 3 patients received adjuvant CTx*
- 5 patients >70 years
- 6 patients refused

* 1 non-responder, 1 partial responder and 1 MPR

Disease recurrence

With a median follow-up of 13.1 months (1.4 - 57.4), there have been no disease recurrences



Green bars = NICHE-1 cohort
Blue bars = NICHE-2 cohort

ypN- = tumor-free lymph nodes; ypN+ = lymph nodes with tumor, including micrometastases; ypN(i+) = lymph nodes with isolated tumor cells

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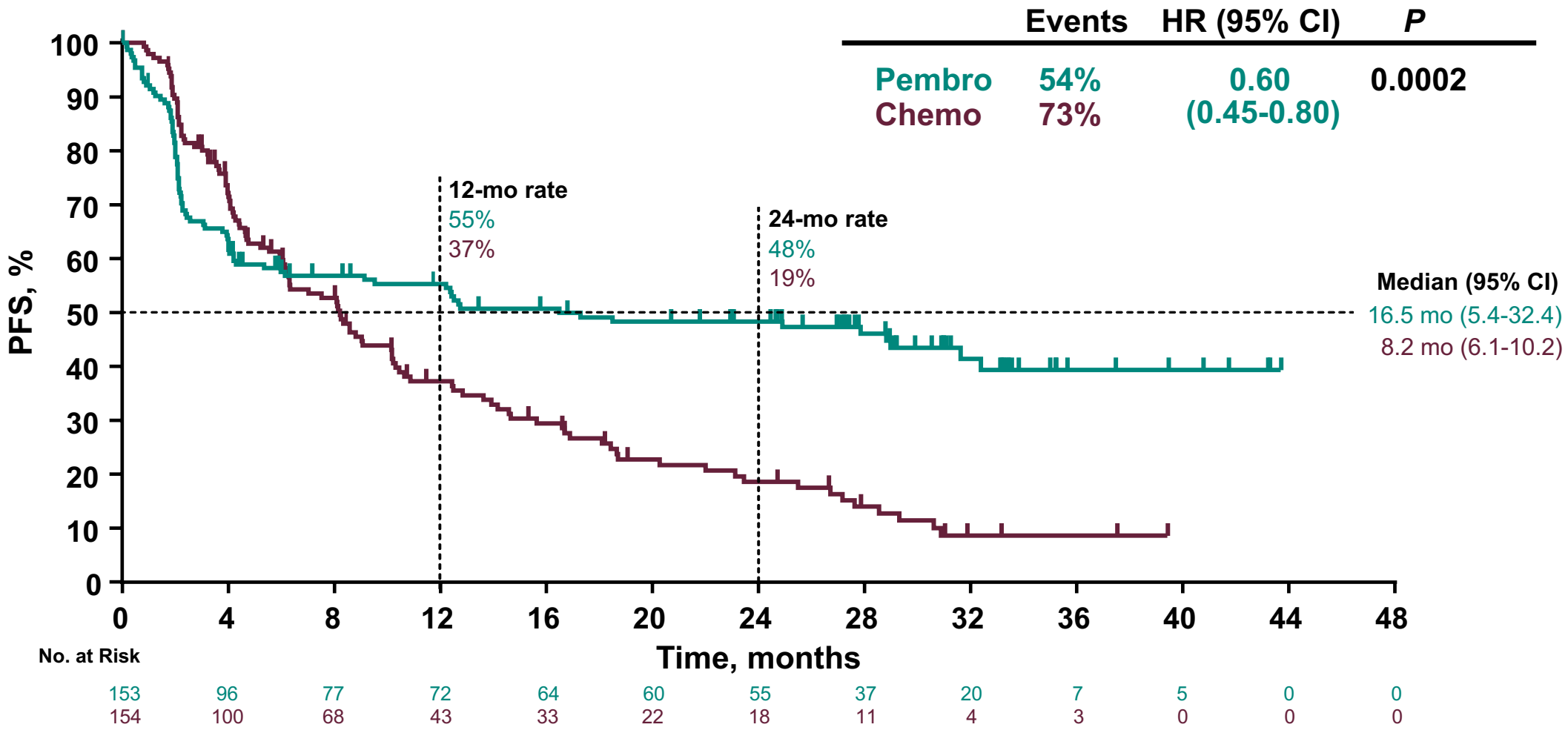
Keynote 177: 1L in MSI-H mCRC



Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR; Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

Shiu et al. ASCO GI 2021

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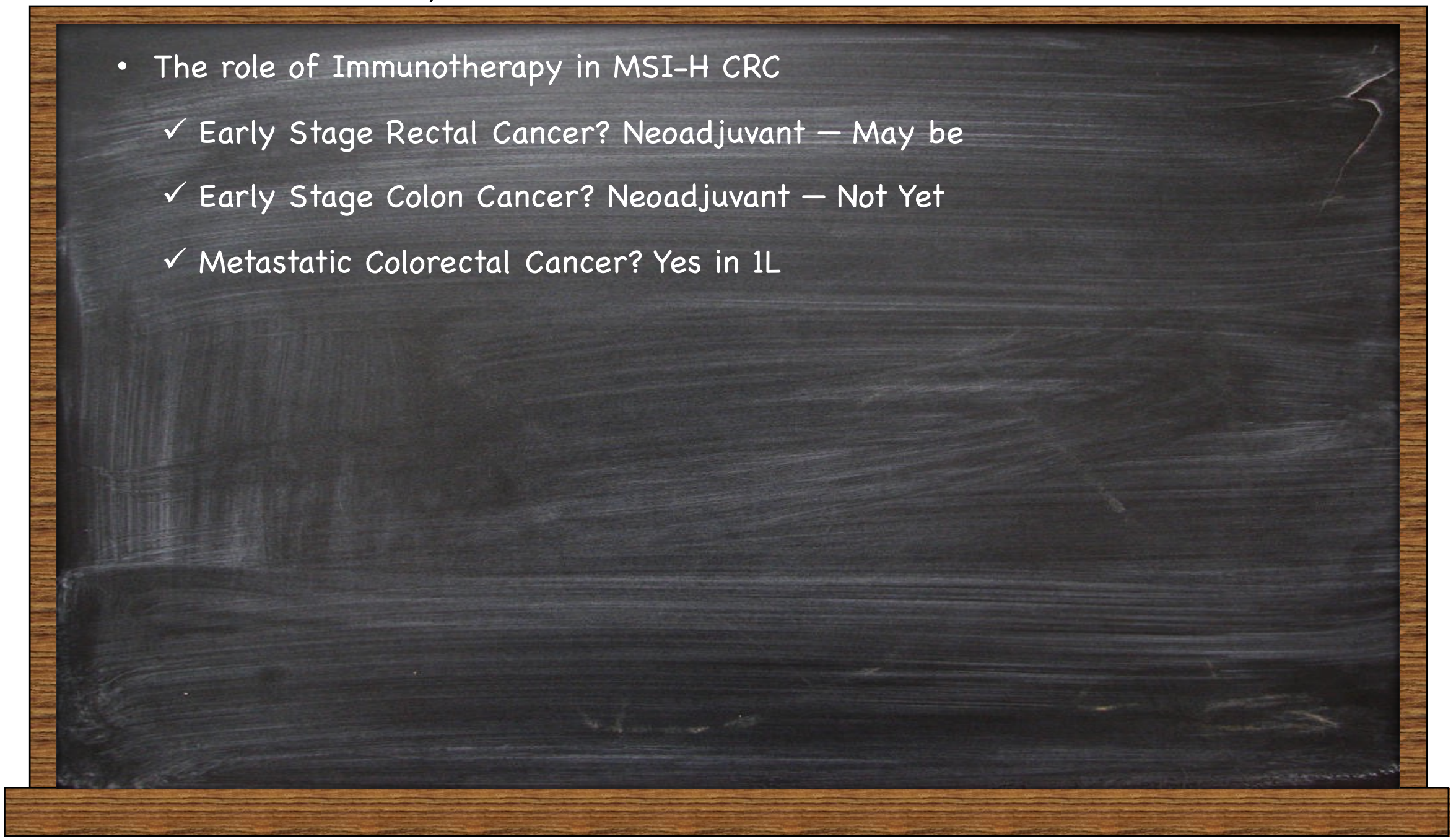

