CEDARS-SINAI MEDICAL CENTER

Advances in rectal cancer treatment

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Disclosure Statement

- Advisory/honoraria from Amgen, Astellas, Clinical Congress Consultants

Objectives

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1. Review recent standard of care developments

2. Highlight developments in the pipeline

Stage II/III rectal cancer

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T3-T4 or node + disease

Chemoradiation → **TME** → **Chemotherapy**

4 months

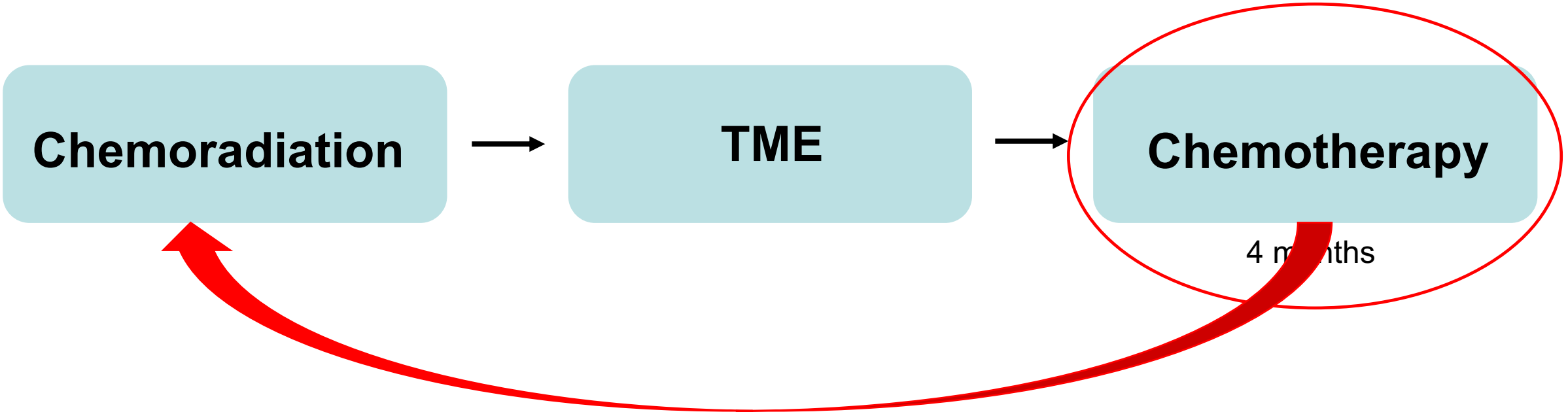
5-year local relapse rate of 5-10%

Pathologic complete response (pCR) rates <20%

Deaths are from metastatic disease
- 5 year DFS approx. 65%
- 5 year OS approx. 75%

Sauer R, et al. NEJM. 2004;351:1731-1740
Roh M, et al. JCO. 2009;27:5124-5130
Gunderson LL, et al. JCO. 2010;28:256-263
Allegra CJ, et al. JNCI. 2015;107(11)

Total neoadjuvant therapy (TNT)



Although intended to, 20-50% do not receive adjuvant chemotherapy

Delays between initiation of adjuvant therapy post-op (ranged 4-12 weeks)

Dose reductions in adjuvant chemo due to toxicities

Biagi JJ, et al. JAMA. 2011;305:2335-2342
Gresham G, et al. Clin Colorectal Cancer. 2015;14:41-45
Khrizman P, et al. JCO. 2013;31:30-388

TNT

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T3-T4 or node + disease

Table 1. Patient and Treatment Characteristics

Characteristic	Patients, No. (%) ChemoRT With Planned Adjuvant Chemotherapy (n = 320)	TNT (n = 308)	*P* Value
Age, y			
<55	128 (40.0)	161 (52.3)	
55-75	152 (47.5)	127 (41.2)	<.001
>75	40 (12.5)	20 (6.5)	
Sex			
Male	192 (60.0)	181 (58.8)	.81
Female	128 (40.0)	127 (41.2)	
Period			
2009-2011	217 (67.8)	28 (9.1)	
2012-2013	65 (20.3)	133 (43.2)	<.001
2014-2015	38 (11.9)	147 (47.7)	
Tumor height (cm) above anal verge			
<5	98 (30.6)	102 (33.1)	
5-10	175 (54.7)	143 (46.4)	.55
>10	47 (14.7)	63 (20.5)	
Imaging for pretreatment staging[a]			
ERUS	85 (34.7)	12 (4.1)	
MRI	84 (34.3)	165 (56.1)	<.001
ERUS and MRI	76 (31.0)	117 (39.8)	
cT stage			
cT1	3 (0.9)	2 (0.6)	
cT2	20 (6.3)	19 (6.2)	
cT3	277 (86.6)	251 (81.5)	.06
cT4	20 (6.2)	36 (11.7)	
cN stage			
cN0	94 (29.4)	43 (14.0)	<.001
cN positive	226 (70.6)	265 (86.0)	
Surgery within 12 mo			
Yes	296 (92.5)	235 (76.3)	<.001
No	24 (7.5)	73 (23.7)	
Type of surgery			
Open	156 (52.7)	65 (27.8)	<.001
Minimally invasive	140 (47.3)	169 (72.2)	
Days to surgery, median (IQR)[b]	56 (48-71)	63 (52-75)	.002
Weeks to surgery[b,c]			
<8	153 (51.7)	82 (34.9)	
8-12	100 (33.8)	108 (46.0)	.001
12-26	41 (13.9)	36 (15.3)	
>26	2 (0.6)	9 (3.8)	
Postoperative chemotherapy[d]			
No	63 (21.5)	214 (94.7)	<.001
Yes	230 (78.5)	12 (5.3)	
Ileostomy after low anterior resection			
No	33 (14.5)	23 (12.5)	.56
Yes	195 (85.5)	161 (87.5)	
Days to ileostomy closure, median (IQR)	192 (166-243)	89 (71-107)	<.001
Ileostomy closure within 15 weeks[e]			
No	176 (91.2)	44 (28.0)	<.001
Yes	17 (8.8)	113 (72.0)	
Months of follow-up, median (range)	40 (6-92)	23 (6-71)	<.001

Abbreviations: ChemoRT, chemoradiation; ERUS, endorectal ultrasound; MRI, magnetic resonance imaging; TNT, total neoadjuvant therapy.

[a] Data were available for 245 patients in the chemoRT with planned adjuvant chemotherapy cohort and 294 patients in the TNT cohort.

[b] After completion of neoadjuvant treatment.

[c] Excluding patients in nonoperative protocols, ie, patients who did not undergo surgery within 12 months after completion of neoadjuvant therapy.

[d] In patients who underwent surgery within 12 months.

[e] In patients who underwent LAR with diverting ileostomy within 12 months.

Cercek A, et al. JAMA. 2018;4:e180071

TNT

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T3-T4 or node + disease

Table 2. Responses to Treatment

Treatment Group[a]	All Patients, No.	All Patients, Sustained cCR, No. (%)[b]	Surgery Within 12 Months, No.	Surgery Within 12 Months, pCR, No. (%)[b]	Complete Response (pCR and Sustained cCR) at 12 Months, No. (%)
ChemoRT with planned adjuvant chemotherapy					
Stage II	94	9 (9.6)	82	14 (17.1)	23 (24.5)
Stage III	226	10 (4.4)	214	35 (16.4)	45 (19.9)
Total	320	19 (5.9)	296	49 (16.6)	68 (21.3)
TNT					
Stage II	43	23 (53.5)	20	0	23 (53.5)
Stage III	265	44 (16.6)	215	43 (20.0)	87 (32.8)
Total	308	67 (21.8)	235	43 (18.3)	110 (35.7)

Abbreviations: cCR, clinical complete response; pCR, pathologic complete response; TNT, total neoadjuvant therapy.

[a] Stages are clinical.

[b] pCR rates are percentages of patients among those who underwent resection within 12 months after completion of neoadjuvant therapy. cCR rates are percentages of patients among all patients in each cohort.

