Lingering Questions in the Selection and Sequence of Therapy for Patients with mCRC

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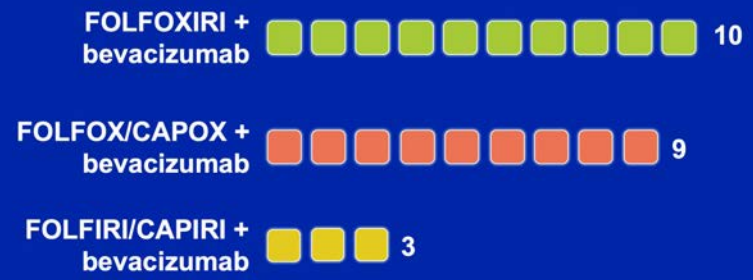
What is your usual first-line treatment for a 65-yo patient with extensive, moderately symptomatic, left-sided, MSS, pan-RAS WT, BRAF WT mCRC?

EGFR inhibitor	13
Bevacizumab	9

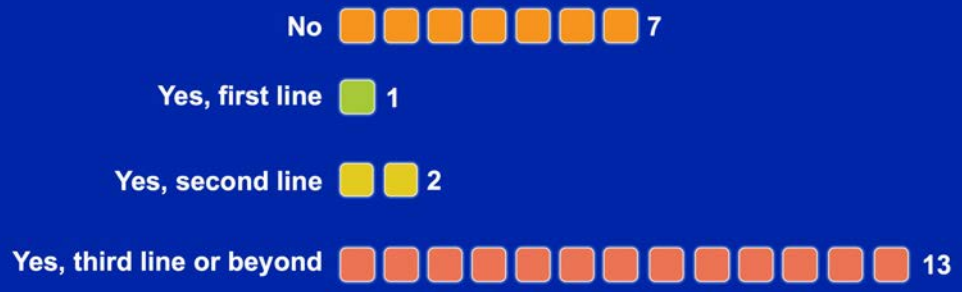
FOLFIRI/CAPIRI + panitumumab (2), FOLFOX/CAPOX + bevacizumab (2), FOLFOX + cetuximab (1), FOLFOXIRI (1), FOLFIRI/CAPIRI + erlotinib (1), FOLFIRI + panitumumab (1)

What is your usual first-line treatment for a 65-yo patient with extensive, moderately symptomatic, right-sided, MSS, pan-RAS WT, BRAF WT mCRC?



FOLFOXIRI + erlotinib (1)

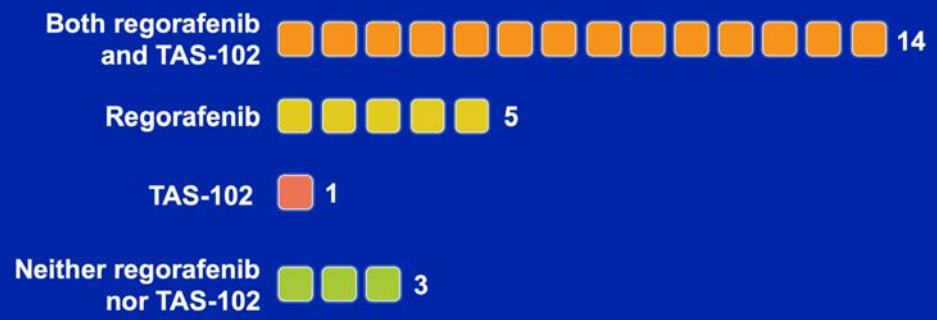
Do you generally administer EGFR inhibitors to patients with right-sided mCRC?



Sequencing of chemobiologic agents

- Tumor sidedness and use of EGFR antibodies
- Optimal dosing of regorafenib
- TAS-102: Neutropenia, use in combination with bevacizumab

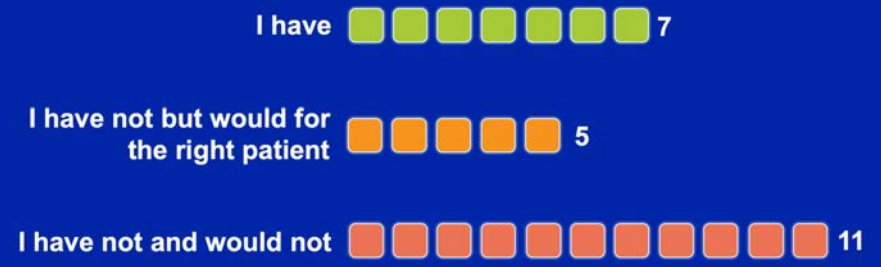
Consider the last patient in your practice who died of mCRC. Did the patient receive…



When administering regorafenib to a younger patient with a good performance status, what is your usual starting dose, and do you generally escalate to 160 mg*?

*All escalations are as tolerated

Have you or would you use TAS-102 in combination with bevacizumab outside of a clinical trial setting?



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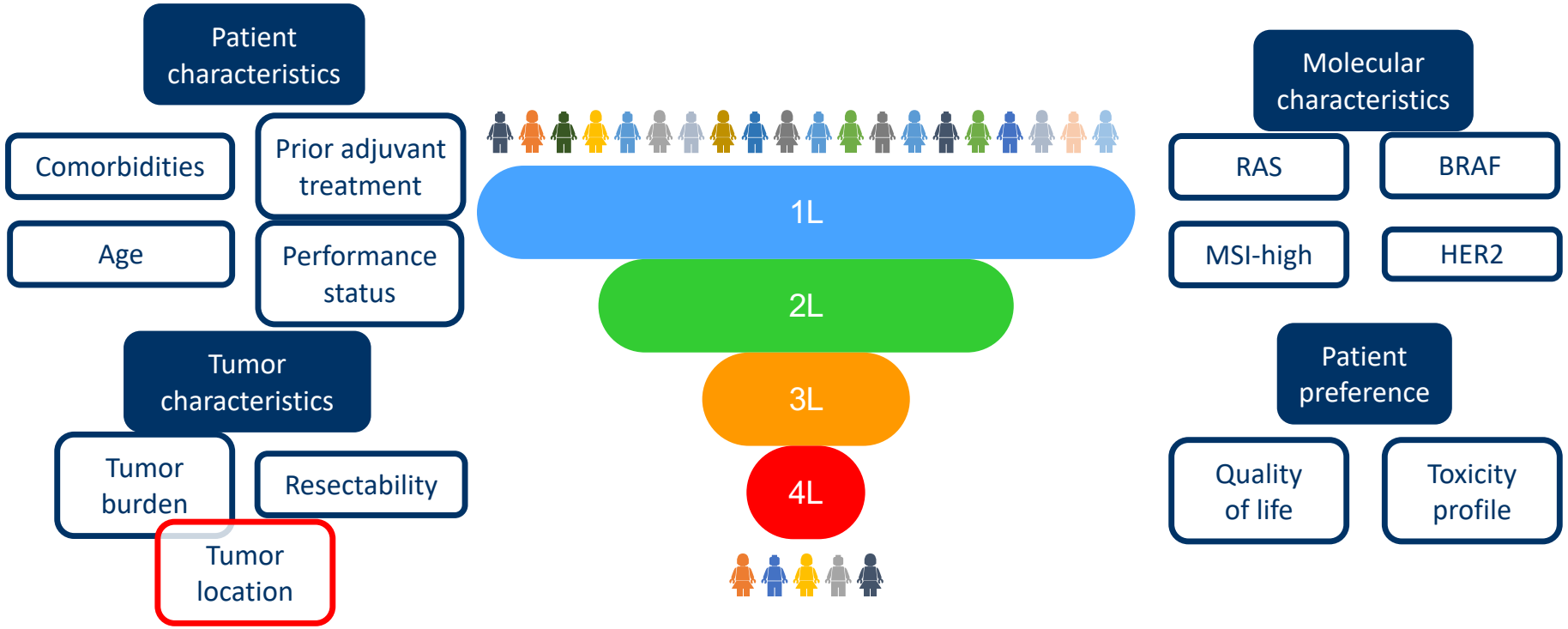
Disclosures

Advisory Committee, Consulting Agreements and Contracted Research	Amgen Inc, Bayer HealthCare Pharmaceuticals, Caris Life Sciences, Celgene Corporation, Indivumed GmbH, Roche Laboratories Inc, Taiho Oncology Inc
Speakers Bureau	Amgen Inc, Bayer HealthCare Pharmaceuticals, Celgene Corporation, Merck, Roche Laboratories Inc, Taiho Oncology Inc