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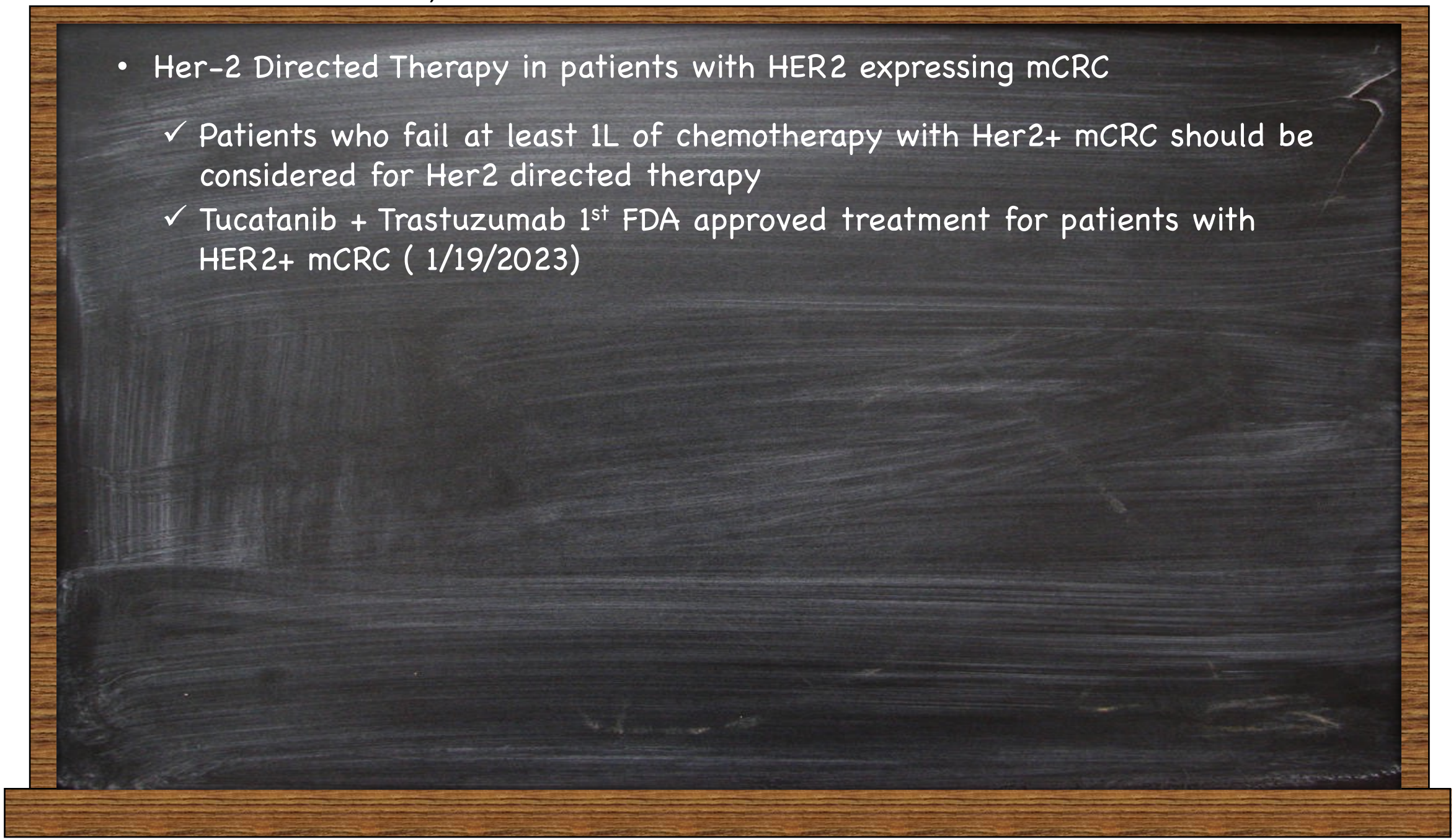
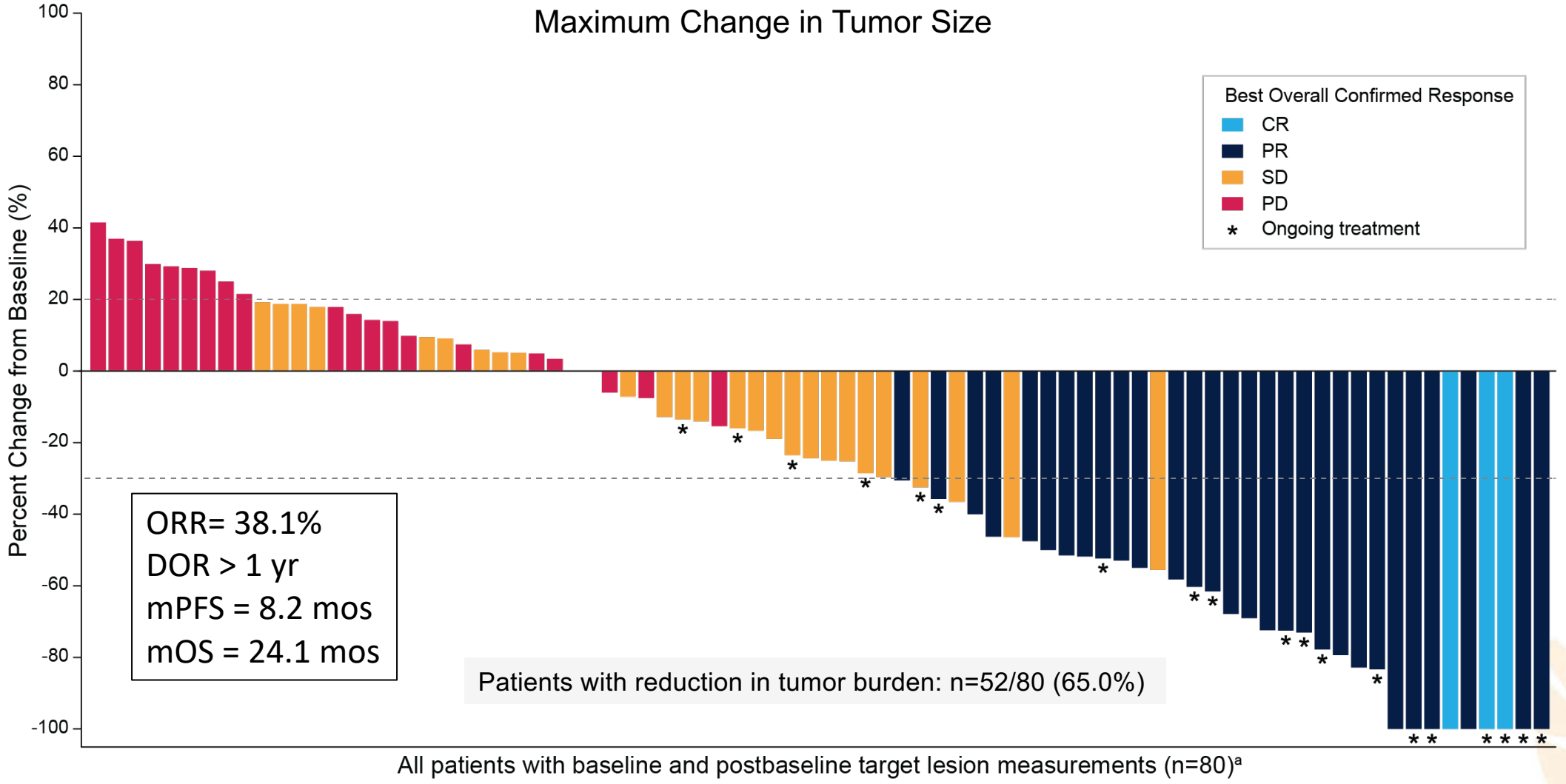