Cercek A, et al. JAMA. 2018;4:e180071

TNT

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T3-T4 or node + disease

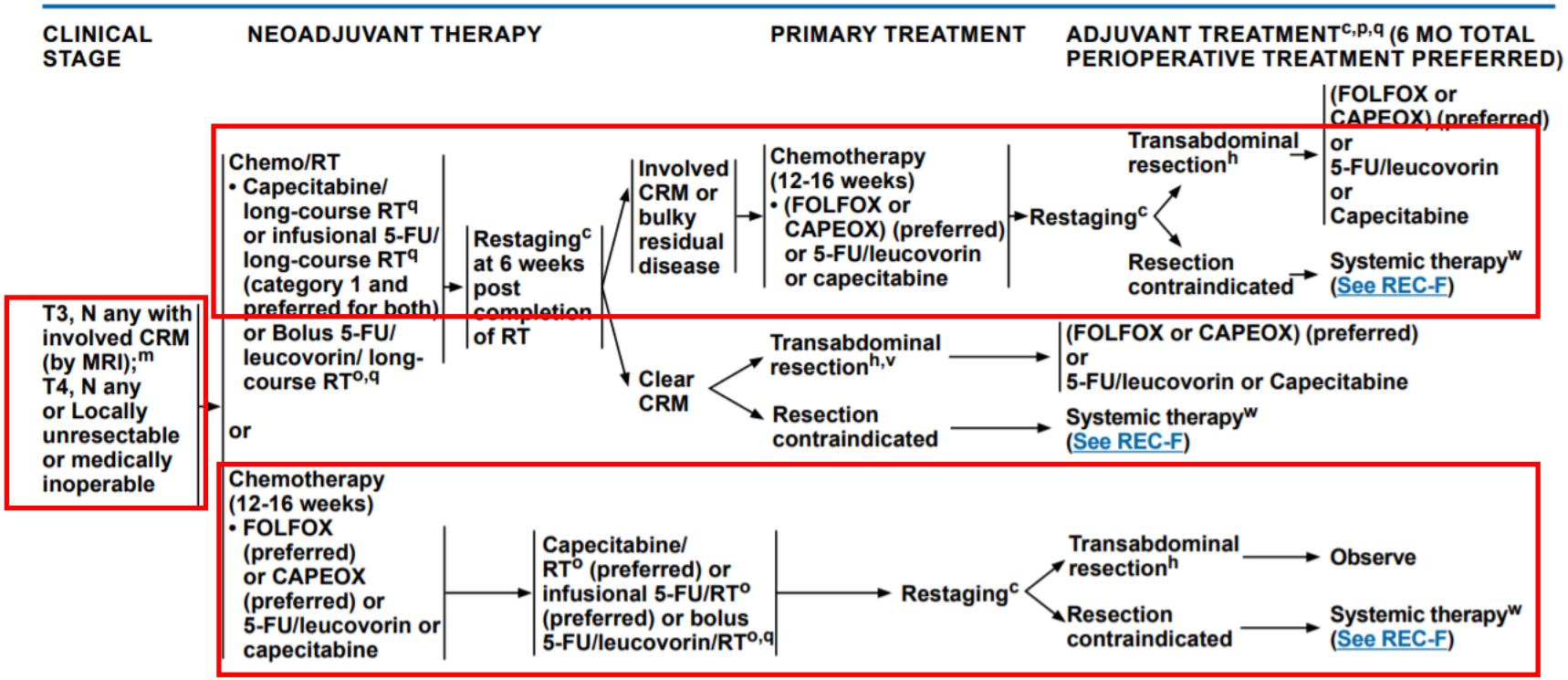
Chemotherapy → **Chemoradiation** → **TME**

4 months

Chemoradiation → **Chemotherapy** → **TME**

4 months

TNT



Rectal Cancer. NCCN Guidelines 2018;Version 3.2018.

CSMC TNT trials

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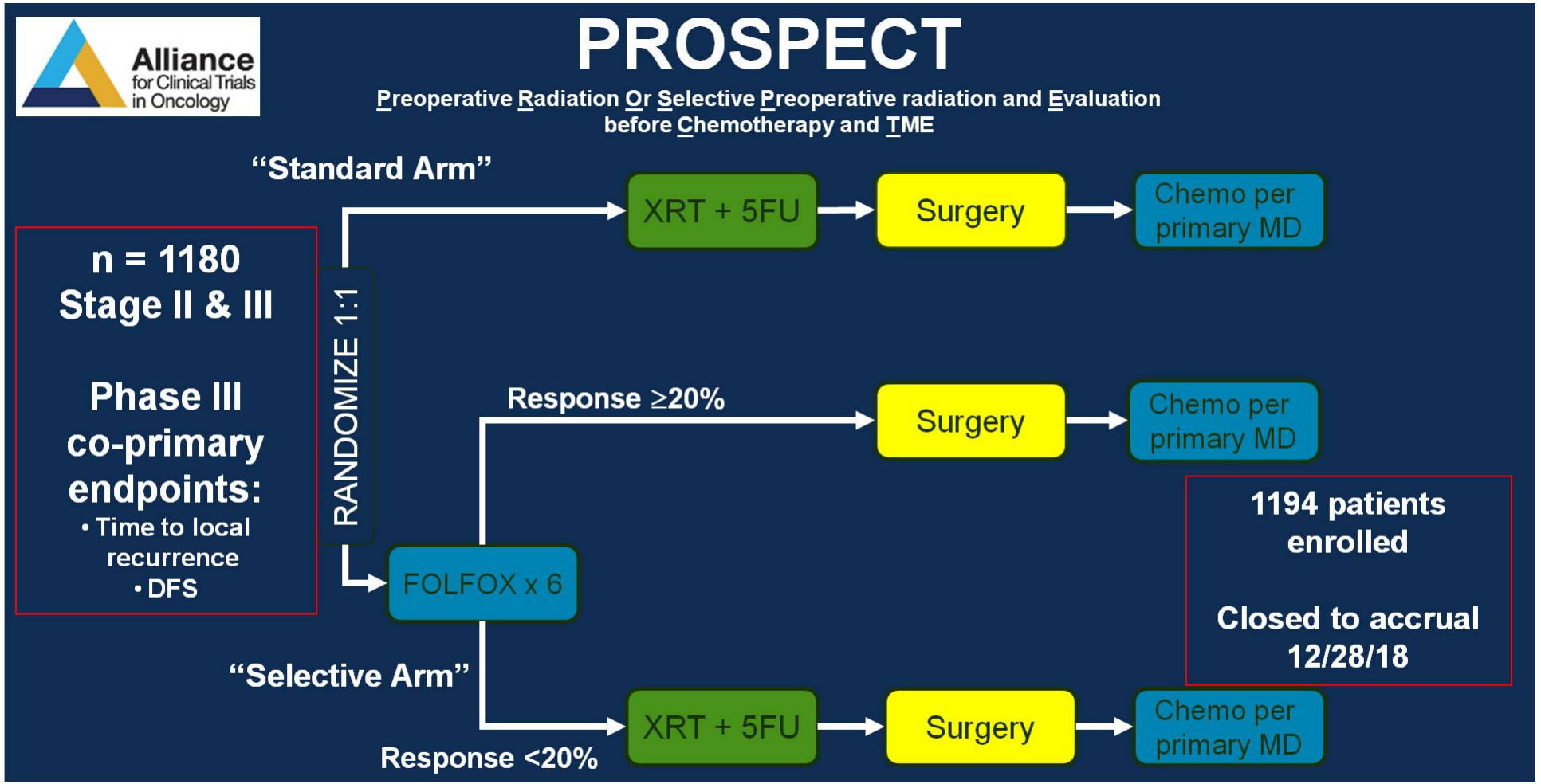

Schrag D, et al. NCT01515787

CSMC TNT trials

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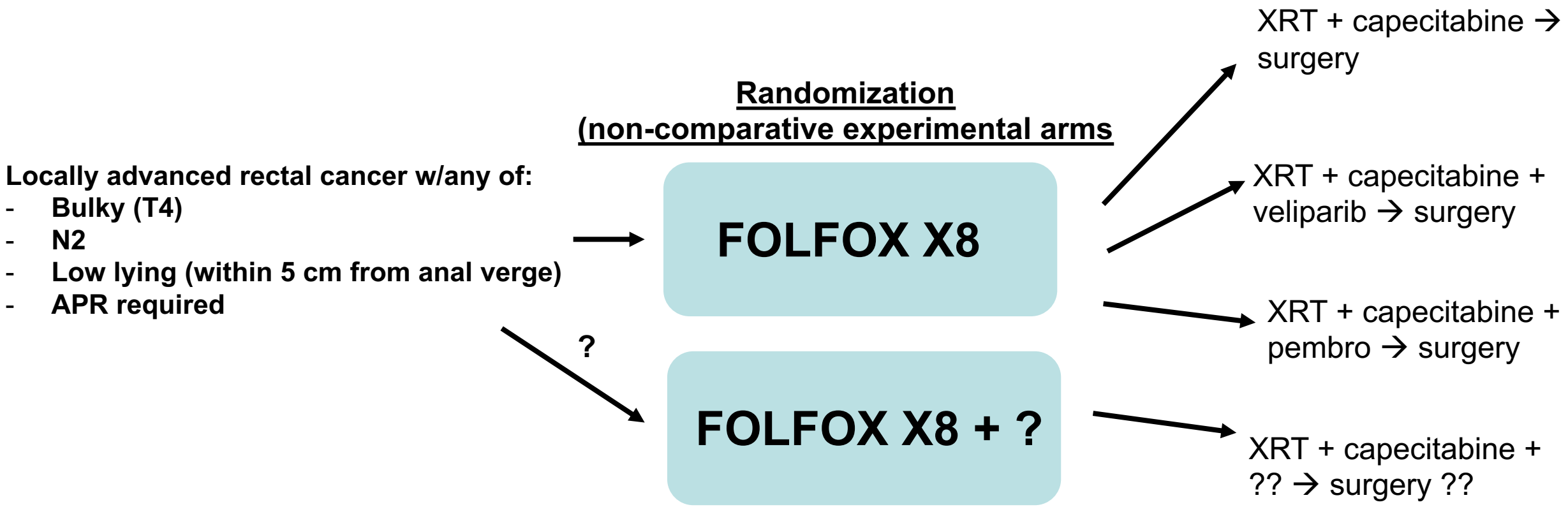
NRG-GI002 TNT Phase II Schema