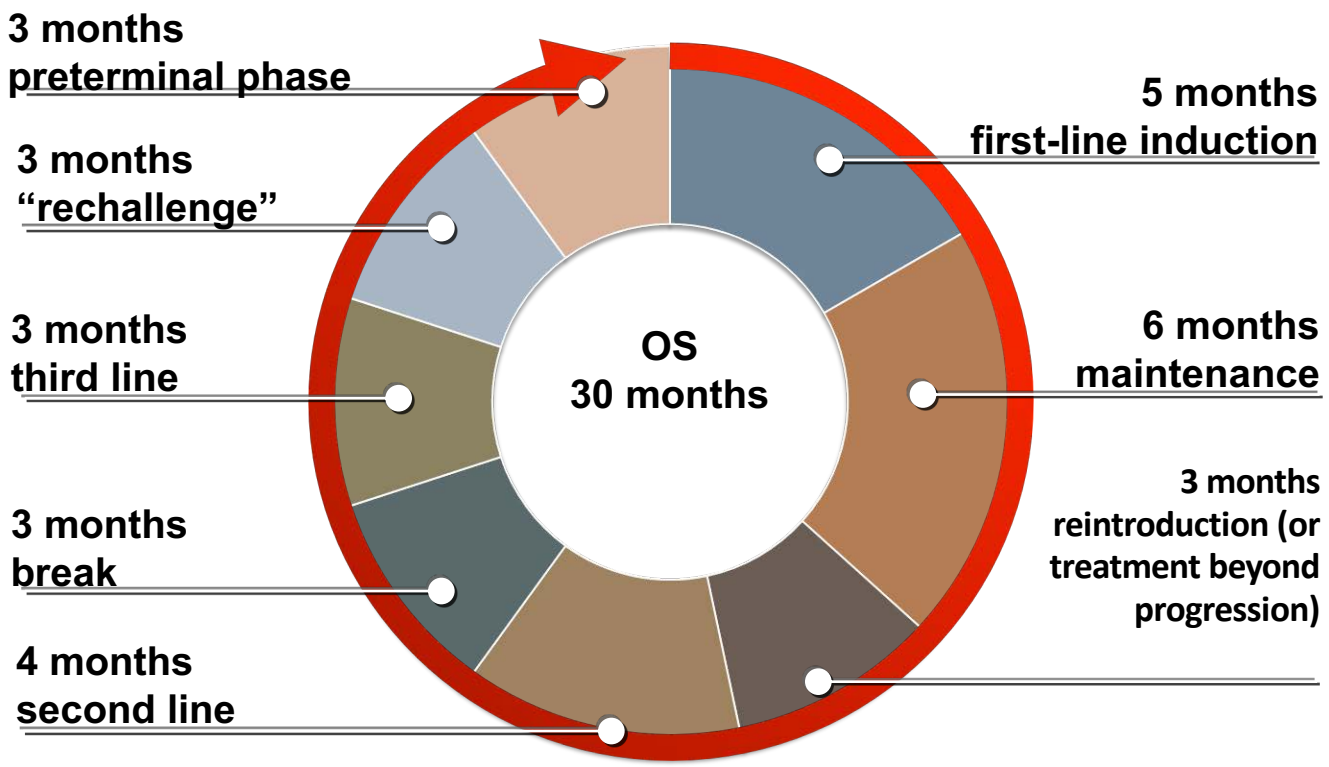
What influences treatment choices in mCRC?



Therapy tailored according to individual patient needs

2019: A classical case of mCRC

Right or Left
MSI or MSS
RAS/RAF
HER2
Other markers?
Need for response
QOL



FU/Ox/Iri
a new
standard?

Courtesy: Alberto Sobrero

Refractory Colon Cancer: Many options, new data

- EGFR targeted therapy
- BRAF targeted therapy
- TAS 102
- Regorafenib
- HER2 as a target
- Immune Therapy
- Precision Medicine
- Recycled chemotherapy
- Biologics beyond progression
- Maintenance therapy 1 and sometimes 2 and 3!

Sequence and how to decide

- Do you have to be right?
- Biomarker or not?
- Do you need a response or is stable disease OK?
- Survival benefit proven?
- Likely toxicity
- Patient preferences, includes insurance issues

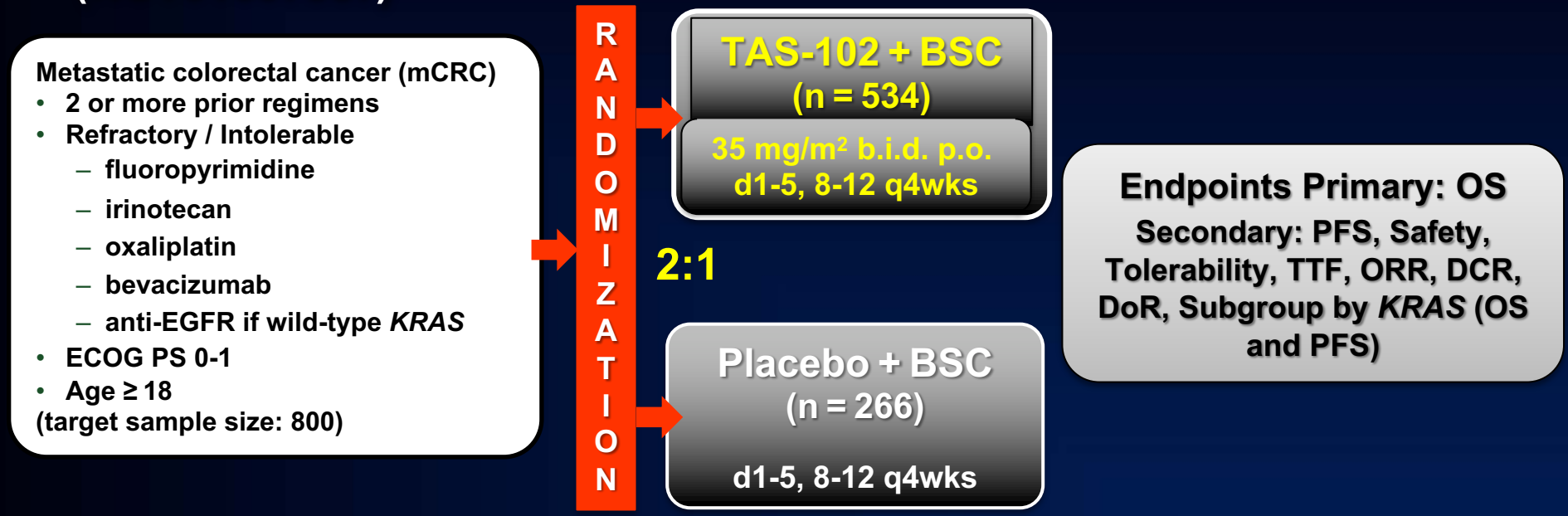
Basic Rules

- Possible advantage to “induction” chemo but don’t go too long
- Use EGFR therapy when you need a response
  - Only RAS and maybe BRAF WT
  - Only left sided?
- Maintenance therapy helps
- Unclear on stage IV NED
- Don’t leave known survival on the table