Tucatinib + Trastuzumab: Change in Tumor Size



a Four patients who did not have baseline and/or post-baseline target lesion measurements are excluded

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Data cutoff: 28 Mar 2022

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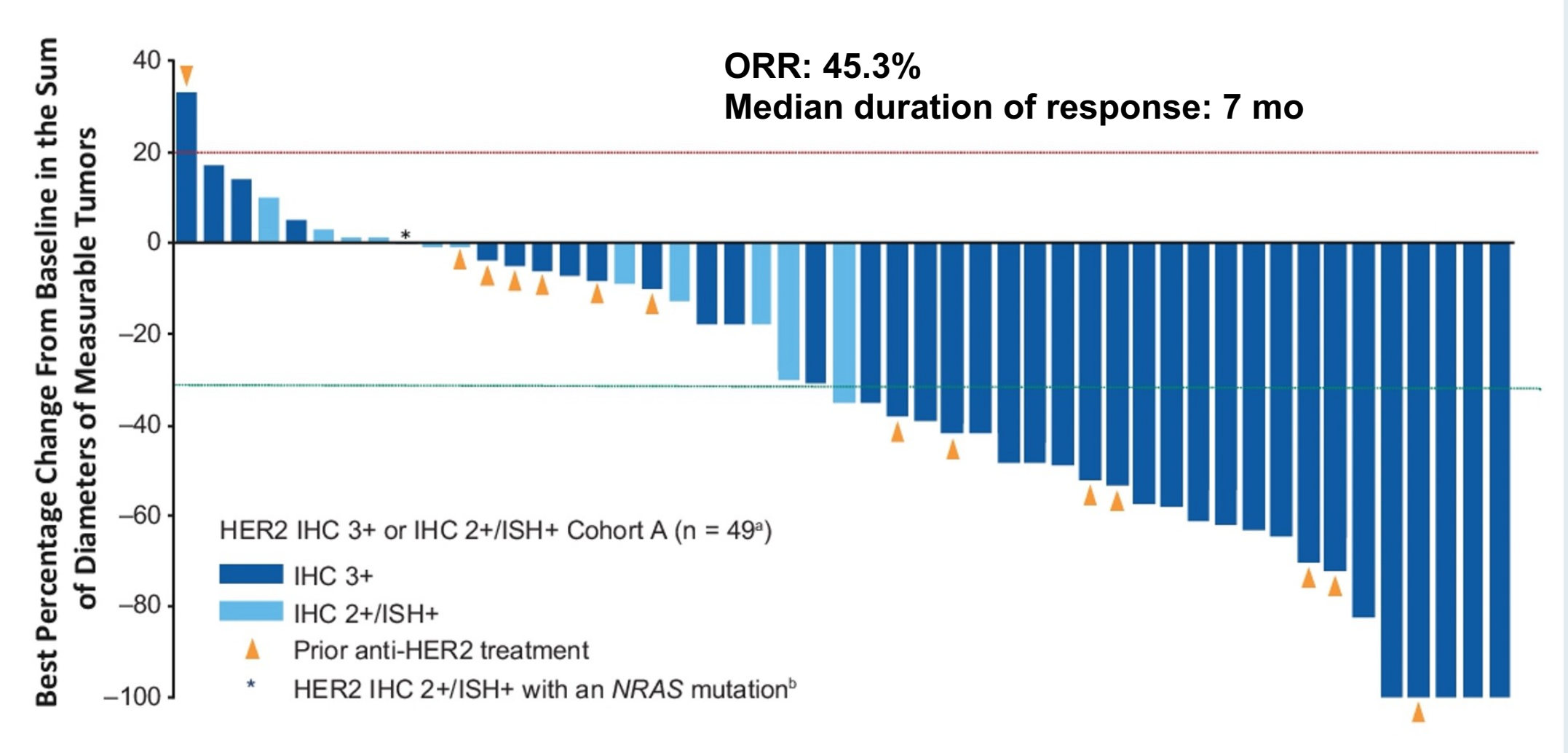
- Her-2 Directed Therapy in patients with HER2 expressing mCRC
  - ✓ Patients who fail at least 1L of chemotherapy with Her2+ mCRC should be considered for Her2 directed therapy
  - ✓ Tucatanib + Trastuzumab (TT) 1st FDA approved treatment for patients with HER2+ mCRC (1/19/2023)
    - Well Tolerated with most toxicities as G1
  - ✓ Consideration for Trastuzumab Deruxtecan post TT
    - Toxicity concerns including ILD (6%)

DESTINY-CRC01 Primary Endpoint: Objective Response Rate (ORR) in Cohort A (IHC 3+ or IHC 2+/ISH+, N = 53)



Yoshino T et al. Gastrointestinal Cancers Symposium 2022;Abstract 119.

RTP RESEARCH TO PRACTICE

Discussion Question

How do you generally sequence regorafenib and TAS-102 for your patients with mCRC? What is your usual starting dose of regorafenib? In which situations should bevacizumab be added to TAS-102?