George, TJ et al. JCO. 2018;36:TPS876

TNT vs. chemoRT

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TNT, ideal for:

- Low rectal tumors, requiring APR
- Threatened circumferential radial margin
- Lymph node positive (especially multiple positive LNs 4 or more, i.e., N2)
- LNs outside mesorectum (pelvic LNs)
- T4 tumors

ChemoRT, ideal for:

- High rectal tumors, requiring LAR
- Clear circumferential radial margin
- Node negative or positive (3 or less LN, i.e., N1)
- LNs within mesorectum (no pelvic LNs)
- T3 tumors

Lefevre, J et al. JCO. 2019;37:483

Stage IV rectal cancer

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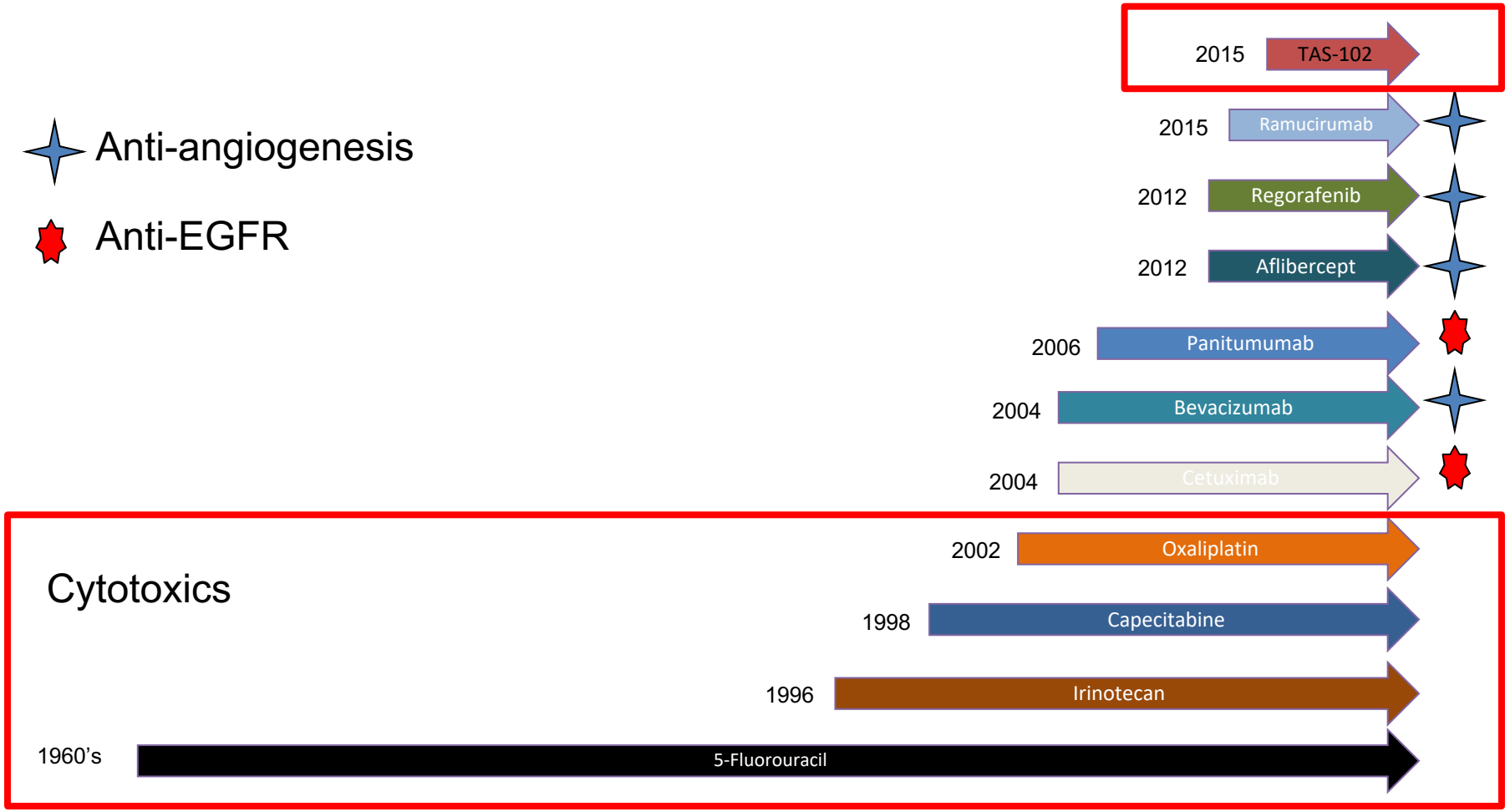
Cytotoxic Backbones



Slide courtesy of M Fakih.