Global Randomized Phase III Study

RECOURSE: Refractory Colorectal Cancer Study

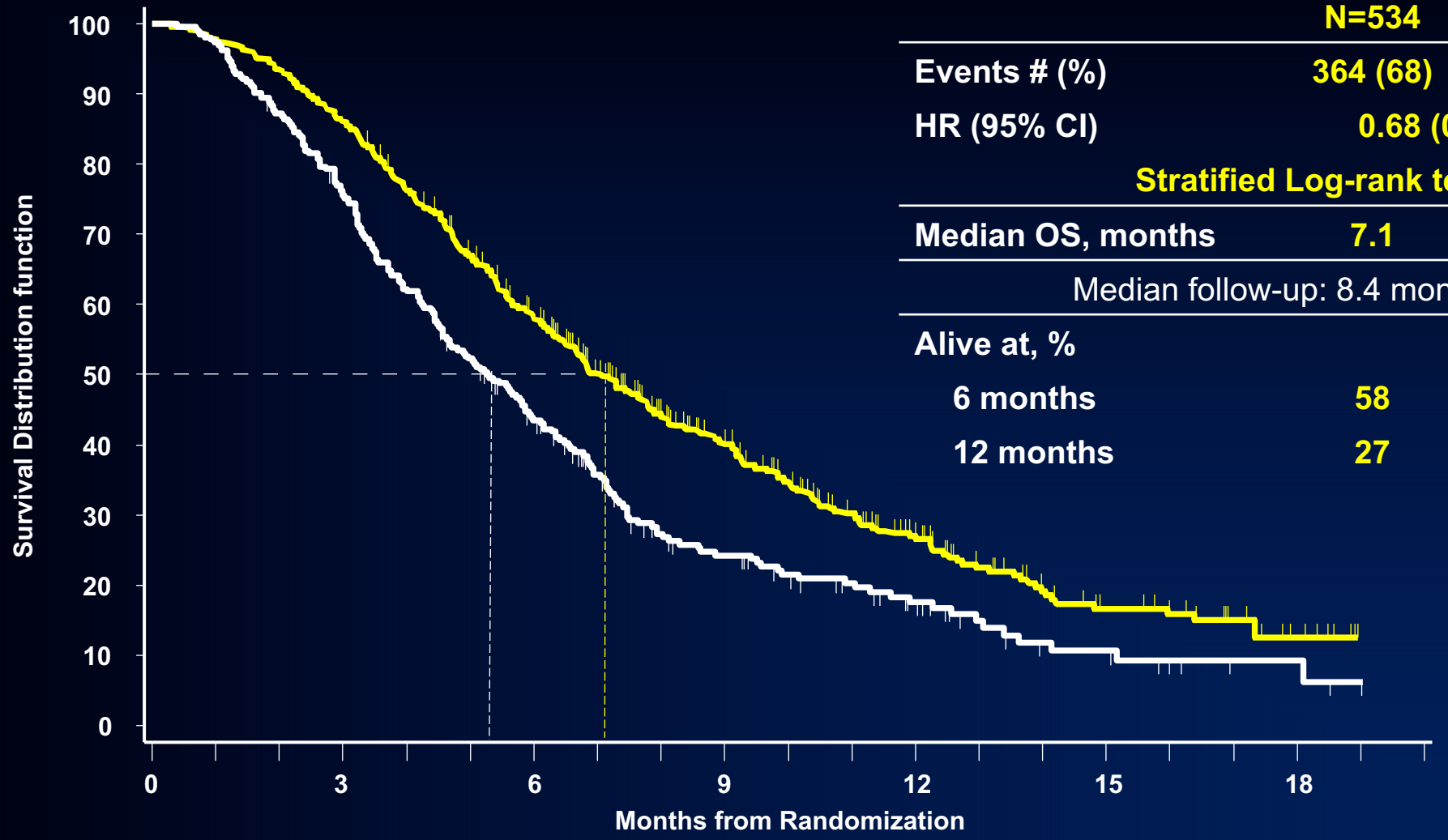
(NCT01607957)



- Treatment continuation until progression, intolerant toxicity or patient refusal
- Multicenter, randomized, double-blind, placebo-controlled, phase III
  - Stratification: *KRAS* status, time from diagnosis of metastatic disease, geographical region
- Sites: 13 countries, 114 sites
- Enrollment: June 2012 to October 2013

Mayer et al., NEJM 2015

Overall Survival



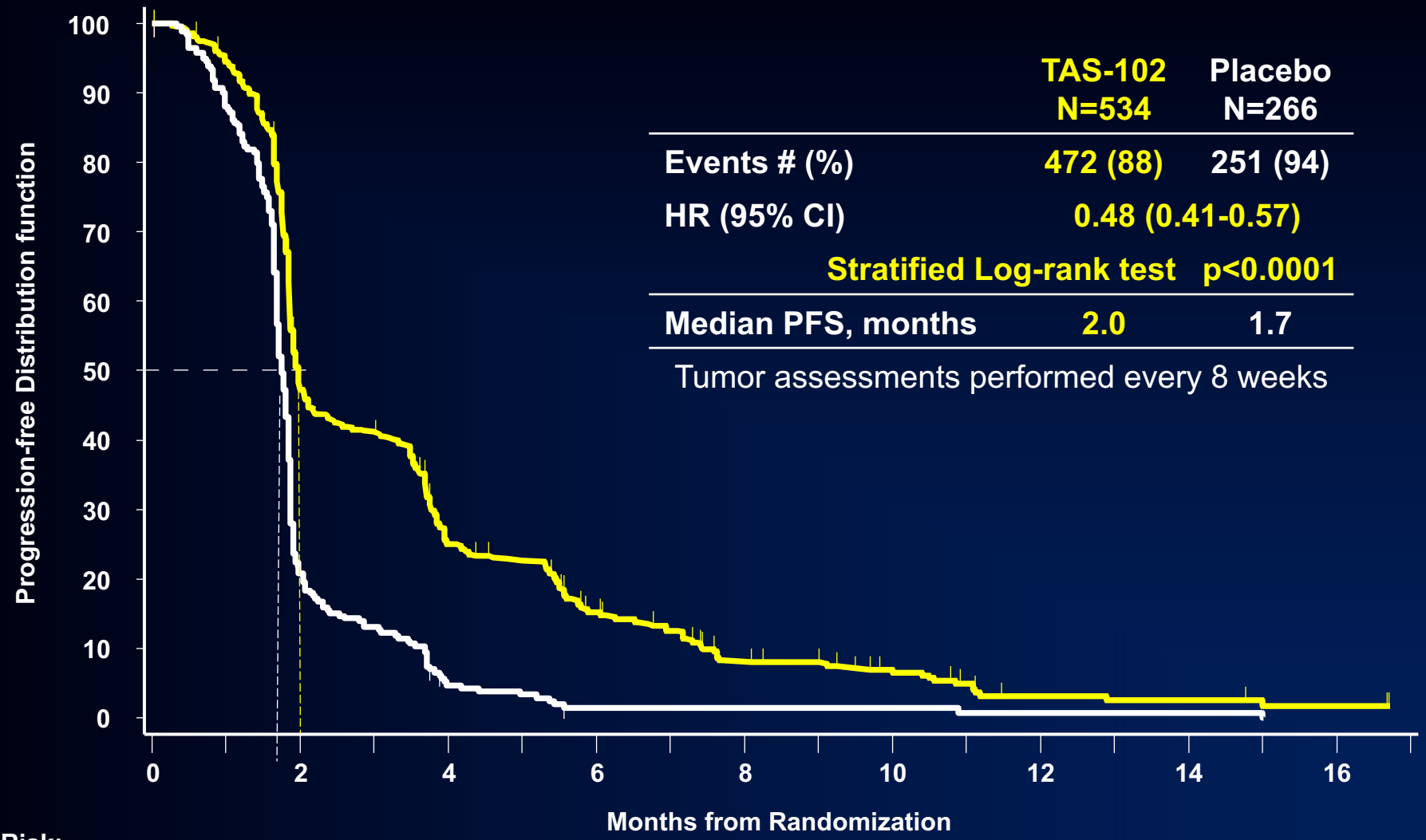
	TAS-102 N=534	Placebo N=266
Events # (%)	364 (68)	210 (79)
HR (95% CI)	0.68 (0.58-0.81)	
	Stratified Log-rank test	p<0.0001
Median OS, months	7.1	5.3
Median follow-up: 8.4 months		
Alive at, %		
6 months	58	44
12 months	27	18

N at Risk:

TAS-102	534	459	294	137	64	23	7
Placebo	266	198	107	47	24	9	3

Mayer et al., NEJM 2015

Progression-free Survival



	TAS-102 N=534	Placebo N=266
Events # (%)	472 (88)	251 (94)
HR (95% CI)	0.48 (0.41-0.57)	
	Stratified Log-rank test	p<0.0001
Median PFS, months	2.0	1.7

