How I Treat Metastatic Colon Cancer in 2023

MLS Cleveland

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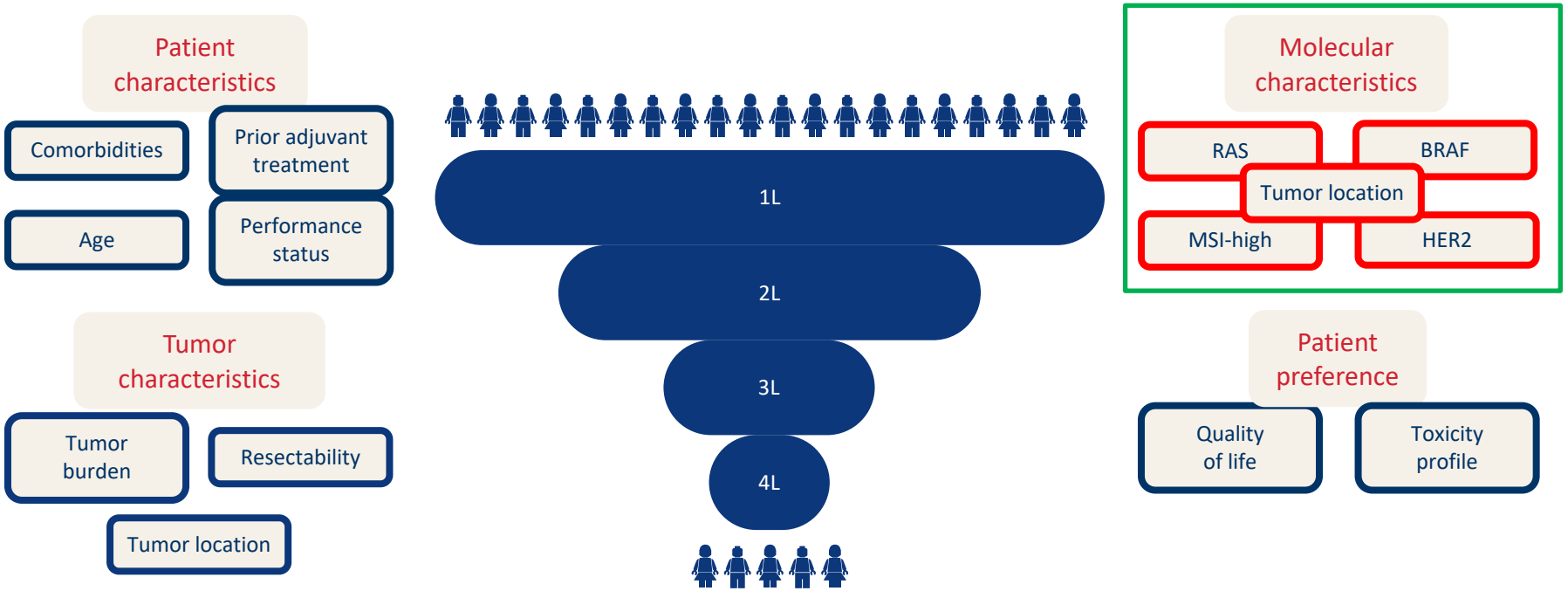
Case Comprehensive Cancer Center