Stage IV rectal cancer

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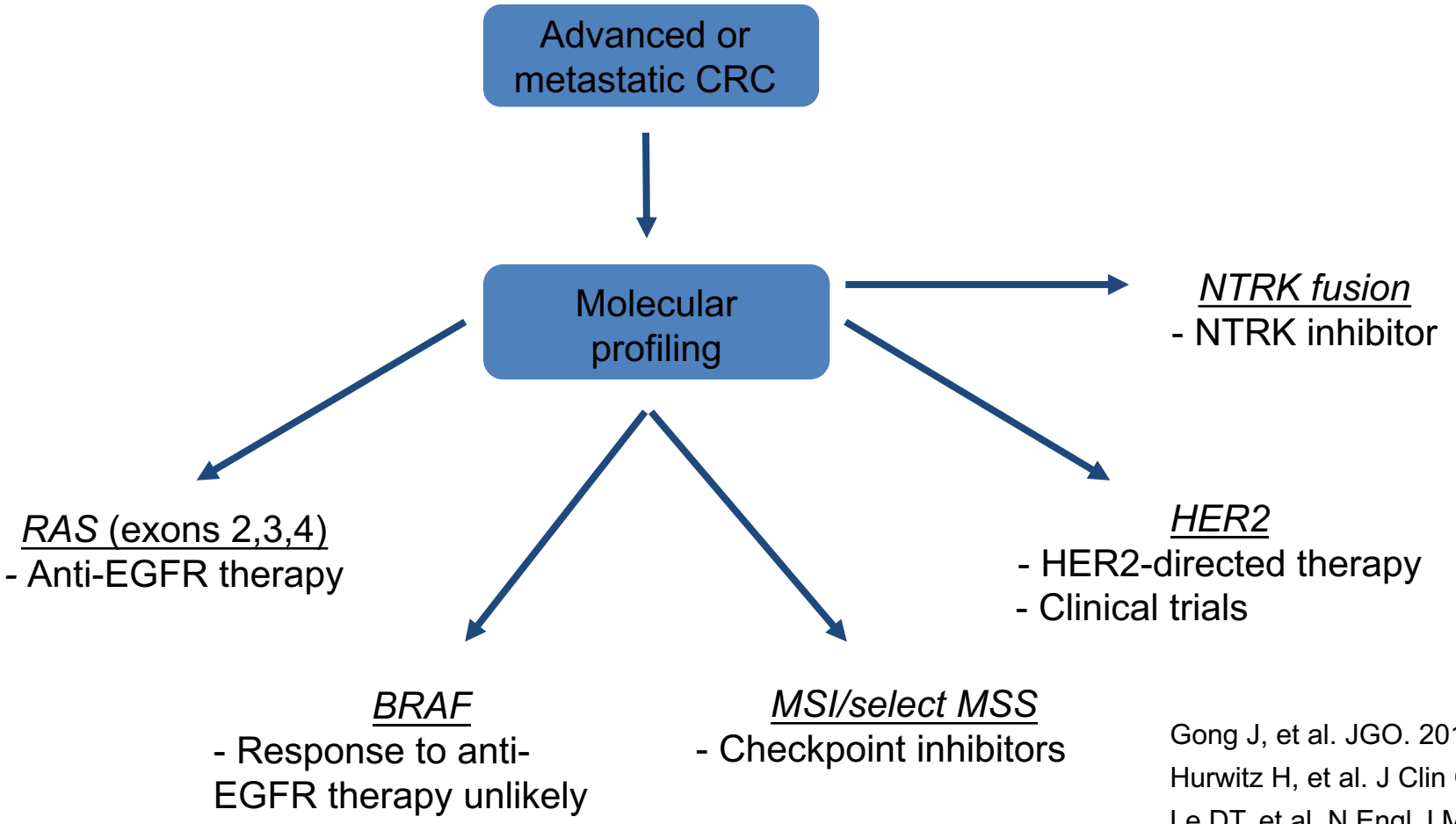
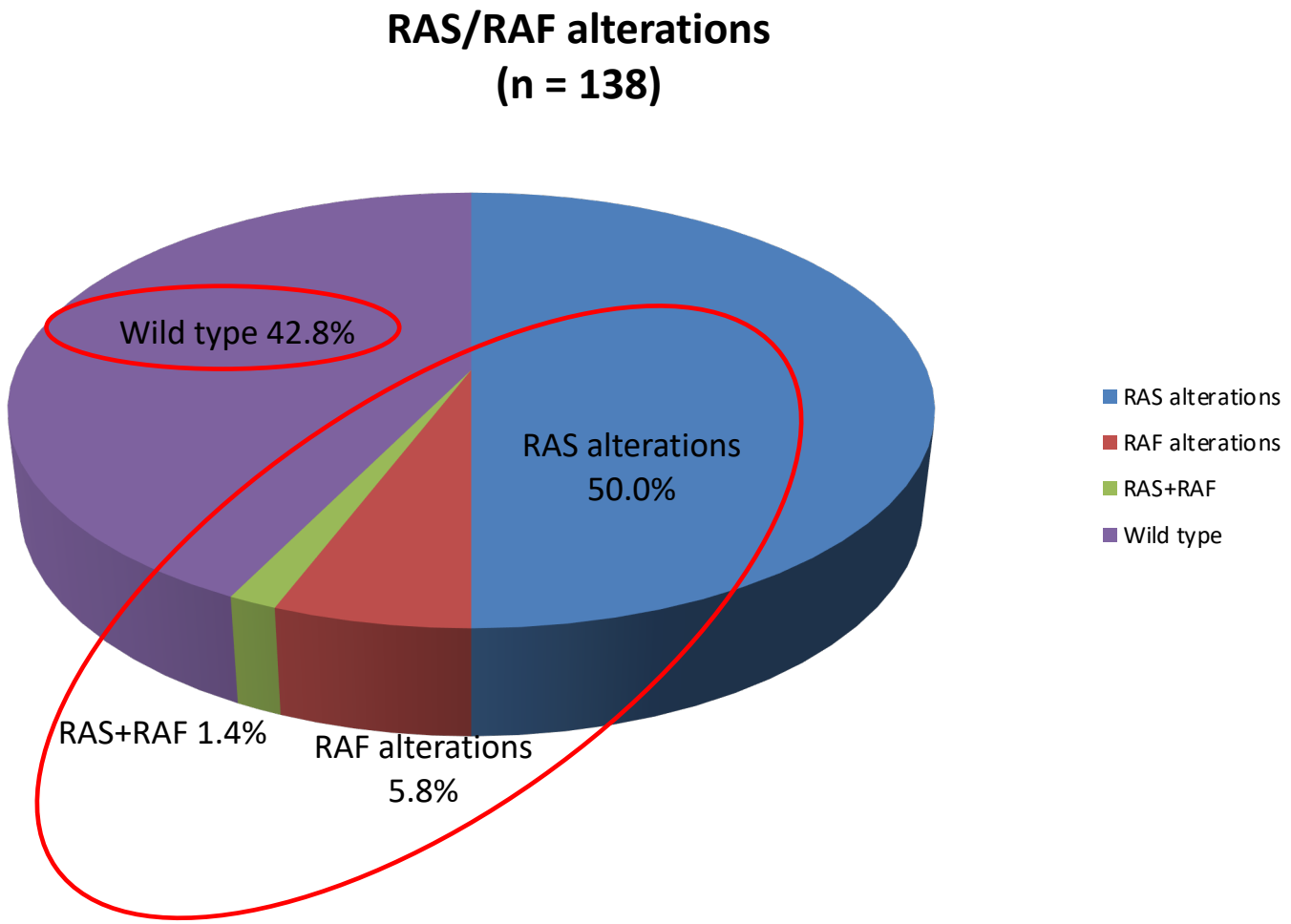
Molecularly Driven



Gong J, et al. JGO. 2016;7:687-704.
Hurwitz H, et al. J Clin Oncol. 2016;35:Abstr 676.
Le DT, et al. N Engl J Med. 2015;372:2509-20
Sartore-Bianchi A, et al. Lancet. 2016;17:738-746.

Stage IV rectal cancer



Gong J, et al. Oncotarget. 2017;doi:10.18632/oncotarget.15030.

Stage IV rectal cancer (RAS)

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FIRST-LINE

EGFR-inhibitors

Study	n= size	Arms	ORR	PFS	OS
COIN (32)	1,630	XELOX or FOLFOX *vs.* same combination + cetuximab	57% *vs.* 64% (P=0.049)	Median 8.6 *vs.* 8.6 months (HR 0.96; 95% CI, 0.82–1.12; P=0.60); *FOLFOX + cetuximab (HR 0.72; 95% CI, 0.53–0.98; P=0.037)	Median 17.9 *vs.* 17.0 months (HR 1.04; 95% CI, 0.87–1.23; P=0.67)
NORDIC-VII (33)	571	FLOX *vs.* cetuximab + FLOX *vs.* cetuximab + intermittent FLOX	ITT: 41% *vs.* 49% *vs.* 47% (OR 1.35; 95% CI, 0.90–2.02; P=0.15); KRAS-wt: 47% *vs.* 46% *vs.* 51% (OR 0.96; 95% CI, 0.55–1.69; P=0.89)	ITT: median 7.9 *vs.* 8.3 *vs.* 7.3 months (HR 0.89; 95% CI, 0.72–1.11; P=0.31); KRAS-wt: 8.7 *vs.* 7.9 *vs.* 7.5 months (HR 1.07; 95% CI, 0.79–1.45; P=0.66)	ITT: median 20.4 *vs.* 19.7 *vs.* 20.3 months (HR 1.06; 95% CI, 0.83–1.35; P=0.67); KRAS-wt: 22.0 *vs.* 20.1 *vs.* 21.4 months (HR 1.14; 95% CI, 0.80–1.61; P=0.48)
OPUS (34)	344	FOLFOX4 + cetuximab *vs.* FOLFOX4	KRAS-wt: 61% *vs.* 37% (OR 2.54; 95% CI, 1.24–5.23; P=0.011); KRAS-mutant: 33% *vs.* 49% (OR 0.51; 95% CI, 0.22–1.15; P=0.106)	KRAS-wt: median 7.7 *vs.* 7.2 months (HR 0.57; 95% CI, 0.358–0.0.907; P=0.0163); KRAS-mutant: 5.5 *vs.* 8.6 months (HR 1.83; 95% CI, 1.095–3.056; P=0.0192)	NR
PRIME (35)	1,183	Panitumumab + FOLFOX4 *vs.* FOLFOX4	KRAS-wt: 55% *vs.* 48% (OR 1.35, P=0.068) KRAS-mutant: 40% *vs.* 40% (value NR)	KRAS-wt: median 9.6 *vs.* 8.0 months (HR 0.80; 95% CI, 0.66–0.97; P=0.02); KRAS-mutant: median 7.3 *vs.* 8.8 months (HR 1.29; 95% CI, 1.04–1.62; P=0.02)	KRAS-wt: median 23.9 *vs.* 19.7 months (HR 0.83; 95% CI, 0.67–1.02; P=0.072); KRAS-mutant: 15.5 *vs.* 19.3 months (HR 1.24; 95% CI, 0.98–1.57; P=0.068)
CRYSTAL (36)	1,198	FOLFIRI + cetuximab *vs.* FOLFOX	KRAS-wt: 57.3% *vs.* 39.7% (OR 2.069; 95% CI, 1.515–2.826; P<0.001); KRAS-mutant: 31.3% *vs.* 36.1% (OR 0.822; 95% CI, 0.544–1.242; P=0.35)	KRAS-wt: median 9.9 *vs.* 8.4 months (HR 0.696; 95% CI, 0.558–0.867; P=0.0012); KRAS-mutant: 7.4 *vs.* 7.7 months (HR 1.171; 95% CI, 0.887–1.544; P=0.26)	KRAS-wt: median 23.5 *vs.* 20.0 months (HR 0.796; 95% CI, 0.670–0.946; P=0.0093); KRAS-mutant: 16.2 *vs.* 16.7 months (HR 1.035; 95% CI, 0.834–1.284; P=0.75)

Gong J, et al. J Gastrointest Oncol 2016;7:687-704.