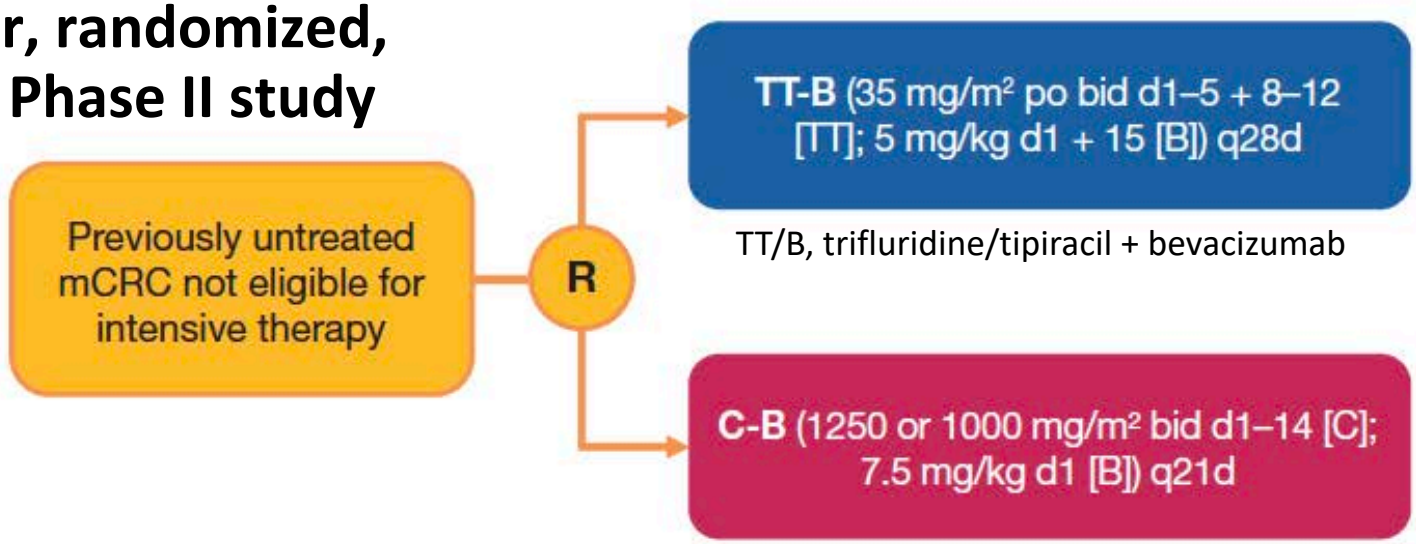
Tumor assessments performed every 8 weeks

N at Risk:									
TAS-102	534	238	121	66	30	18	5	4	2
Placebo	266	51	10	2	2	2	1	1	0

Mayer et al., NEJM 2015

Refractory mCRC: TASCO-1

Multicenter, randomized, open-label Phase II study



Primary endpoint
- PFS

Secondary endpoints
- OS, ORR, DCR, tumor response
- Safety, tolerability

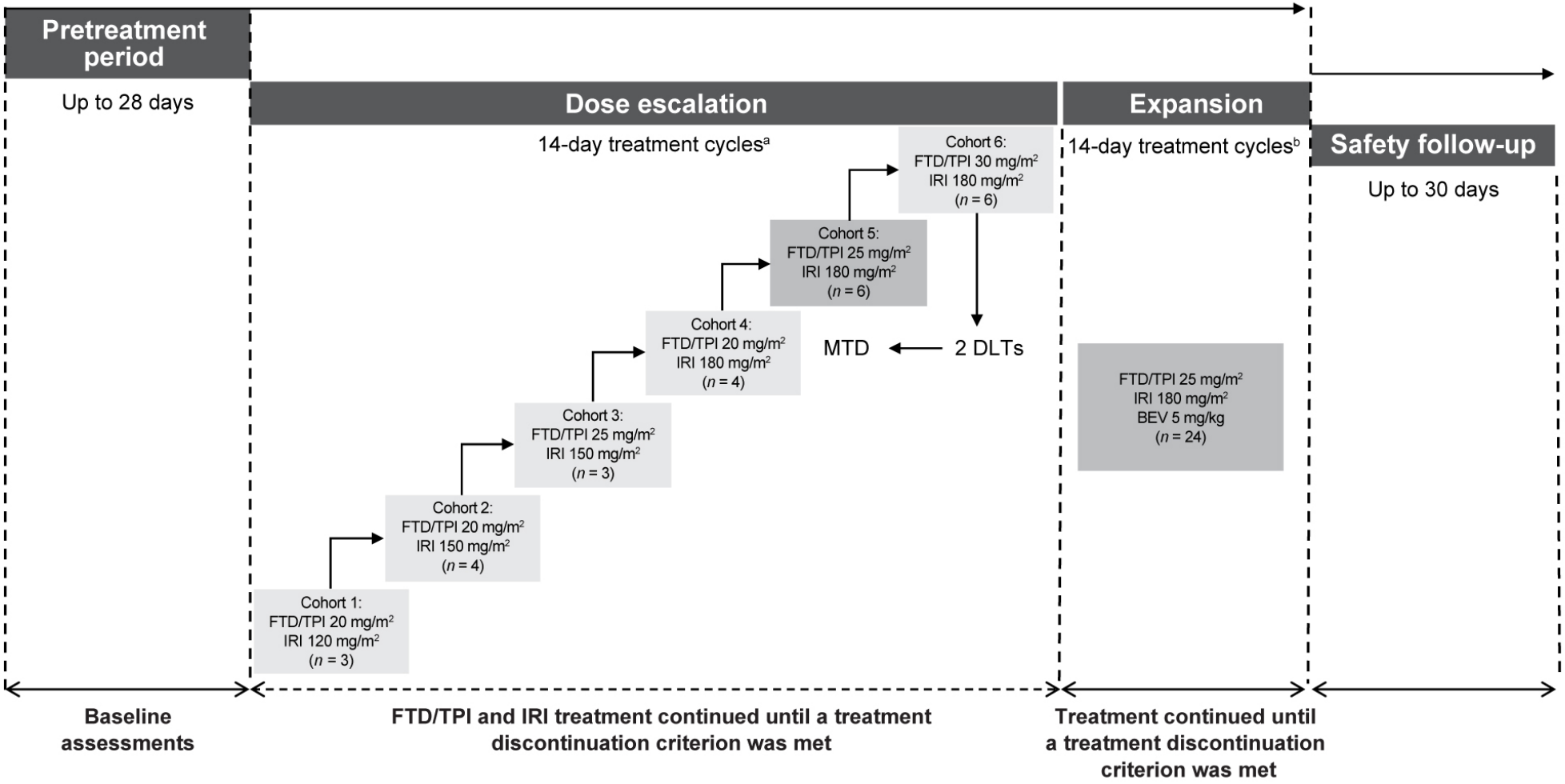
- Median PFS was 9.2 months TT/B vs 7.8 months
  - (HR) of 0.71 (95% confidence interval [CI] 0.48-1.06)
- Preliminary median OS was 18 months TT/B vs 16.2 months C-B
  - HR of 0.56 (95% CI, 0.32-0.98)

What comes next if this is 1L?

BID, twice daily; CI, confidence interval; DCR, disease control rate; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth

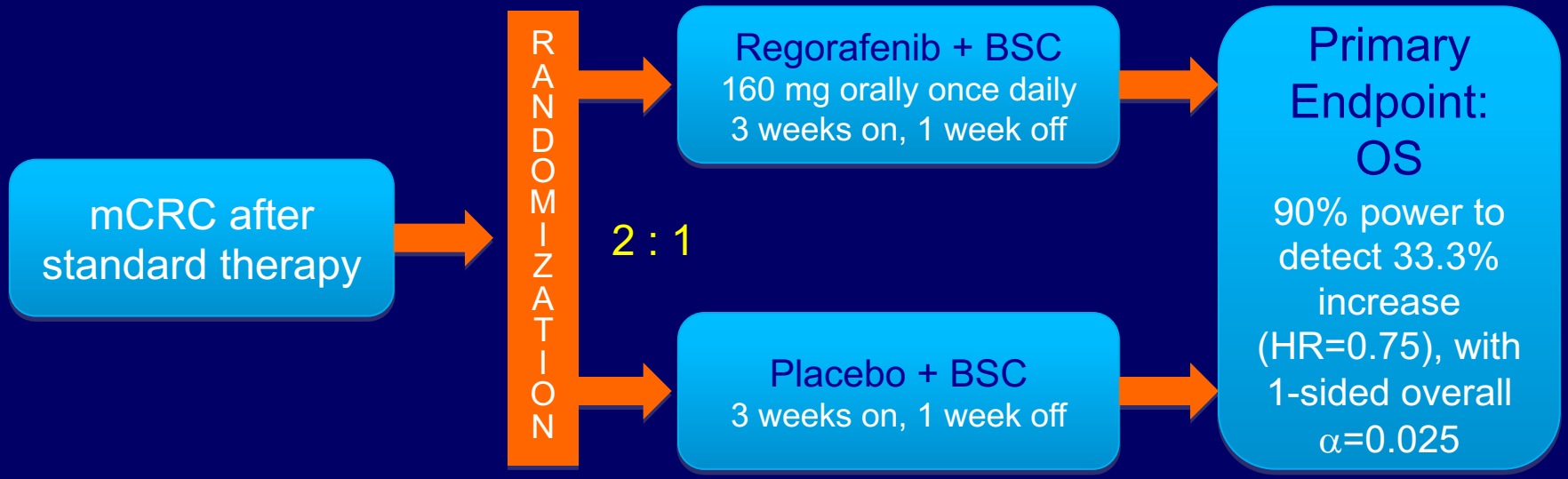
Lesniewski-Kmak K, et al. *Ann Oncol*. 2018;29 (suppl 5; abstr O-022).