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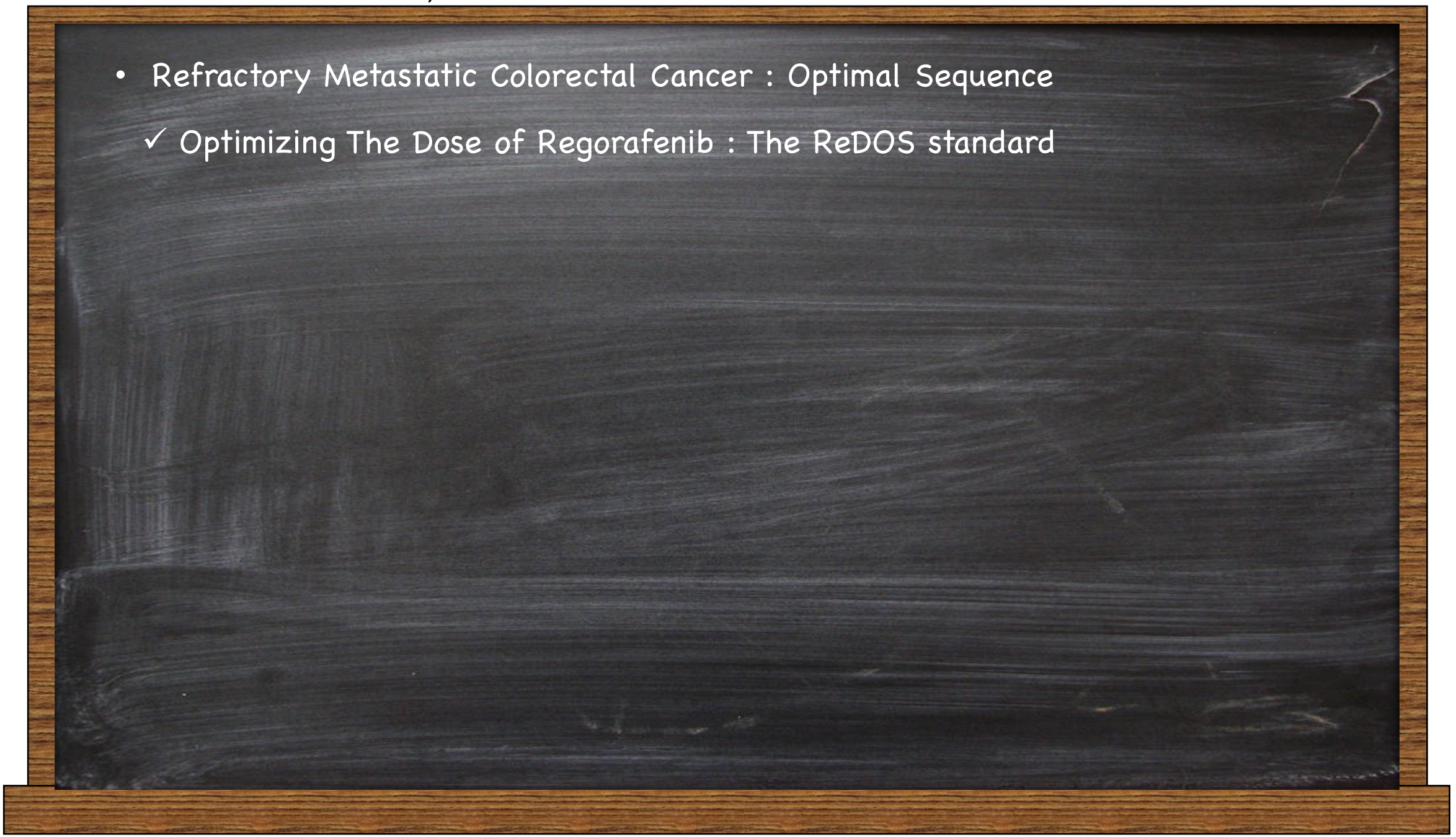


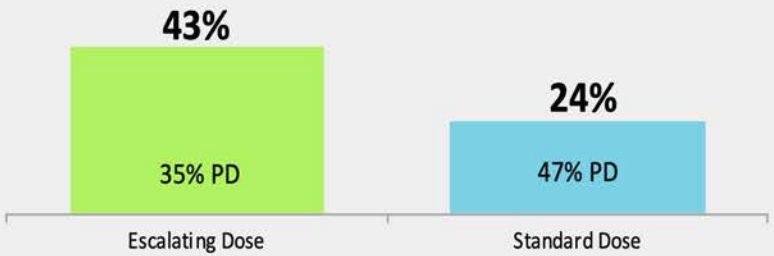
ReDOS : Improving Tolerability while Optimizing Outcome

ReDOS[1] Dose Escalation Schedule

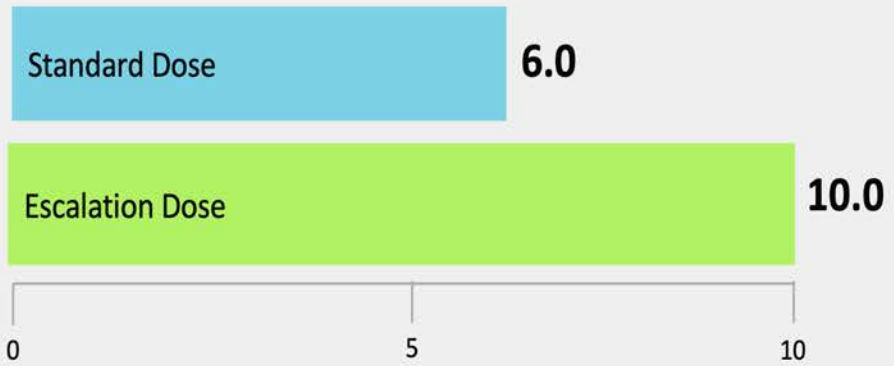
	Cycle 1				Cycle 2
Week	1	2	3	4	1
Once-daily dose	80 mg	120 mg	160 mg	Dosing-free interval	Last dose from cycle 1

ReDOS Dose Optimization Study[1] Results

Percentage Patients Starting Treatment at Cycle 3
(primary endpoint)
P = .0281



Median OS (months)