Stage IV rectal cancer (RAS)

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CHEMOREFRACTORY

EGFR-inhibitors

Study	n= size	Arms	ORR	PFS	OS
BOND (24)	329	Cetuximab + irinotecan *vs.* cetuximab	22.9% (95% CI, 17.5–29.1) *vs.* 10.8% (95% CI, 5.7–18.1, P=0.007)	Median 4.1 *vs.* 1.5 months (P<0.001)	Median 8.6 *vs.* 6.9 months (P=0.48)
CO.17 (25)	572	Cetuximab + BSC *vs.* BSC	PR 8.0% *vs.* 0.0% (P<0.001); SD 31.4% *vs.* 10.9% (P<0.001)	HR 0.68 (95% CI, 0.57–0.80; P<0.001)	HR 0.77 (95% CI, 0.64–0.92; P=0.005)
CO.17 post hoc analysis (26)	394	Cetuximab + BSC *vs.* BSC	KRAS-wt: 12.8% *vs.* 0.0% (P value NR)	KRAS-wt: median 3.7 *vs.* 1.9 months (HR 0.40; 95% CI, 0.30–0.54; P<0.001)	KRAS-wt: median 9.5 *vs.* 4.8 months (HR 0.55; 95% CI, 0.41–0.74; P<0.001)
408 (27)	463	Panitumumab + BSC *vs.* BSC	10% *vs.* 0.0% (P<0.0001)	HR 0.54 (95% CI, 0.44–0.66; P<0.0001)	HR 1.00 (95% CI, 0.82–1.22; P=0.81)
408 post hoc analysis (28)	427	Panitumumab + BSC *vs.* BSC	17% (KRAS-wt) *vs.* 0% (KRAS-mutant, P value NR, both arms combined)	KRAS-wt: median 12.3 *vs.* 7.3 weeks (HR 0.45; 95% CI, 0.34–0.59); KRAS-mutant: median 7.4 *vs.* 7.3 weeks (HR 0.99; 95% CI, 0.73–1.36; P<0.0001)	KRAS-wt *vs.* KRAS-mutant: HR, 0.67 (95% CI, 0.55– 0.82; P value NR, both arms combined)
20100007 (29)	377	Panitumumab + BSC *vs.* BSC	KRAS-wt (exon 2): 27.0% *vs.* 1.6% (HR 24.9; 95% CI, 7.5–123.8; P<0.0001); RAS-wt (exons 3,4 KRAS and NRAS): 31.0% *vs.* 2.3 (HR 20.0; 95% CI, 5.9–101.6; P<0.0001)	KRAS-wt (exon 2): 3.6 *vs.* 1.7 months (HR 0.51; 95% CI, 0.41–0.64; P<0.0001); RAS-wt (exons 3,4 KRAS and NRAS): 5.2 *vs.* 1.7 months (HR 0.46; 95% CI, 0.35–0.59; P<0.0001)	KRAS-wt (exon 2): 10.0 *vs.* 7.4 months (HR 0.73; 95% CI, 0.57–0.93; P=0.0096); RAS-wt (exons 3,4 KRAS and NRAS): 10.0 *vs.* 6.9 months (HR 0.70; 95% CI, 0.53–0.93; P=0.0135)
ASPECCT (30)	999	Panitumumab *vs.* cetuximab	OR 1.15 (95% CI, 0.83–1.58; P value NR)	HR 1.00 (95% CI, 0.88–1.14; P value NR)	HR 0.97 (95% CI, 0.84–1.11; P value NR)

Gong J, et al. J Gastrointest Oncol 2016;7:687-704.

Stage IV rectal cancer (BRAF)

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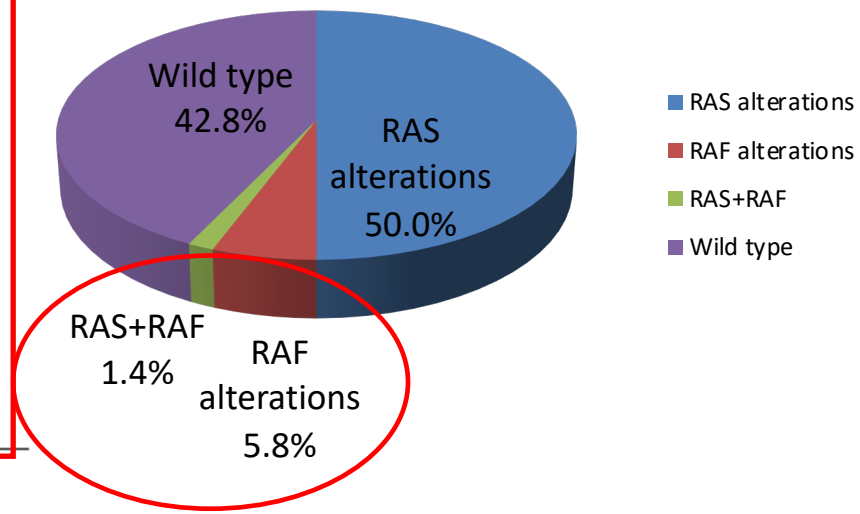
EGFR-inhibitors

Study	Arms	Frequency of BRAF mutants	BRAF-mutant OS (median)	BRAF-wt OS (median)
First-line settings				
CAIRO2 (22,59)	XELOX + bevacizumab	45/519 (8.7%)	15.0 months	24.6 months
	XELOX + bevacizumab + cetuximab		15.2 months	21.5 months
COIN (32)	XELOX or FOLFOX	102/1,316 (7.8%)	10.0 months	20.1 months (KRAS/NRAS/BRAF-wt)
	XELOX or FOLFOX + cetuximab		7.2 months	19.9 months (KRAS/NRAS/BRAF-wt)
NORDIC VII (33)	FLOX +/– cetuximab	55/457 (12.0%)	9.5 months	22.0 months
CRYSTAL (36)	FOLFIRI	60/999 (6.0%)	10.3 months	21.6 months (KRAS/BRAF-wt)
	FOLFIRI + cetuximab		14.1 months	25.1 months (KRAS/BRAF-wt)
PRIME post hoc analysis (35)	FOLFOX4	53/619 (9.0%)	9.2 months	15.8 months
	FOLFOX4 + panitumumab		10.5 months	14.5 months
Second-line settings				
20050181 post hoc analysis (42)	FOLFIRI	45/541 (8.3%)	5.7 months	15.4 months (RAS/BRAF-wt)
	FOLFIRI + panitumumab		4.7 months	18.7 months (RAS/BRAF-wt)
PICCOLO (41)	Irinotecan	68/460 (14.8%)	HR 1.56 (95% CI, 1.08–2.37; P=0.035) of BRAF-mutant *vs.* KRAS/NRAS/BRAF-wt	
	Irinotecan + panitumumab		HR 1.84 (95% CI, 1.10–3.08; P=0.029) of BRAF-mutant *vs.* KRAS/NRAS/BRAF-wt	

RAS/RAF alterations (n = 138)



Gong J, et al. J Gastrointest Oncol 2016;7:687-704.
Gong J, et al. Oncotarget. 2017;doi:10.18632/oncotarget.15030.

Stage IV rectal cancer (BRAF)

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TRIBE

Phase III randomized 508 patients with mCRC who were previously untreated to:

- FOLFIRI-A: Irinotecan 180 mg/m2 IV 60 min + 200 mg/m2 LV + Bevacizumab 5 mg/kg + 5-FU 400 mg/m2 bolus → 2400 mg/m2 FU continuous infusion over 46 h
- FOLFOXIRI- A: Irinotecan 165 mg/m2 IV 60 min + oxaliplatin 85 mg/m2 + 200 mg/m2 LV → 5-FU 3200 mg/m2 continuous over 48 h + bevacizumab

Median OS was 29.8 mo FOLFOXIRI-A vs 25.8 mo FOLFIRI-A (HR 0·80, 95% CI 0.65-0.98, p=0.03).