Metastatic Colon Cancer

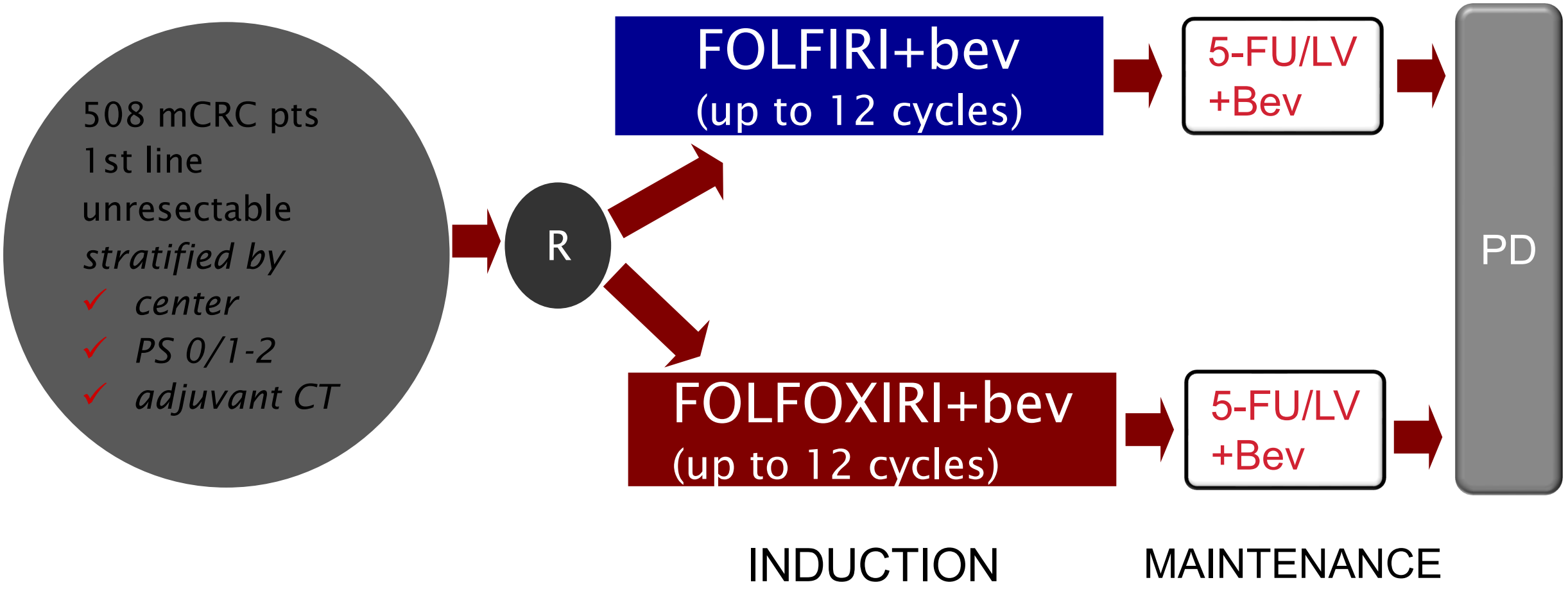
- Intent of treatment
  - Curative
  - Palliative
  - Borderline
- Liver only metastases
  - Resection
  - HAI
  - XRT
  - Ablation
  - Embolization
  - Transplant
- Lung metastases
  - Resection
  - XRT
  - Ablation
- Peritoneal metastases
  - Debulking surgery (?HIPEC)