Phase I Study of Trifluridine/Tipiracil Plus Irinotecan and Bevacizumab in Advanced Gastrointestinal Tumors



Clin Cancer Res. 2020 Jan 10. [Epub ahead of print]
Varghese AM1, Cardin DB2, Hersch J3, Benson A4, Hochster HS5, Makris L6, Hamada K7, Berlin J8, Saltz LB9.

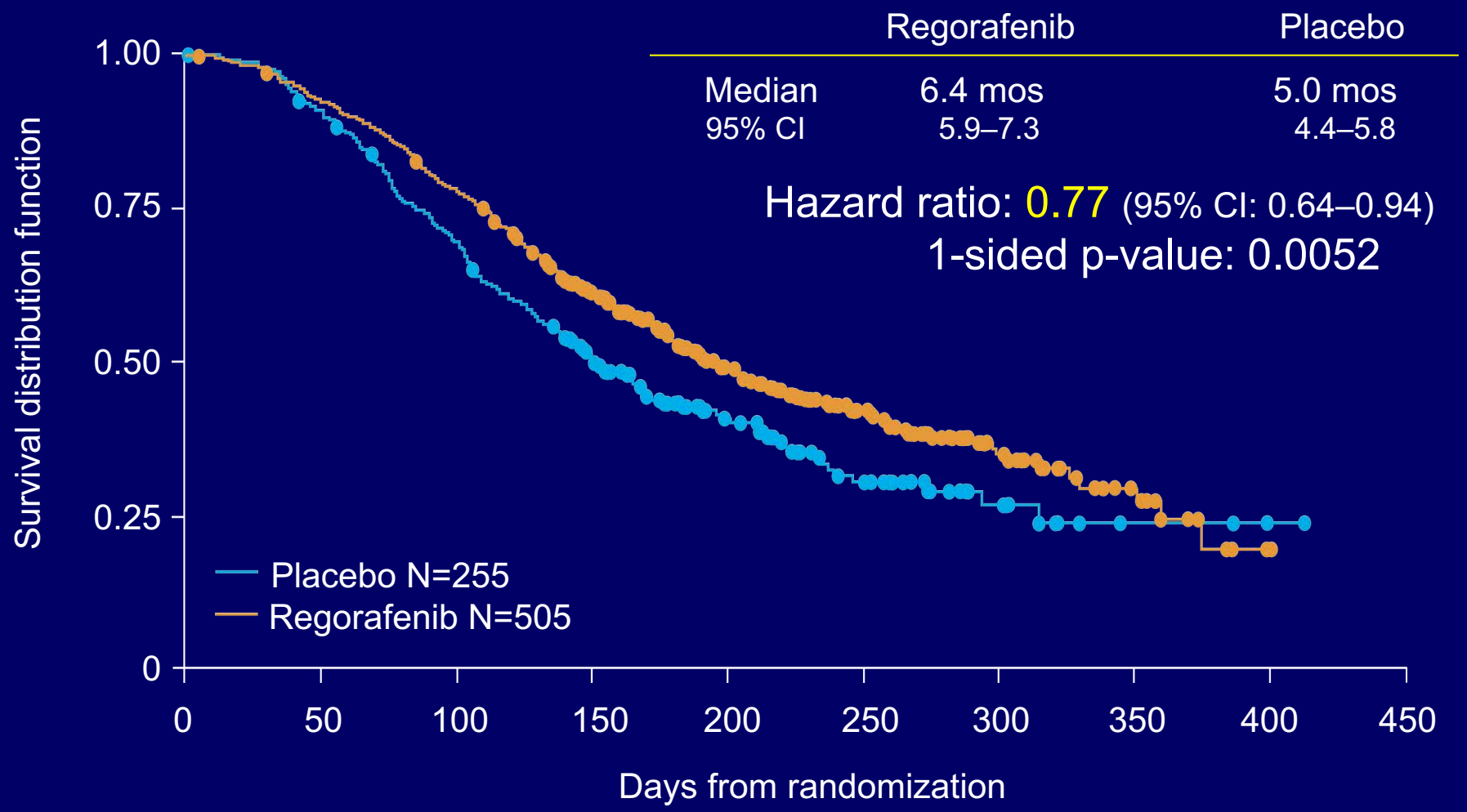
CORRECT study design



- Multicenter, randomized, double-blind, placebo-controlled, phase III
  - 2:1 randomization
  - Strat. factors: prior anti-VEGF therapy, time from diagnosis of mCRC, geographical region
- Global trial: 16 countries, 114 active centers
  - 1,052 patients screened, 760 patients randomized within 10 months
- Secondary endpoints: PFS, ORR, DCR
- Tertiary endpoints: duration of response / stable disease, QOL, pharmacokinetics, biomarkers

Grothey et al., Lancet 2012

Overall survival (primary endpoint)

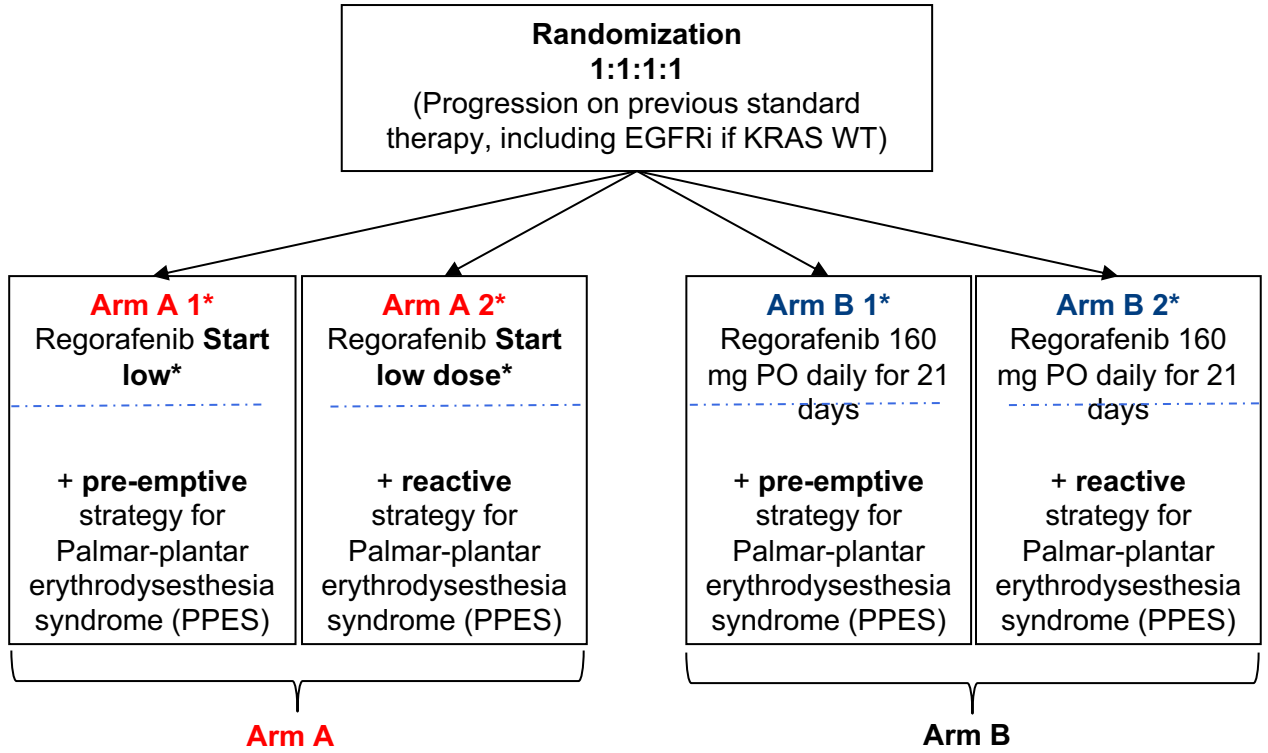


Primary endpoint met prespecified stopping criteria at interim analysis
(1-sided $p<0.009279$ at approximately 74% of events required for final analysis)