Median OS 13.4 mo in the BRAF-mutation-positive, superior over FOLFIRI-A (HR 2.79, 95% CI 1.75-4·46, p<0·0001)

Preferred 1st-line in BRAF-mutated mCRC

Cremolini C, et al. Lancet Oncol 2015;16:1306-1315.

Stage IV rectal cancer (BRAF)

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BEACON Phase III Trial

29 mCRC patients with BRAFv600 mutation in 2nd-3rd-line setting:

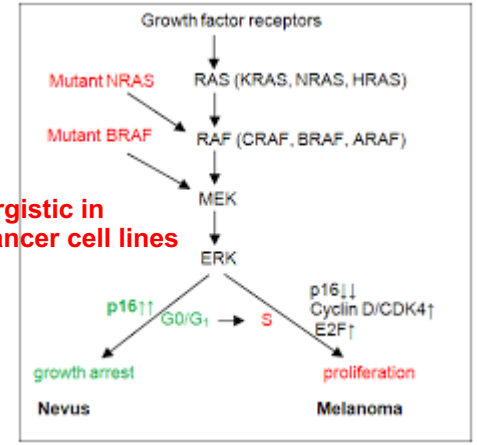
- BRAF inhibitor ENCORAFENIB (300 mg oral daily) + MEK inhibitor BINIMETINIB (45 mg oral BID) + anti-EGFR antibody CETUXIMAB (weekly)

Preferred 2nd-line in BRAF-mutated mCRC

- Confirmed ORR and median PFS (ORR, 48% [95%CI, 29.4-67.5]; PFS, 8.0 mo [95% CI, 5.6-9.3 mo])

- Mature median OS is 15.3 mo (95% CI, 9.6 mo-not reached)

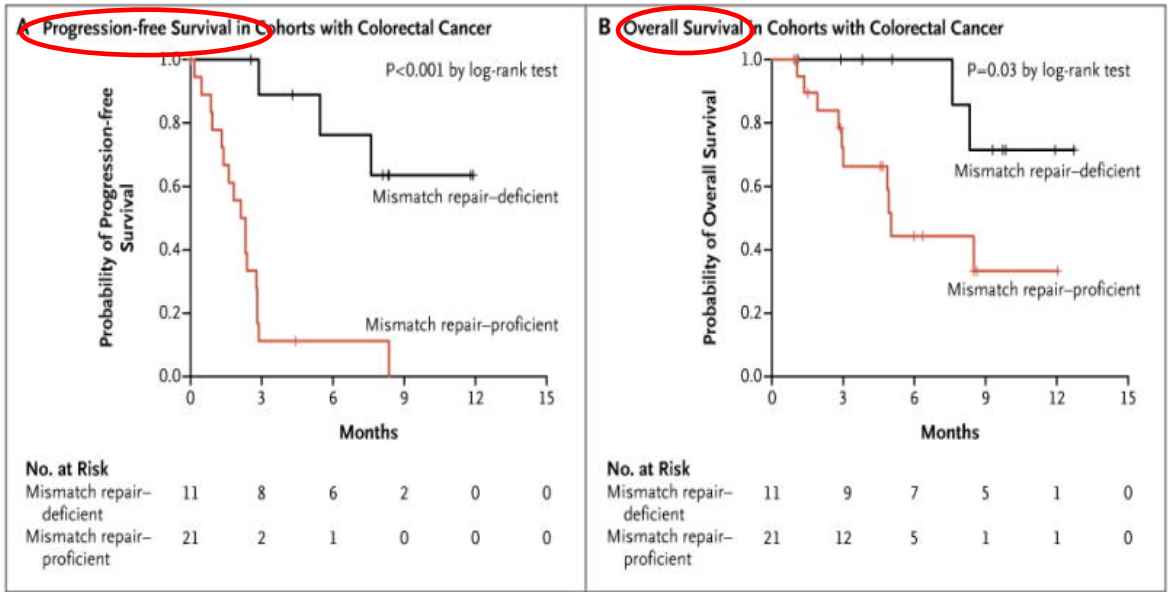
Targeting MEK is synergistic in KRAS/BRAF-mt colorectal cancer cell lines



Gong J, et al. Anticancer Res 2017;37:2831-2838

Kopetz S, et al. JCO 2019;37:688

Stage IV rectal cancer (MSI-H)



- ORR 40% (A) vs. 0% (B)

- Median PFS and OS NR (A) vs. 2.2 mo (95% CI 1.4-2.8) and 5.0 mo (95% CI 3.0-NE) (B)

KEYNOTE-016

- 41 pts treatment-refractory progressive metastatic cancer stratified to:
  - -- (A) dMMR mCRC
  - -- (B) pMMR mCRC
  - -- (C) dMMR non-CRC
- Pembrolizumab 10 mg/kg Q2weeks

Le DT, et al. N Engl J Med. 2015;372:2509-20

Stage IV rectal cancer (MSI-H)

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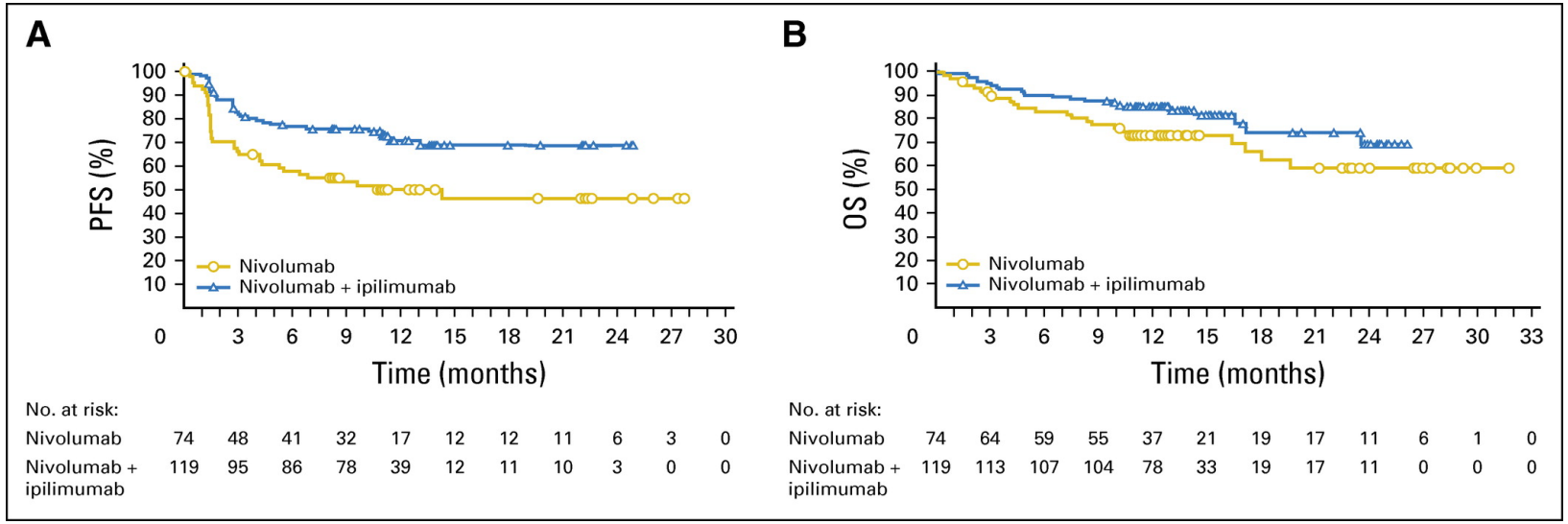
Table 2. ORR, Best Overall Response, and DCR per Investigator Assessment (N = 119)

Response	No. (%)	95% CI
ORR	65 (55)	45.2 to 63.8
Best overall response		
Complete response	4 (3)	
Partial response	61 (51)	
Stable disease	37 (31)	
Progressive disease	14 (12)	
Not determined	3 (3)	
Disease control for ≥ 12 weeks	95 (80)	71.5 to 86.6

Abbreviations: DCR, disease control rate; ORR, objective response rate.