Right Treatment to Right Patient

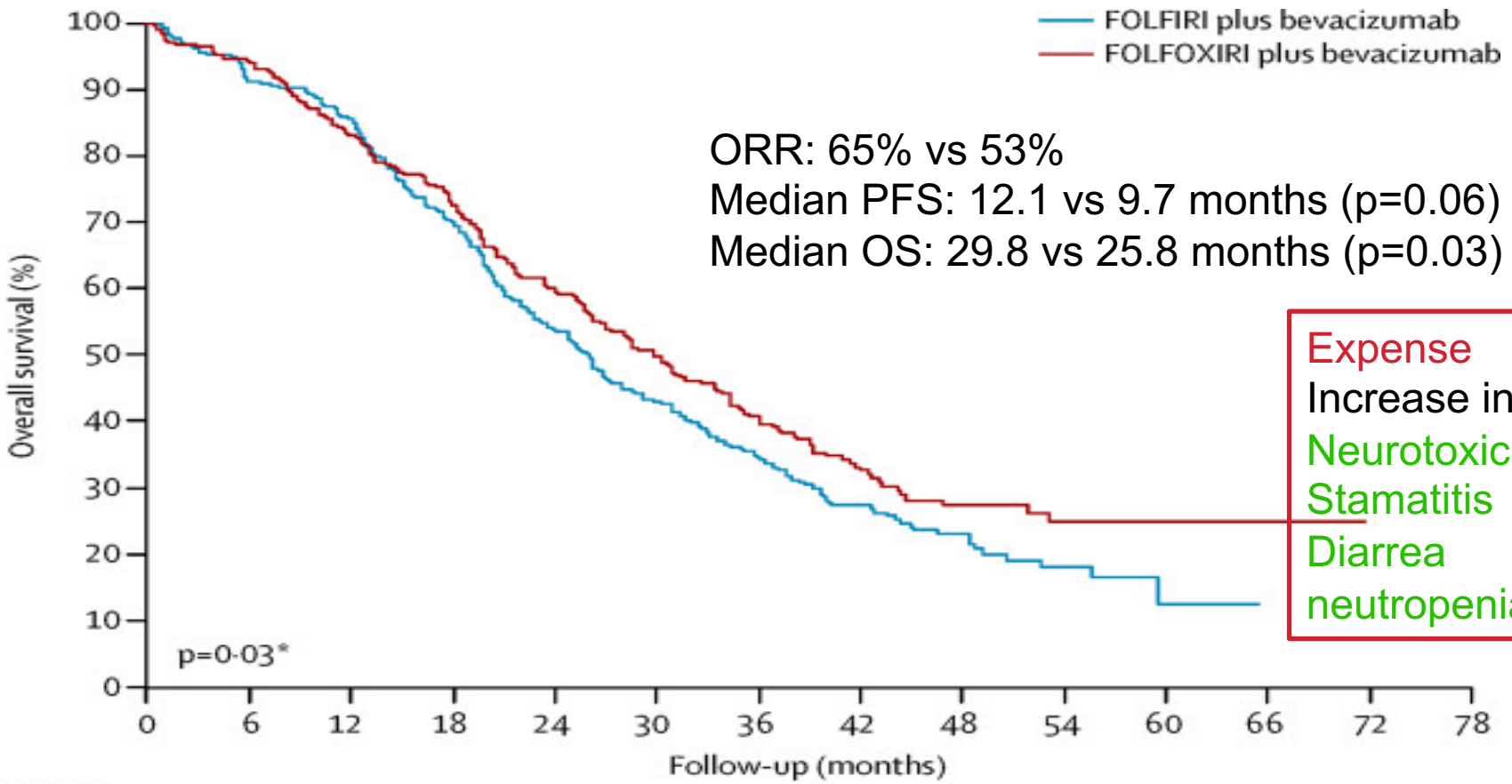


Therapy tailored according to individual patient needs

Chemotherapy Intensification: TRIBE Trial



TRIBE: OVERALL SURVIVAL



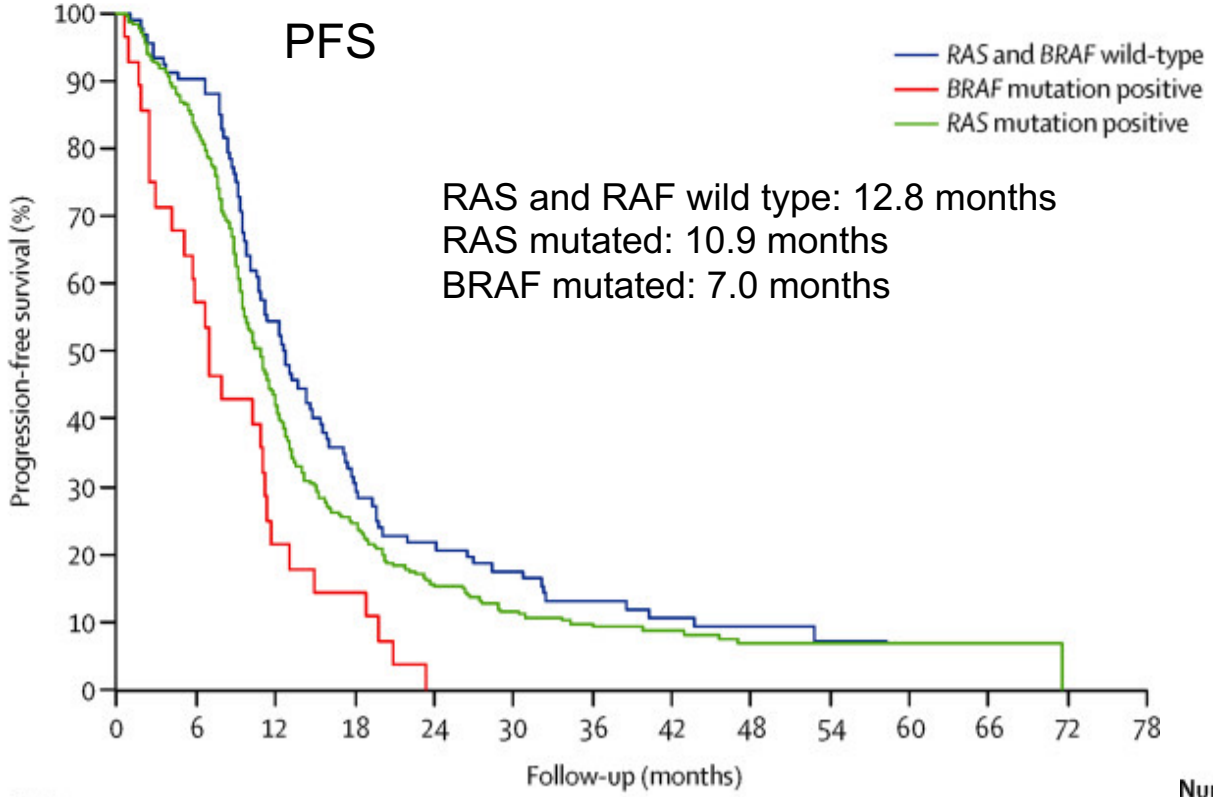
Number at risk														
FOLFIRI plus bevacizumab	256	234	219	179	137	109	86	55	31	15	3	0	0	0
FOLFOXIRI plus bevacizumab	252	236	208	181	148	123	95	57	34	19	9	3	0	0