1 Bekaii-Saab TS, et al. Lancet Oncology , 2019

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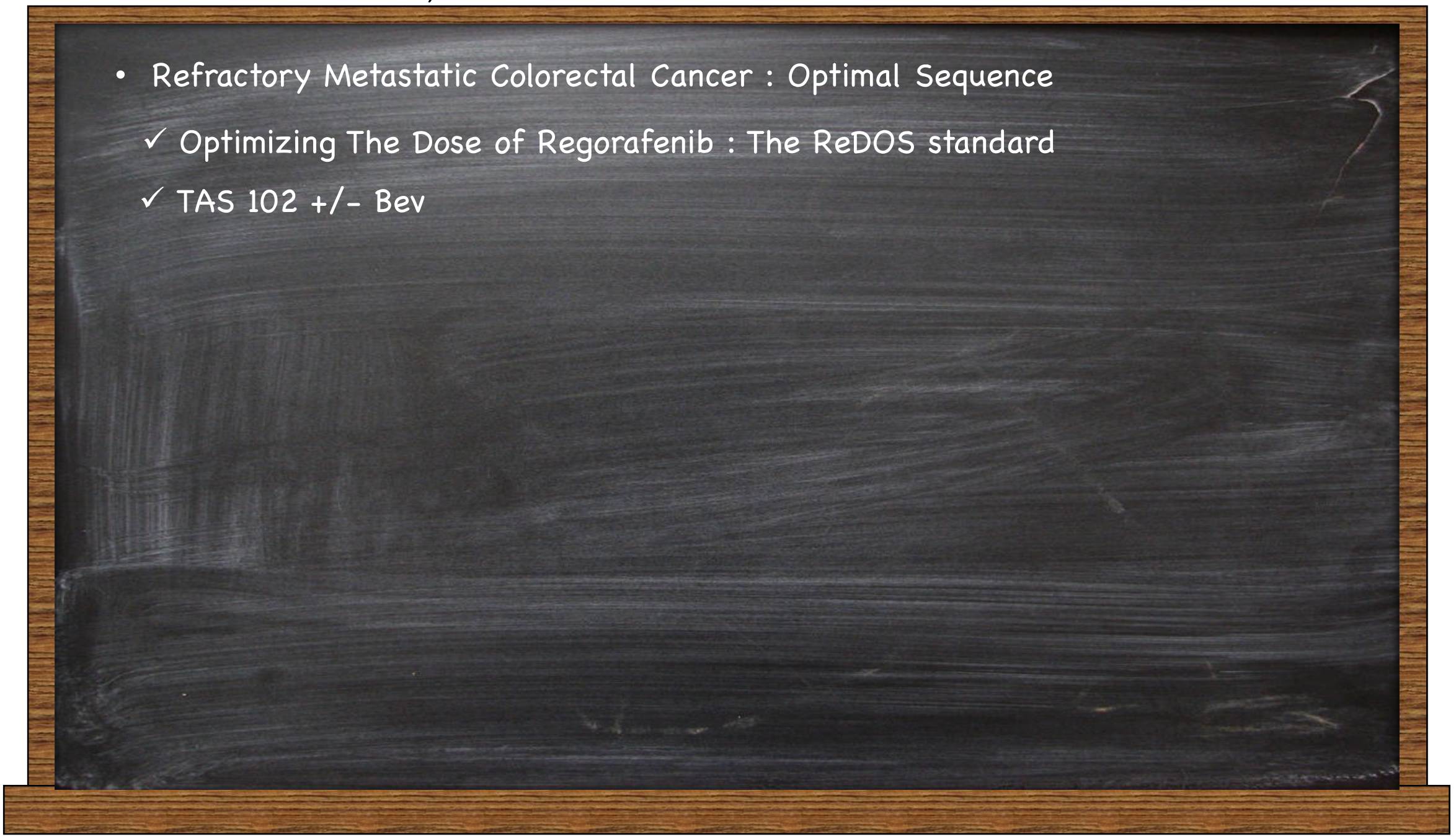
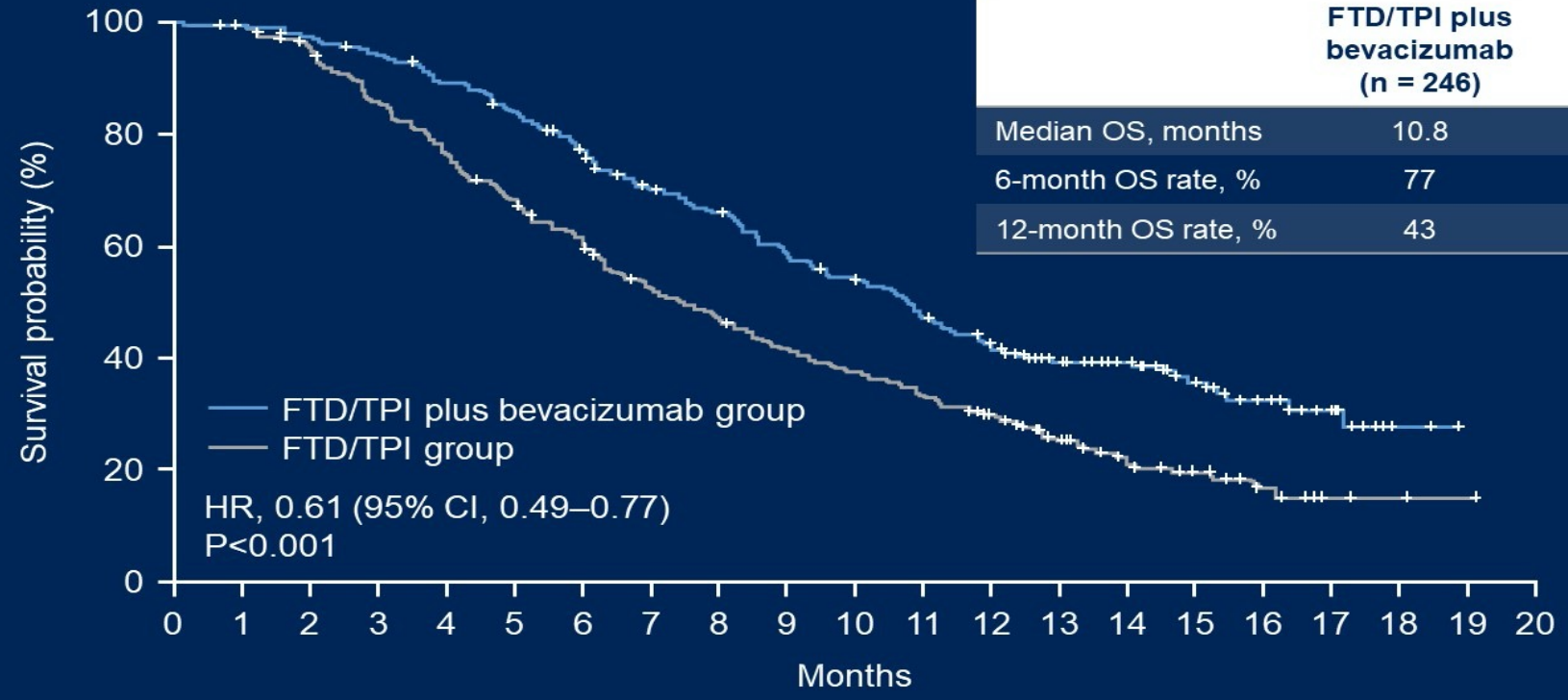


SUNLIGHT study: TAS 102 +/- Bevacizumab

OS in full analysis set (primary endpoint)



	FTD/TPI plus bevacizumab (n = 246)	FTD/TPI (n = 246)
Median OS, months	10.8	7.5
6-month OS rate, %	77	61
12-month OS rate, %	43	30

No. at risk

FTD/TPI plus bevacizumab group	246	244	239	230	217	203	183	160	149	131	119	104	88	69	52	37	24	13	2	0	0
FTD/TPI group	246	242	230	205	184	163	143	120	108	95	85	76	63	44	24	16	10	5	2	1	0

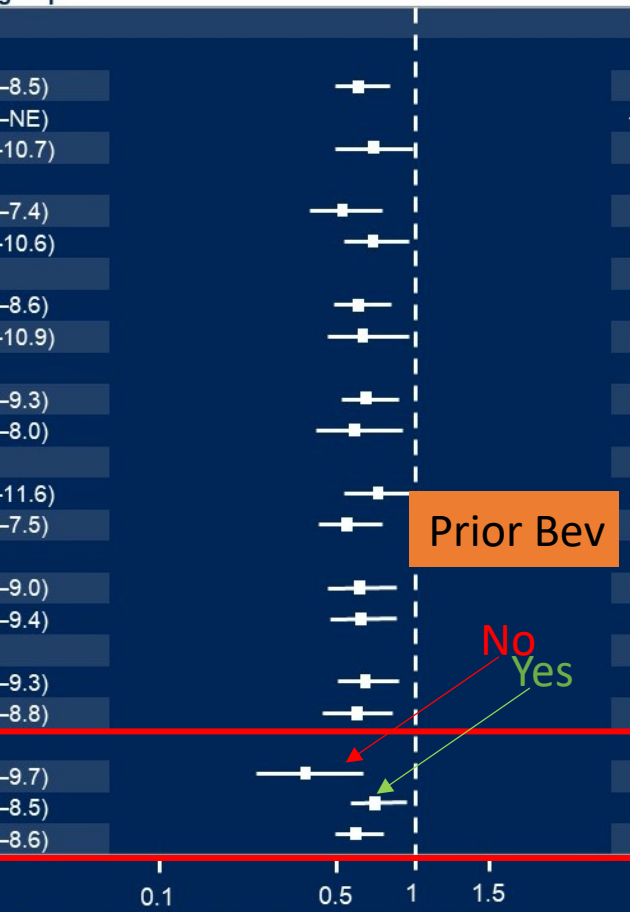
CI, confidence interval; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; OS, overall survival.