Nivolumab (FDA approved)

Nivolumab + ipilimumab (FDA approved)



Overman MJ, et al. JCO. 2018;36:773-779

Stage IV rectal cancer (NTRK)

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Phase I LOXO 101

8/70 w/treatment-refractory advanced solid tumors harboring NTRK fusions

- Larotrectinib doses are 100 mg orally twice daily

- ORR was 100% (eight of eight patients)

- FDA approved November 26, 2018

- Detectable by NGS

Hong DS, et al. Ann Oncol. 2019; doi: 10.1093/annonc/mdy539

Outline

CEDARS-SINAI MEDICAL CENTER

Standard of care developments

In the pipeline

Stage IV rectal cancer (HER2)

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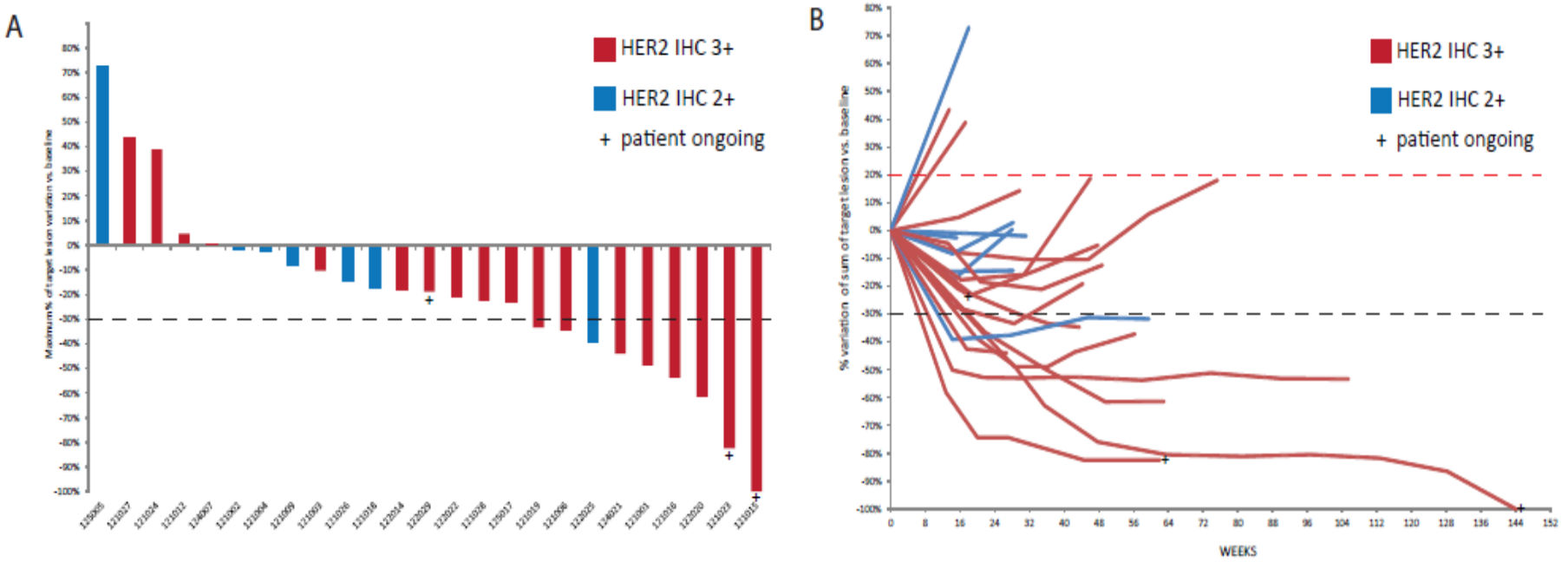
Phase II HERACLES enrolled 27 mCRC patients (KRAS WT and HER2+) refractory to all standard therapies

- IV trastuzumab at 4 mg/kg loading dose followed by 2 mg/kg once per week + oral lapatinib at 1000 mg per day until PD



Most HER2+ mCRC are of L-sided primary (i.e., rectum)

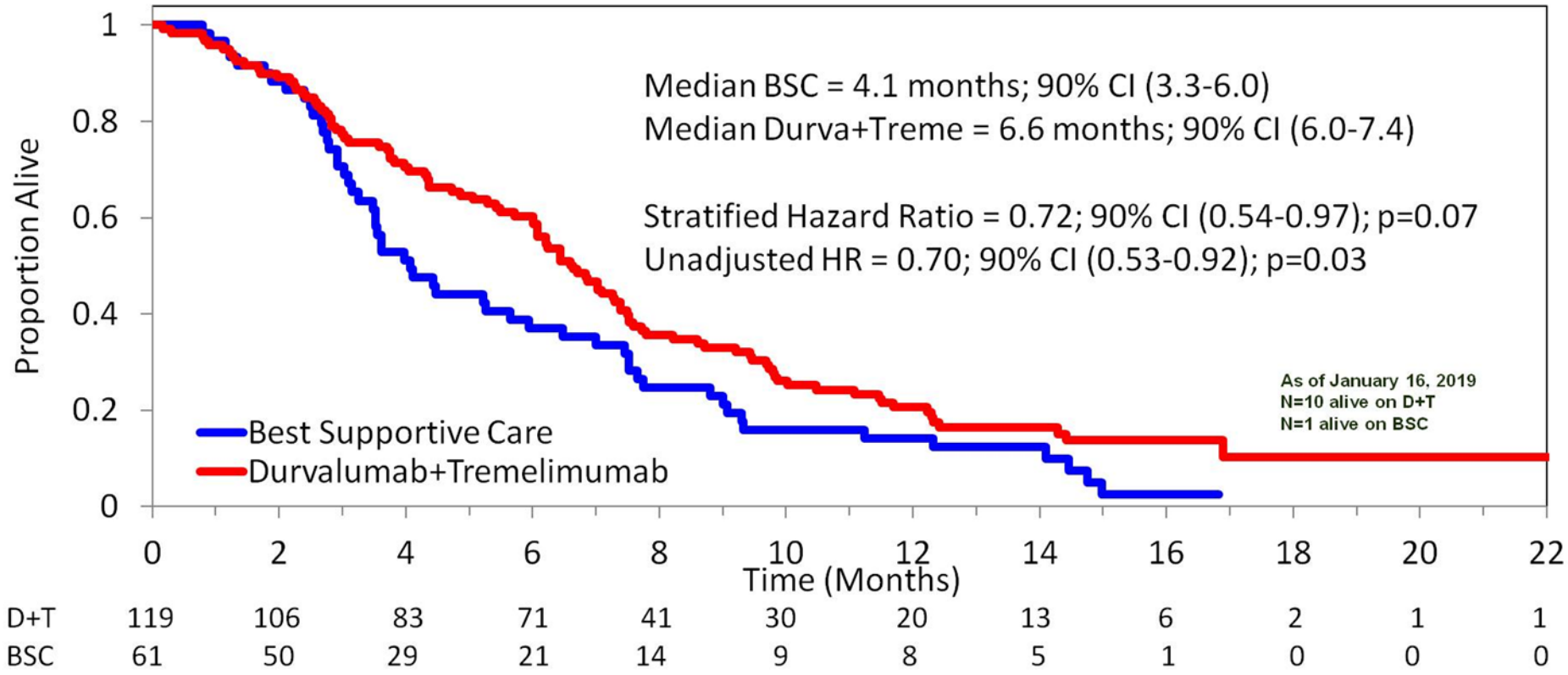
Gong J, et al. Oncotarget. 2017;doi:10.18632/oncotarget.15030.
Sartore-Bianchi A, et al. Lancet Oncol 2016;17:738-746.

Stage IV rectal cancer (MSS)

CEDARS-SINAI MEDICAL CENTER

MSS mCRC (majority, ≥90% tumors)

Phase II refractory mCRC, immunotherapy (checkpoint inhibitors) in MSS mCRC, **42% had TMB >20**



Chen EX, et al. JCO. 2019;37:481

Chen EX, et al. JCO. 2019;37:3512

Stage IV rectal cancer (MSS)

CEDARS-SINAI MEDICAL CENTER

MSS mCRC (majority, ≥90% tumors)

Phase Ib refractory mCRC (n=25) REGONIVO

- 80 mg regorafenib oral daily X21 days on, 7 days off
- Nivolumab 3 mg/kg every 2 weeks

- 30% had tumor reduction

Fukuoka S, et al. JCO. 2019;37:2522

CSMC stage IV rectal cancer (MSS) trials

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Immunomodulators with immunotherapy

BPT-201, a Phase 1 /2 Study of Birinapant in Combination with Pembrolizumab in Patients with Relapsed or Refractory Solid Tumors
- Phase II portion for refractory MSS colorectal pts

CO40939: A PHASE Ib, Multi-center, Open-Label Study to Evaluate the Safety, Efficacy, And Phamakokinetics Of RO6958688 IN Combination With Atelolizumab After Pretreatment WITH OBINUTUZUMAB IN PATIENTS WITH PREVIOUSLY TREATED METASTATIC, MICROSATELLITE-STABLE COLORECTAL ADENOCARCINOMA WITH HIGH CEACAM5 EXPRESSION

NCT02587962

NCT02650713

Watchful waiting

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In era of TNT becoming more implemented…