ORR: 65% vs 53%
Median PFS: 12.1 vs 9.7 months (p=0.06)
Median OS: 29.8 vs 25.8 months (p=0.03)

Expense
Increase incidence of grade 3/4 AEs:
Neurotoxicity
Stamatitis
Diarrea
neutropenia

TRIBE: Molecular subgroup analysis

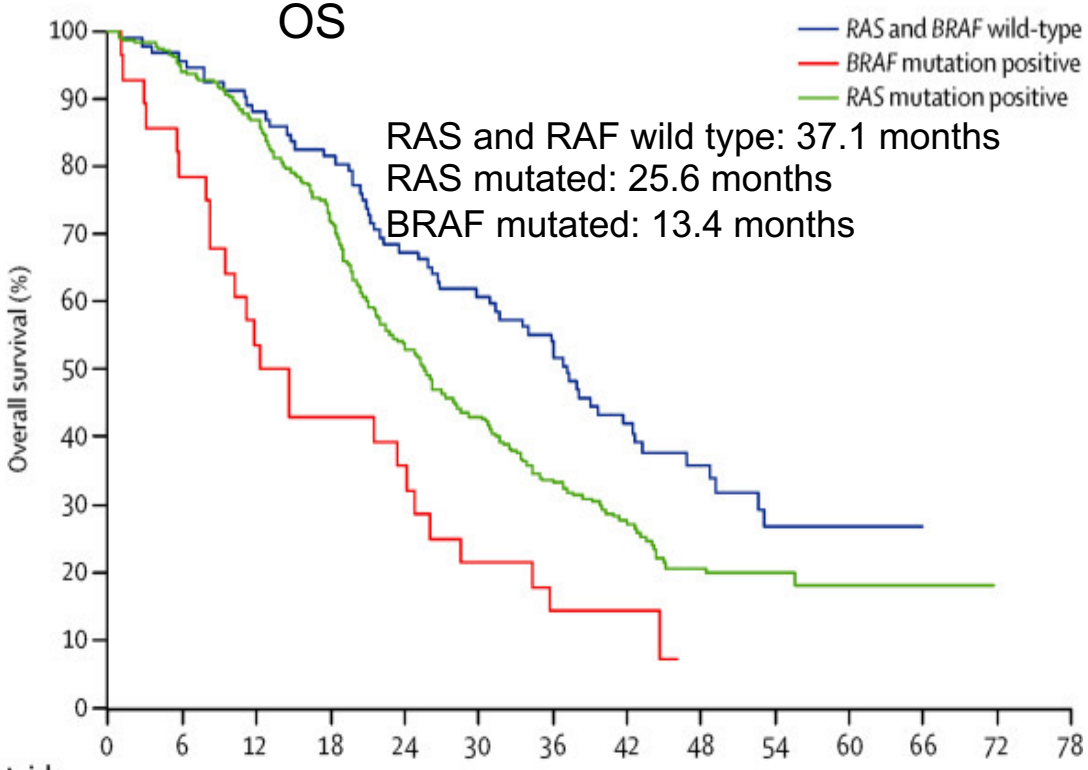
PFS



RAS and RAF wild type: 12.8 months
RAS mutated: 10.9 months
BRAF mutated: 7.0 months

Number at risk														
RAS and BRAF wild-type	93	83	50	28	20	16	12	9	6	2	0	0	0	0
RAS mutation positive	236	196	99	58	37	27	21	15	10	7	2	2	0	0
BRAF mutation positive	28	16	6	4	0	0	0	0	0	0	0	0	0	0