Josep Tabernero et al, presented at ASCO GI 2023, 21st Jan 2023,

SUNLIGHT study: OS by prespecified subgroup

OS by prespecified subgroup

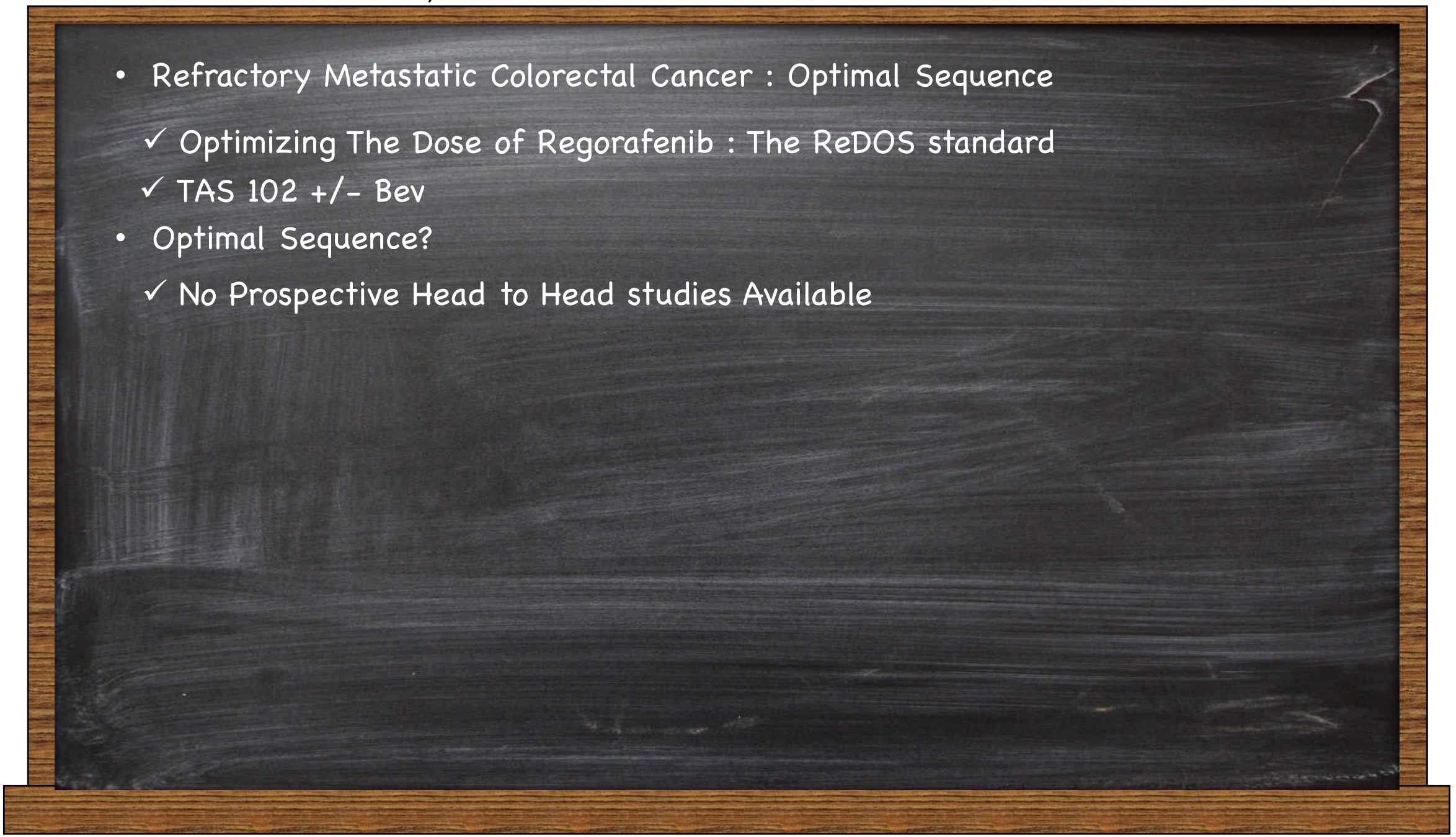
Subgroup	FTD/TPI plus bevacizumab group	FTD/TPI group	FTD/TPI plus bevacizumab group	FTD/TPI group	HR
	No. of events/total no.		Median OS (95% CI)		
Region					
European Union	97/158	121/157	10.6 (9.0–11.8)	7.0 (6.0–8.5)	0.61 (0.47–0.80)
North America	0/8	4/8	NE	6.0 (4.2–NE)	<0.01 (<0.01–NE)
Rest of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



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; NE, not evaluable; OS, overall survival.