Grothey et al. Lancet 2012

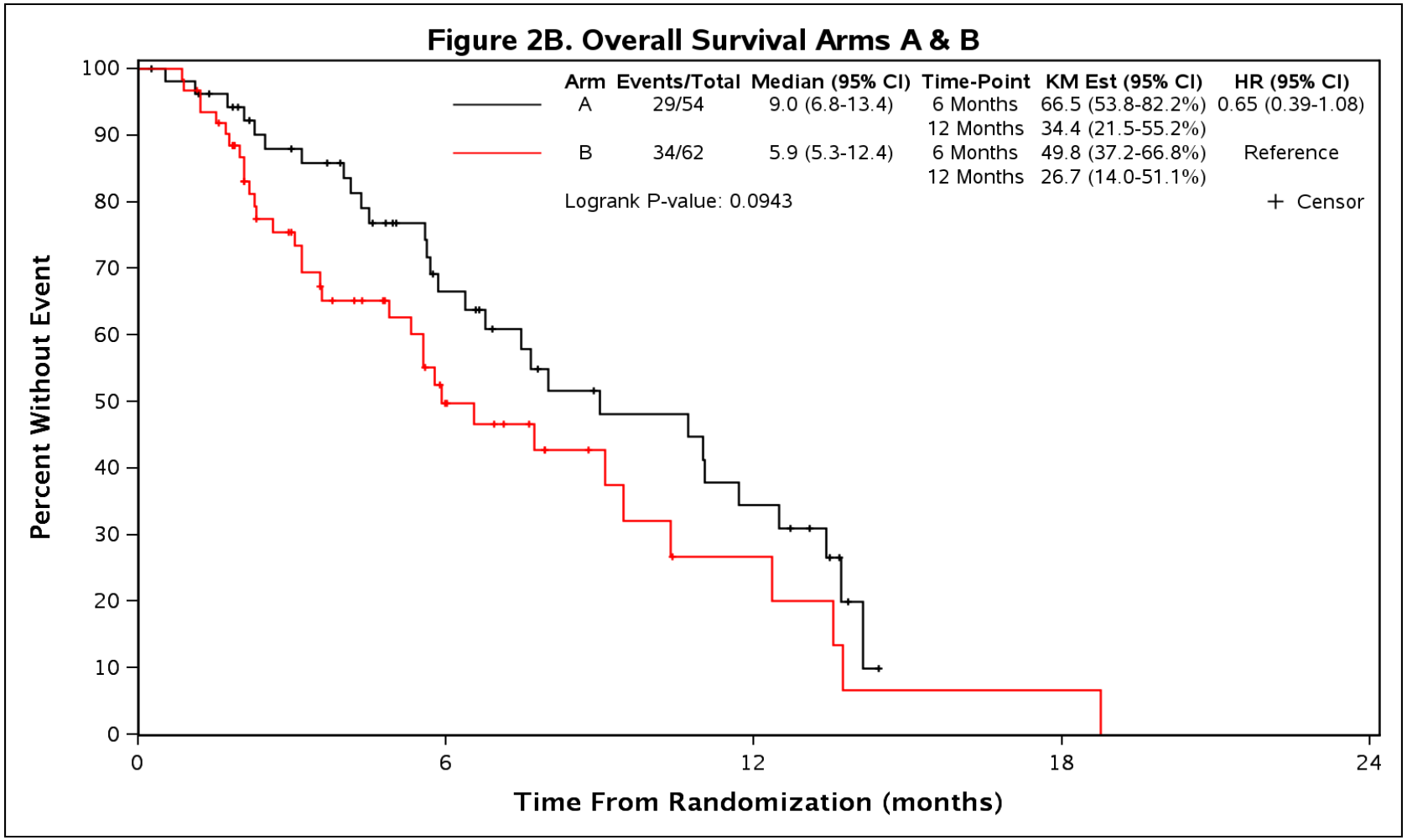
ReDOS design

WEEK of C1		DOSE
1	Starting dose C1	80 mg
2	↓	120 mg
3	End dose C1	160 mg
4		off
WEEK of C2+		**DOSE**
1		**Dose from C1**



1ary endpoint: proportion of patients who complete 2 cycles of protocol treatment and initiate cycle 3 in arm A and arm B
2ary endpoints: OS, PFS, TTP

Phase II ReDOS Study:
OS (secondary endpoint)

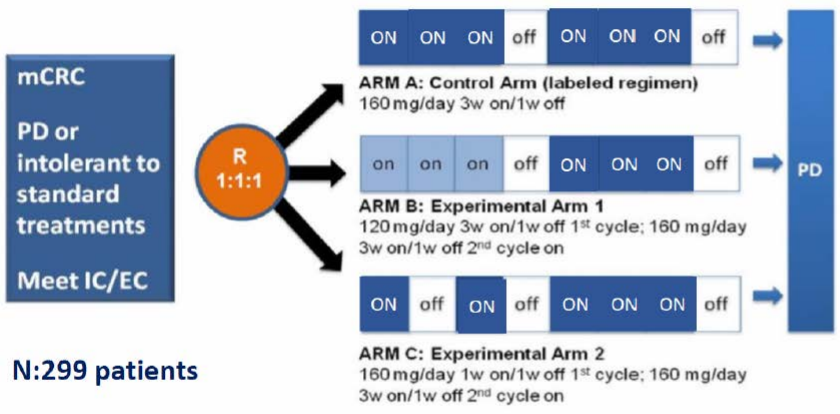


HR, hazard ratio; KM est, Kaplan-Meier estimate; OS, overall survival.

Data on File, ACCRU.

Alternative Regorafanib Dosing

REARRANGE Study Design



Primary endpoint:

- **Safety** :% of patients having G3/G4 AEs during the entire course of the treatment

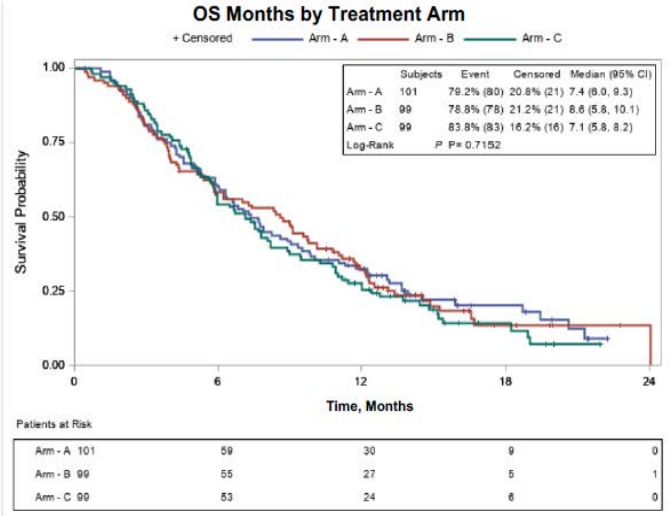
Secondary endpoints:

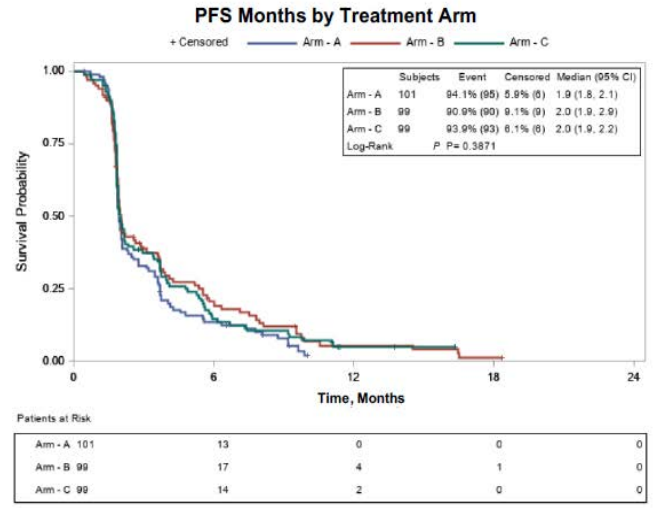
- OS
- PFS
- % of Patients starting C3 on each arm
- Dose intensity
- DCR

DCR = disease control rate; IC/EC = inclusion criteria/exclusion criteria; PD = progressive disease

Argiles G, et al. *Ann Oncol*. 2019;30(Suppl 4): Abstract O-026.