- Relatively high clinical CR rate seen with TNT approach → can pts with rectal cancer be spared of unnecessary surgery?
- retrospective case series: n=113 with cCR → WW and possible salvage vs. n=136 underwent TME with pCR
- Rectal preservation was achieved in 93 of 113 patients (82%) in the WW group
- 5-yr local regrowth rate was 21% in WW, higher rate of distant mets in this WW group
- 5-yr OS 73% (95% CI, 60%-89%) WW group vs. 94% (95% CI, 90%-99%) TME-pCR group
- 5-yr DFS 75% (95% CI, 62%-90%) WW group vs. 92% (95% CI, 87%-98%) TME-pCR group

Smith JJ, et al. JAMA Oncol. 2019;e185896

Watchful waiting

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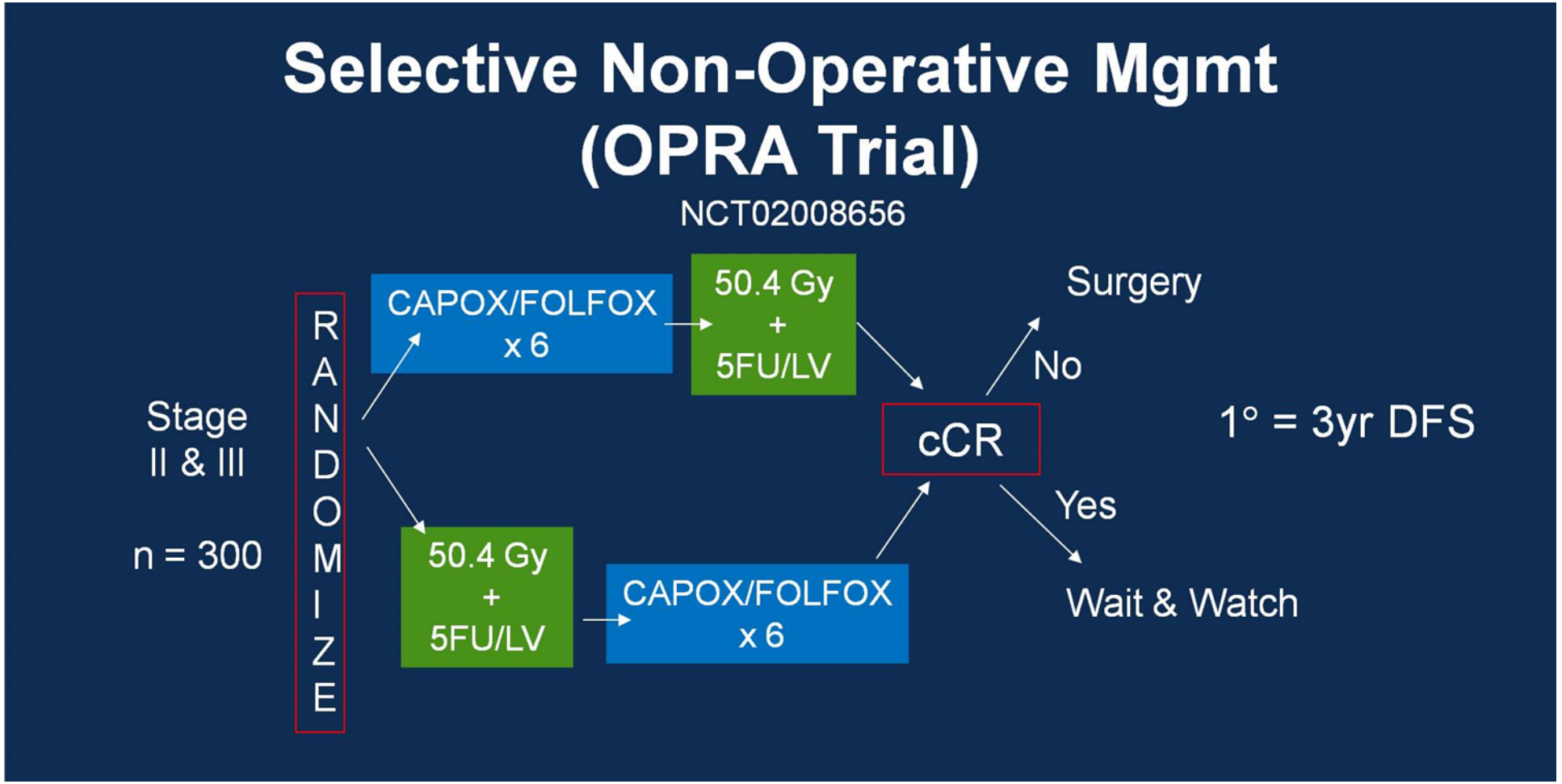
Under investigation…



Smith JJ, et al. BMC Cancer. 2015;15:767

Circulating tumor DNA

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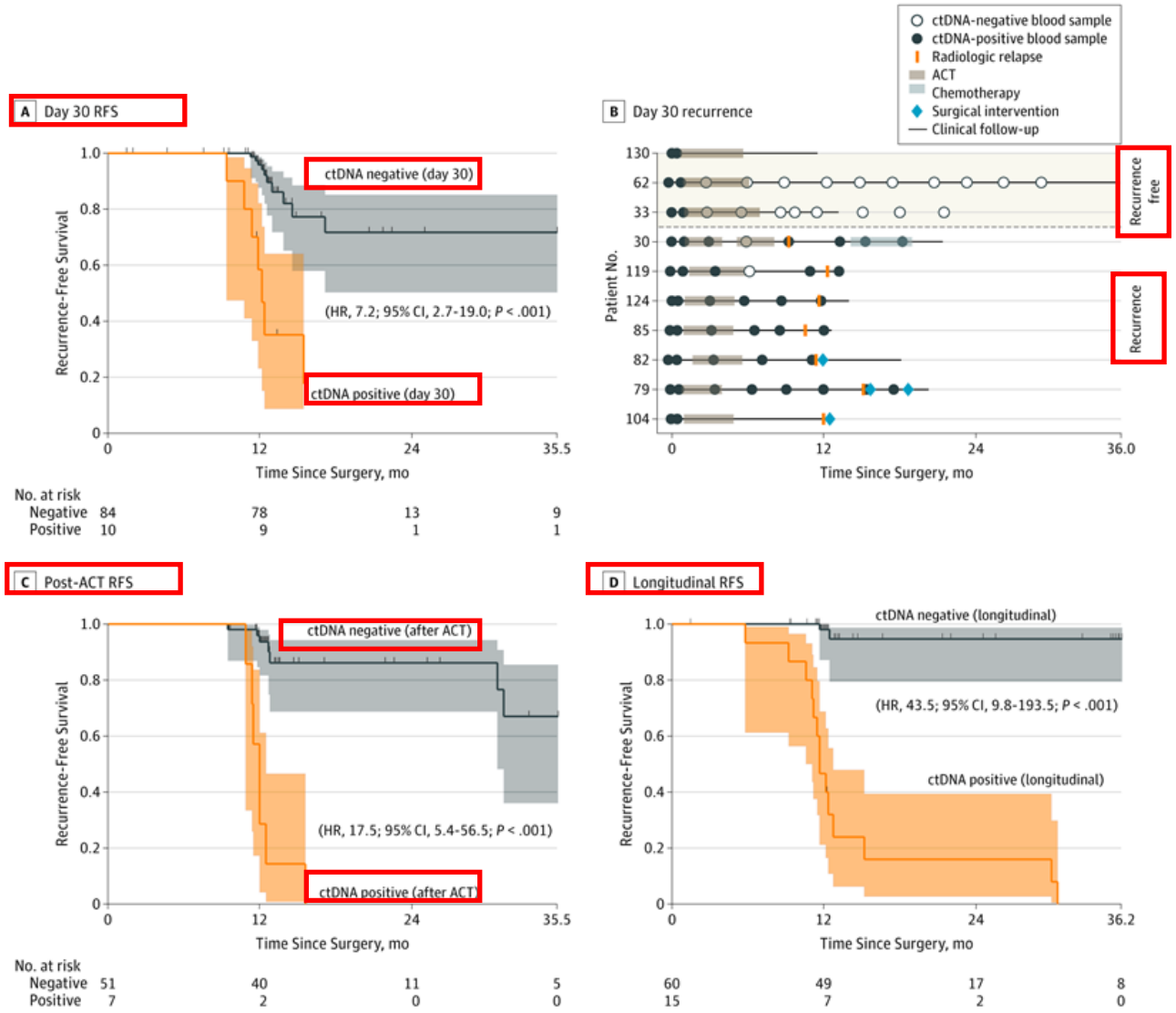
Under investigation…

- 130 patients with stages I to III CRC, ctDNA collected after surgery



Reinert T, et al. JAMA Oncol. 2019; doi: 10.1001/jamaoncol.2019.0528