Josep Tabernero et al, presented at ASCO GI 2023, 21st Jan 2023,

Chalk Talk – Tanios Bekaii-Saab, MD



Sequential treatment Regorafenib (R) and TAS 102 (T) in mCRC

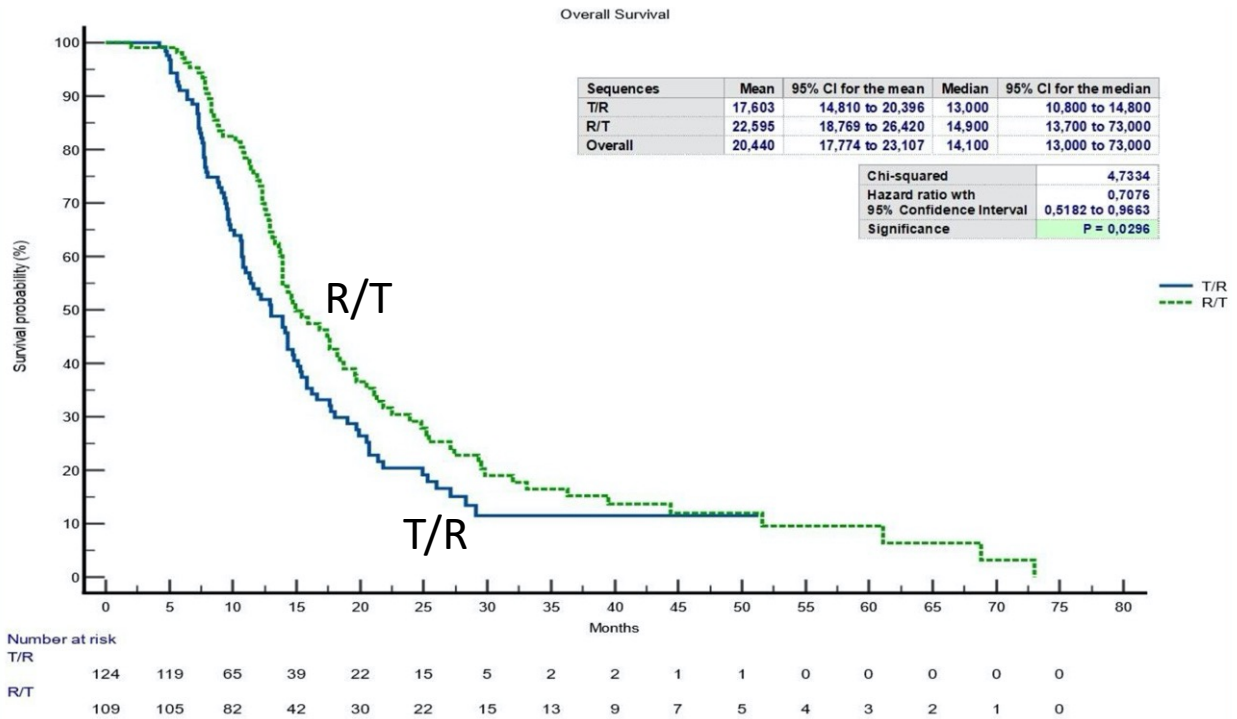


Fig: OS

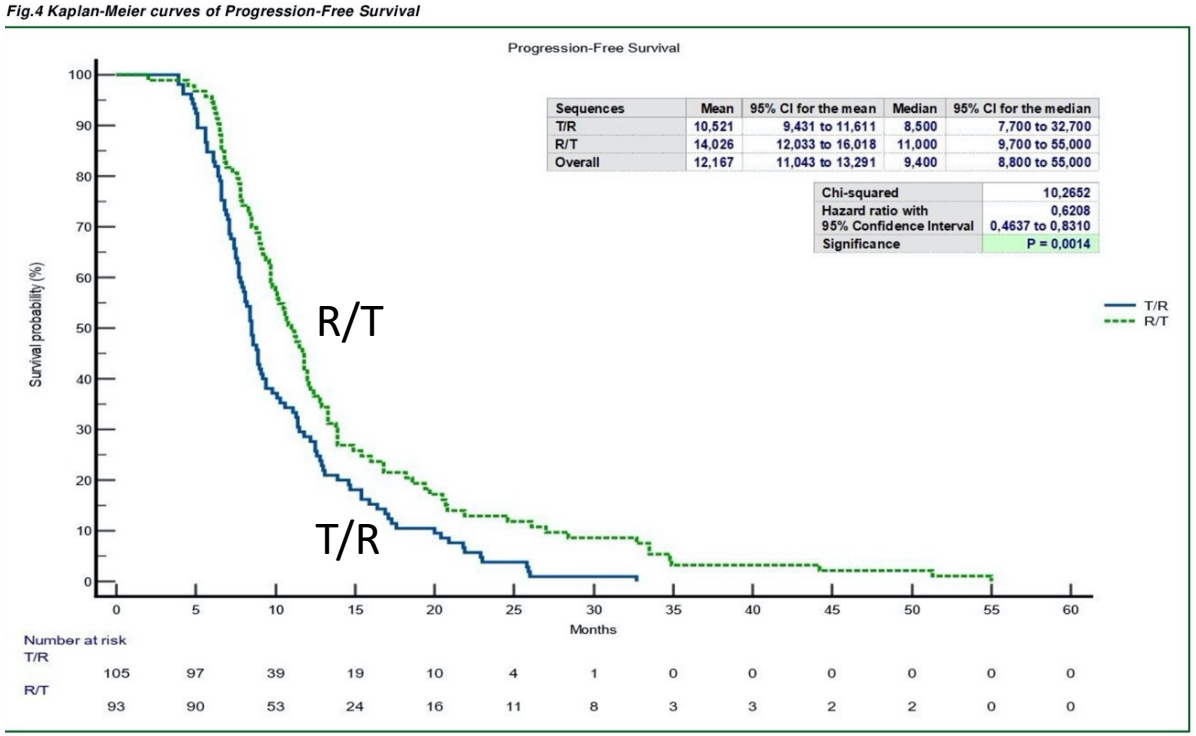


Fig: PFS

PFS and OS were significantly longer in the R/T group.

Carlo Signorelli et al, presented at ASCO GI 2023, J Clin Oncol 41, 2023 (suppl 4; abstr 45)

Chalk Talk – Tanios Bekaii-Saab, MD

- Refractory Metastatic Colorectal Cancer : Optimal Sequence
  - ✓ Optimizing The Dose of Regorafenib : The ReDOS standard
  - ✓ TAS 102 +/- Bev
- Optimal Sequence ?
  - ✓ No H2H studies Available > Different Clinical Scenarios:
    - ✓ Patient with good PS and Liver Function Rego→ TAS 102 + Bevacizumab
    - ✓ Patient with acceptable PS and Good Bone Marrow Function TAS 102 + Beva→ Rego
    - ✓ Fruquintinib if/when approved?

Discussion Question

Given the recent FDA approval of durvalumab in the first-line setting, are you recommending it for most of your patients with newly diagnosed metastatic biliary tract cancer? How are you approaching first-line therapy for your patients who aren't good candidates for gemcitabine/cisplatin?

RTP
RESEARCH
TO PRACTICE

Discussion Question

In general, when do you believe an FGFR inhibitor should be introduced into treatment for patients with metastatic cholangiocarcinoma with an FGFR2 fusion? How do you select among pemigatinib, infigratinib and futibatinib in your practice?