Secondary Endpoints



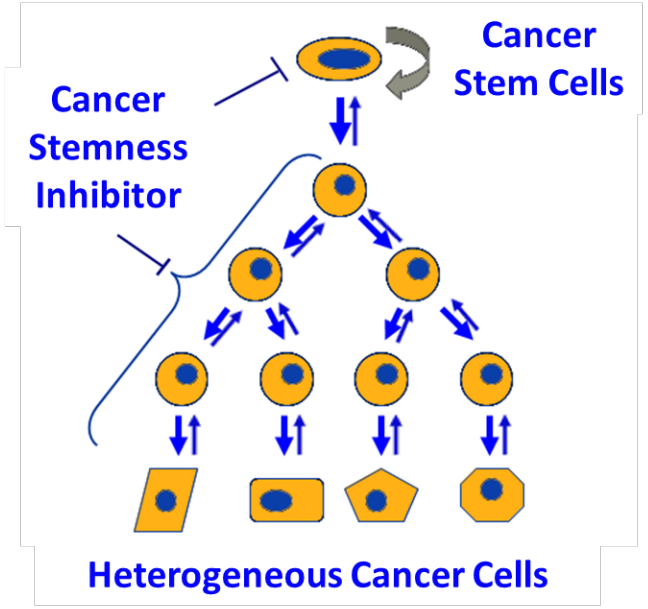


OS Rate	Arm a (n = 101)	Arm B (n = 99)	Arm C (n = 99)
@ 6 months % (95% CI)	59.9 (49.61, 68.76)	58.1 (47.68, 67.15)	54.3 (43.95, 63.52)
@ 12 months % (95% CI)	32.4 (23.38, 41.66)	32.3 (23.14, 41.82)	27.8 (19.25, 37.03)

PFS Rate	Arm a (n = 101)	Arm B (n = 99)	Arm C (n = 99)
@ 6 months % (95% CI)	13.6 (7.69, 21.12)	20.5 (12.88, 29.31)	14.5 (8.39, 22.26)
@ 12 months % (95% CI)	-	5.4 (1.80, 11.84)	5.0 (1.77, 10.75)

Napabucasin, First-in-Class Cancer Stemness Inhibitor

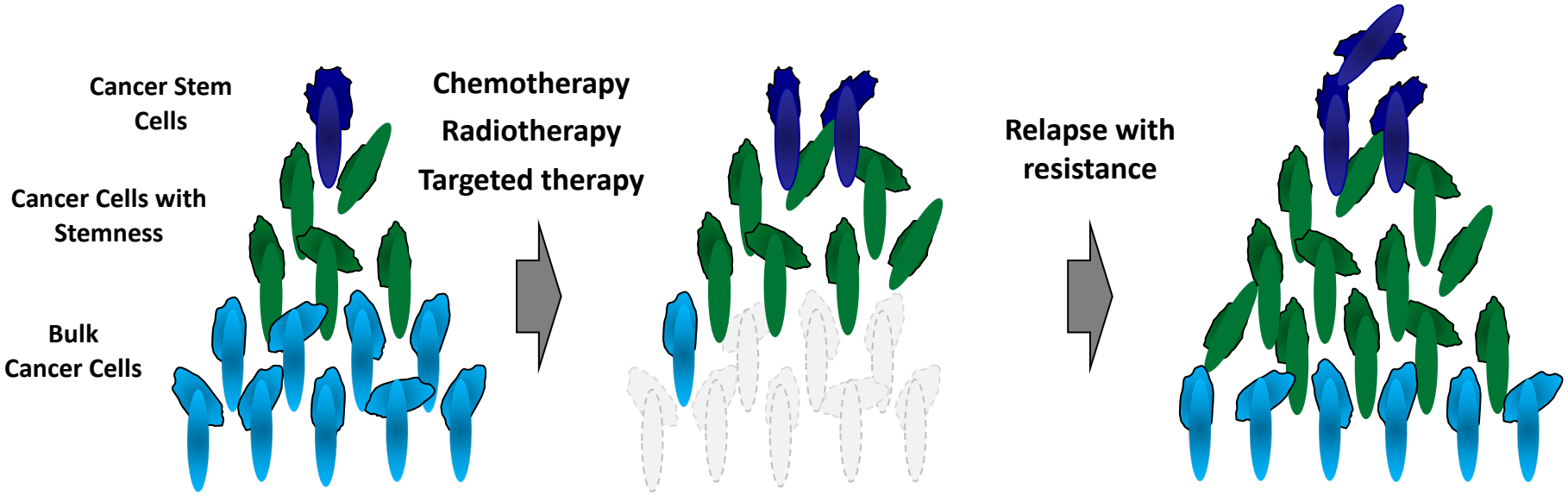
Courtesy J. Bendell
GI ESMO 2017



Why Target Cancer Cell Stemness?

Cancer Stem Cells & Cancer Stemness

- Highly tumorigenic
- Fundamentally responsible for continued malignant growth
- Initiators (seeds) of metastases
- Resistant to chemotherapy and current targeted therapies



Courtesy J. Bendell
GI ESMO 2017

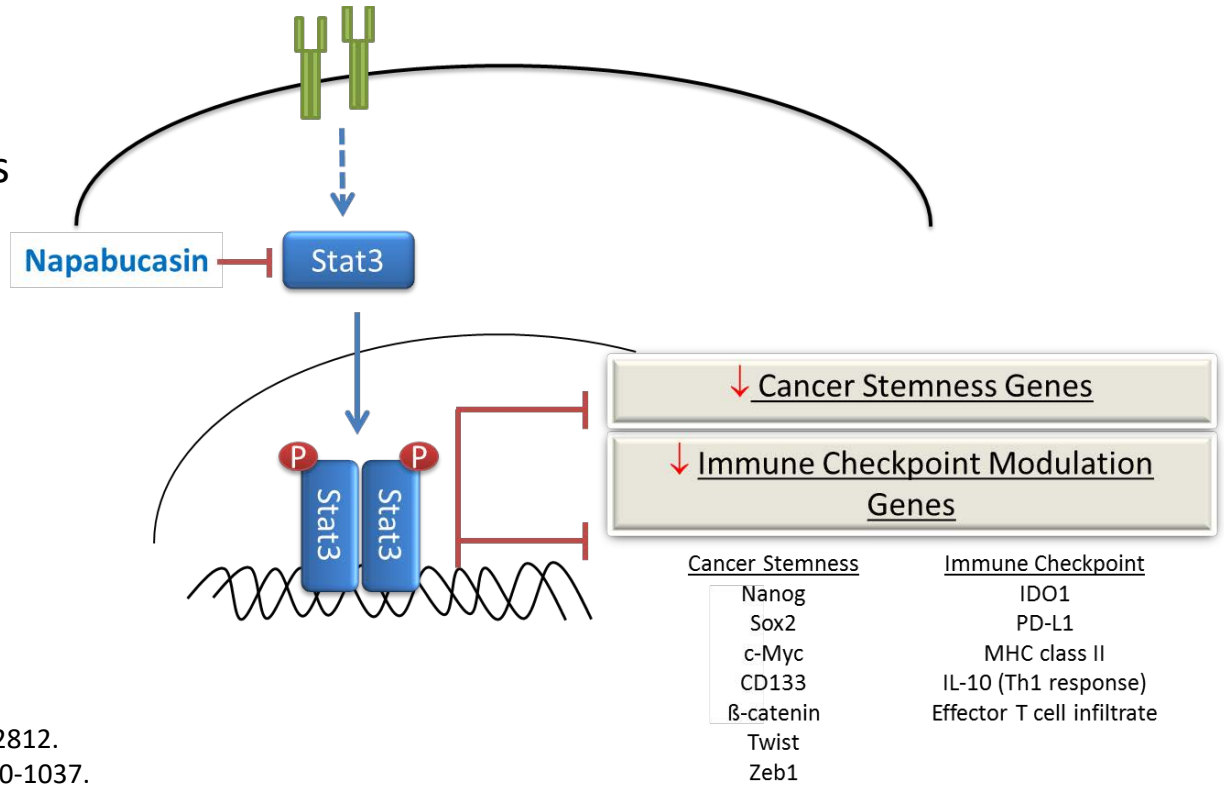
STAT3: A Target for CSC Inhibition

STAT3

- Key regulator of cancer stemness
- STAT3 plays a key role in the survival and proliferation of PDAC cancer stem cells[1,2,3]