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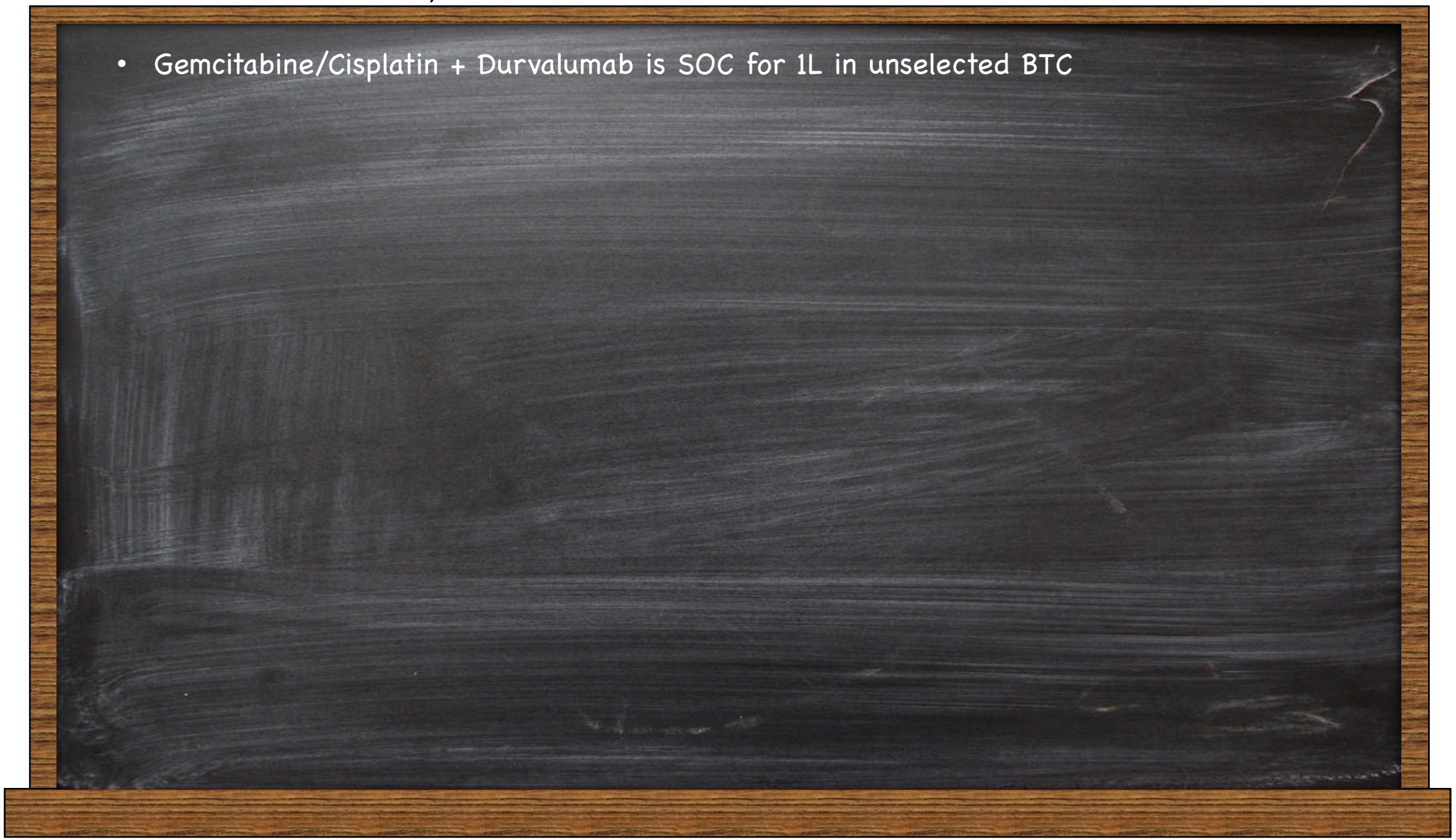
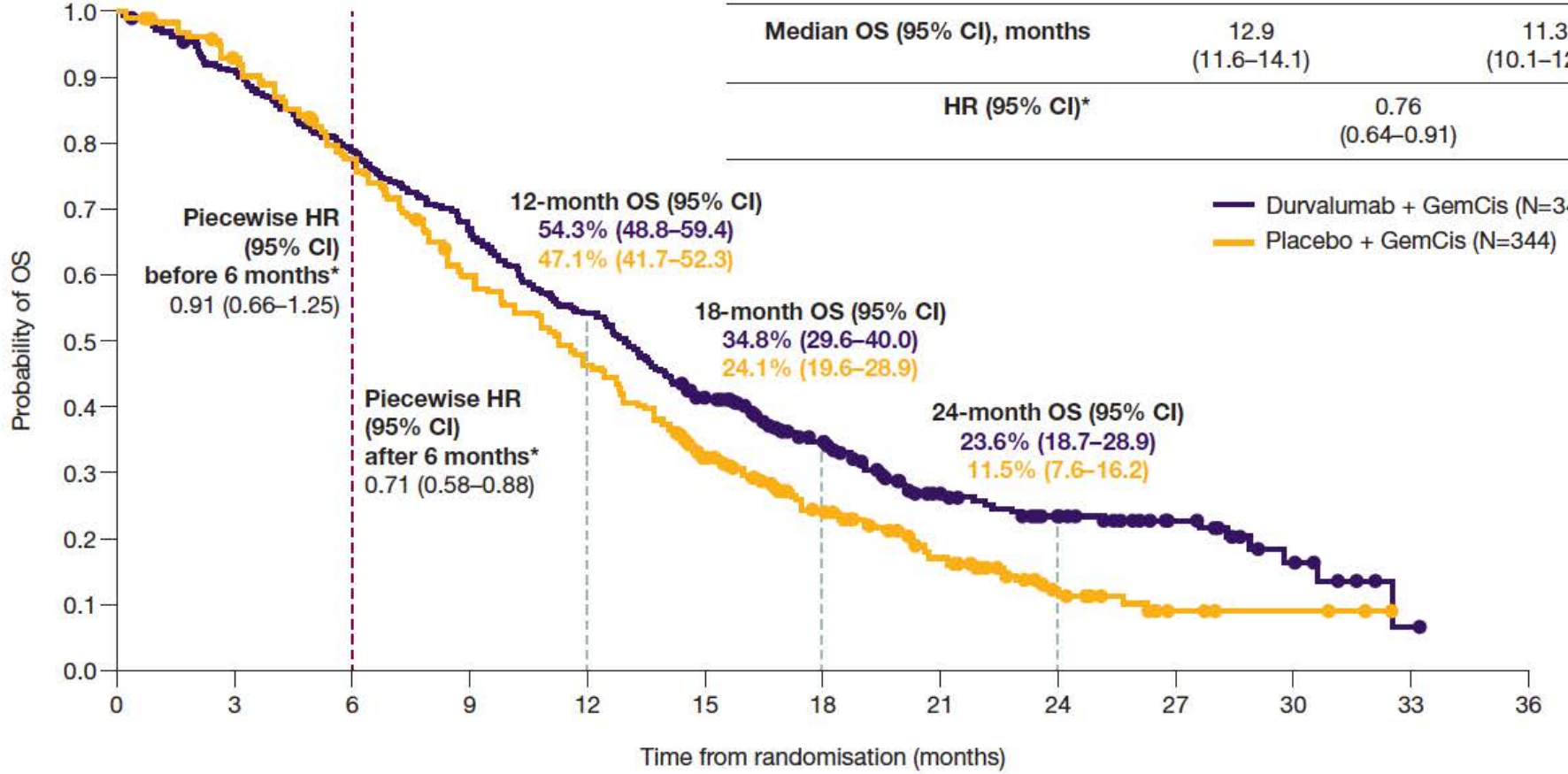
TO PRACTICE

Chalk Talk – Tanios Bekaii-Saab, MD



TOPAZ-1: Primary OS Endpoint with Durvalumab and Gemcitabine/Cisplatin for Advanced Biliary Tract Cancer

	Durvalumab + GemCis (N=341)	Placebo + GemCis (N=344)
Median OS (95% CI), months	12.9 (11.6–14.1)	11.3 (10.1–12.5)
HR (95% CI)*	0.76 (0.64–0.91)	



Oh D-Y et al. ESMO 2022;Abstract 56P.

Chalk Talk – Tanios Bekaii-Saab, MD

- Gemcitabine/Cisplatin + Durvalumab is SOC for 1L in unselected BTC
- Gemcitabine/Cisplatin +/- Pembro (KN 966) 1L BTC - Positive
- Biweekly Gemcitabine/Cisplatin + Every 4 weeks Durva – Preferred in my practice
- BTC = Target rich disease with FGFR2 fusions in ~ 5-10% of IHCA
  - ✓ 3 agents approved for IHCA with FGFR2 fusions following Gem/Cis failure → Pemigatinib , Futibatinib and Infigratinib*
    - RR ~ 30-40% + can be durable in many
    - Watch for hypophosphatemia, skin and ocular toxicities, + other
    - Pemigatinib → Futibatinib may allow to optimize sequential use in my practice
- Future directions → 1L study with Pemigatinib vs. Gem/Cis in pts with FGFR2 fusions