Napabucasin

- Oral inhibitor of STAT3
- Blocks CSC self renewal
- Kills CSC and cancer cells

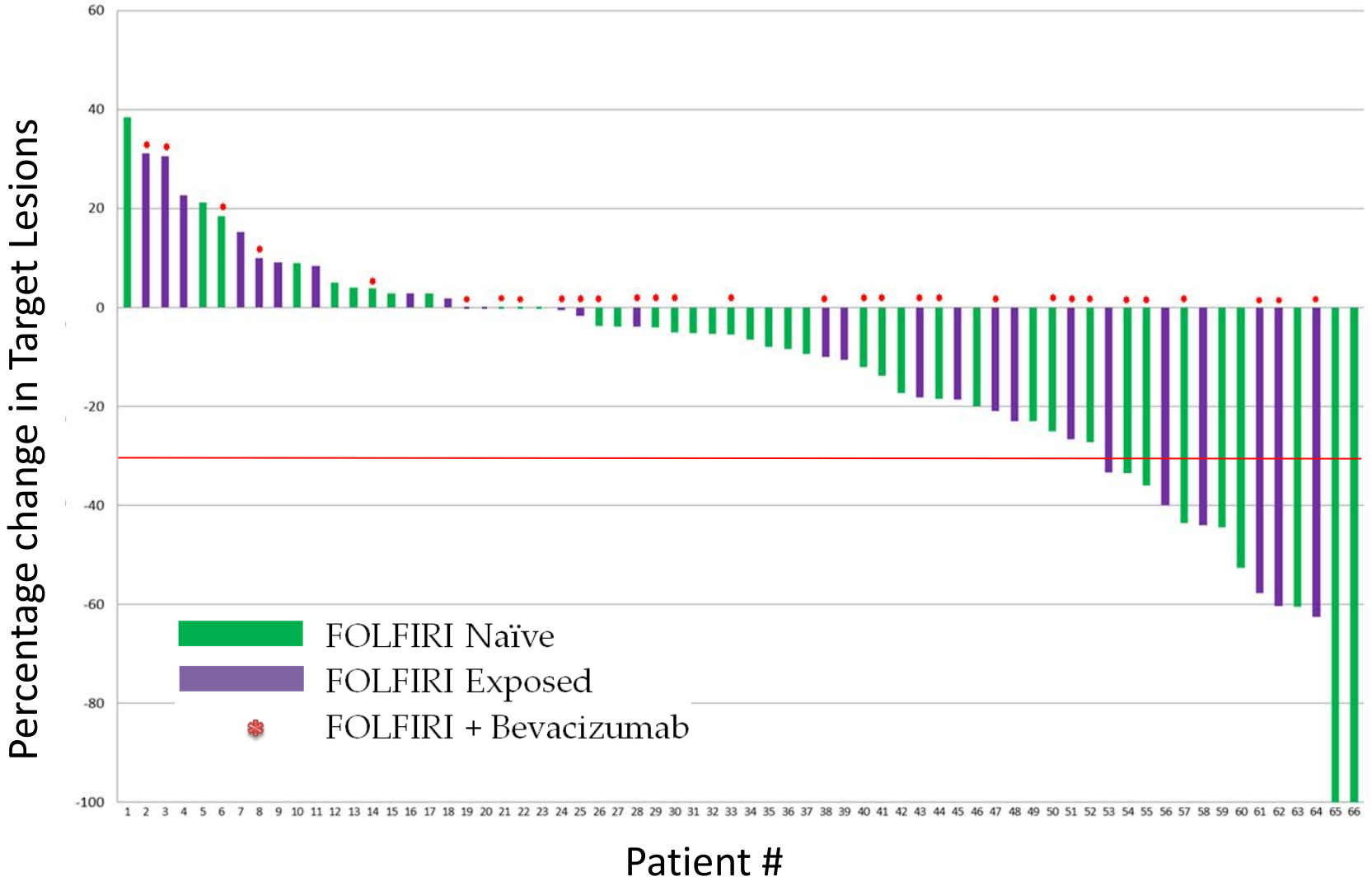


1. Lee C et al. *J Clin Oncol*, 2008; 26(17), 2806-2812.
2. Li C, et al. *Cancer Research*, 2007; 67(3), 1030-1037.
3. Li Y, et al. *Proc Natl Acad Sci USA,* 2015; 112(6):1839-1844.

Signs of Anti-Cancer Activity

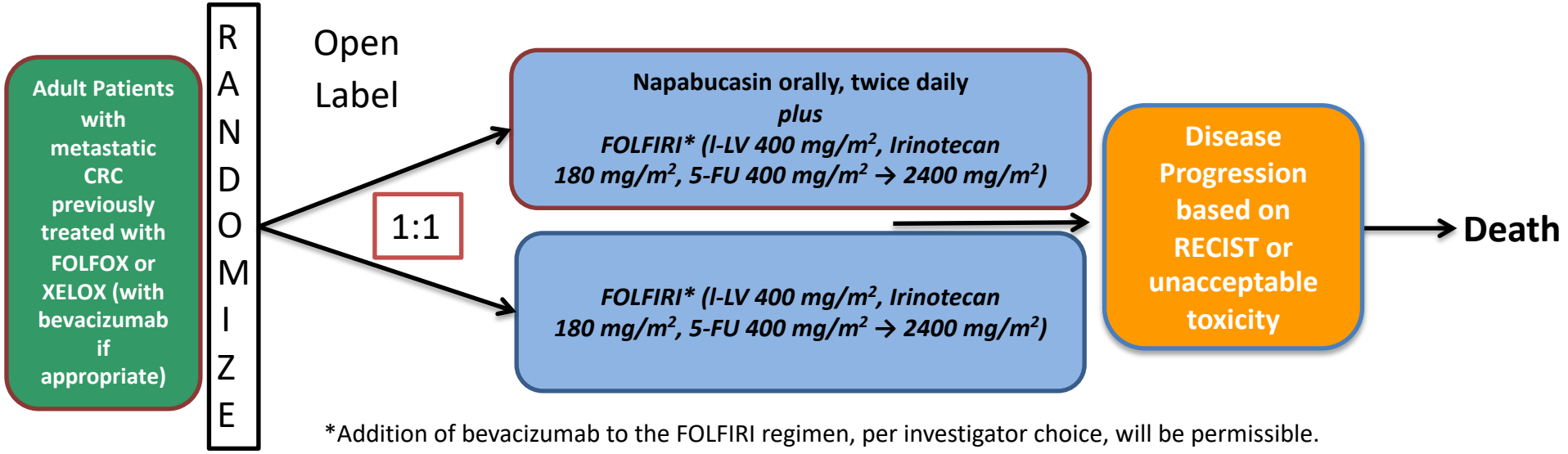
Best Response in pts treated with Napabucasin and FOLFIRI +/- bev

Courtesy J. Bendell
GI ESMO 2017



CanStem303C: Global Phase III Study

Courtesy J. Bendell
GI ESMO 2017



*Addition of bevacizumab to the FOLFIRI regimen, per investigator choice, will be permissible.

Primary Endpoints

- OS

Secondary Endpoints

- PFS
- ORR
- DCR
- Safety
- QoL