OS

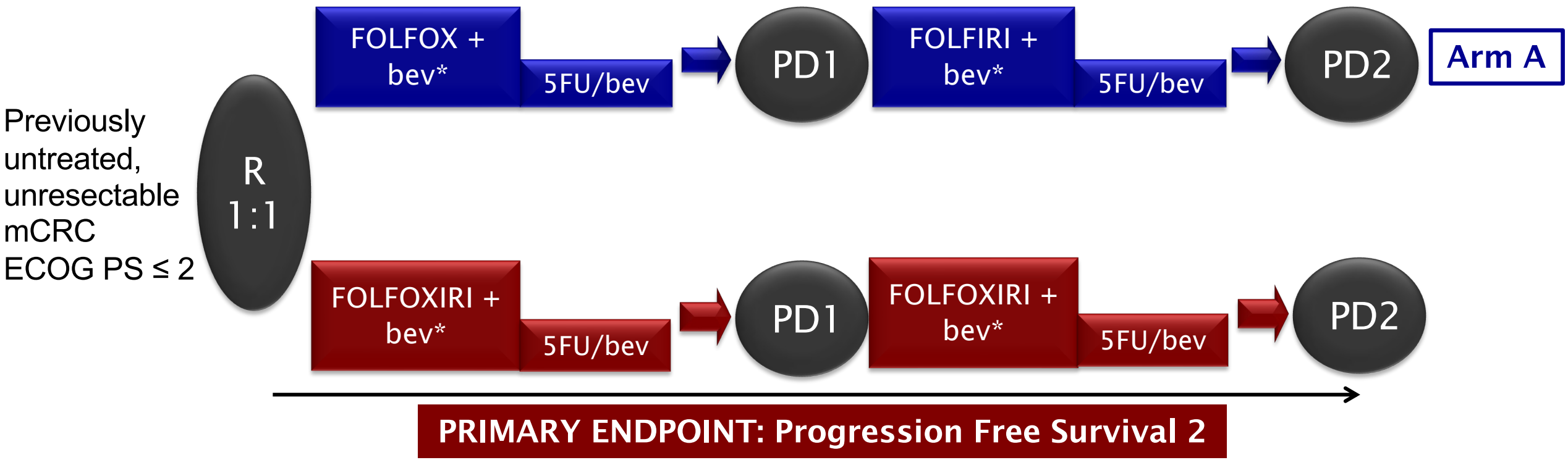


RAS and RAF wild type: 37.1 months
RAS mutated: 25.6 months
BRAF mutated: 13.4 months

Number at risk														
RAS and BRAF wild-type	93	88	81	75	61	55	46	31	18	10	4	0	0	0
RAS mutation positive	236	222	205	170	124	101	76	47	26	15	4	2	0	0
BRAF mutation positive	28	22	15	12	10	6	4	3	0	0	0	0	0	0

Cremolini et al. Lancet oncology 2015

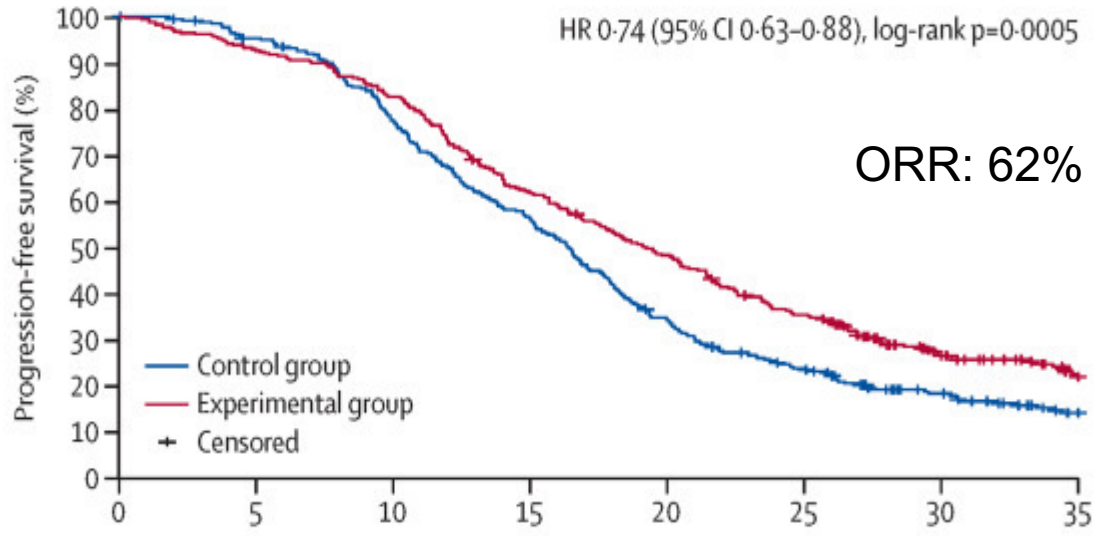
TRIBE 2 trial: Planned Sequential Therapy



TRIBE-2: PFS

PFS 1

Median PFS1: 12 vs 9.8 months

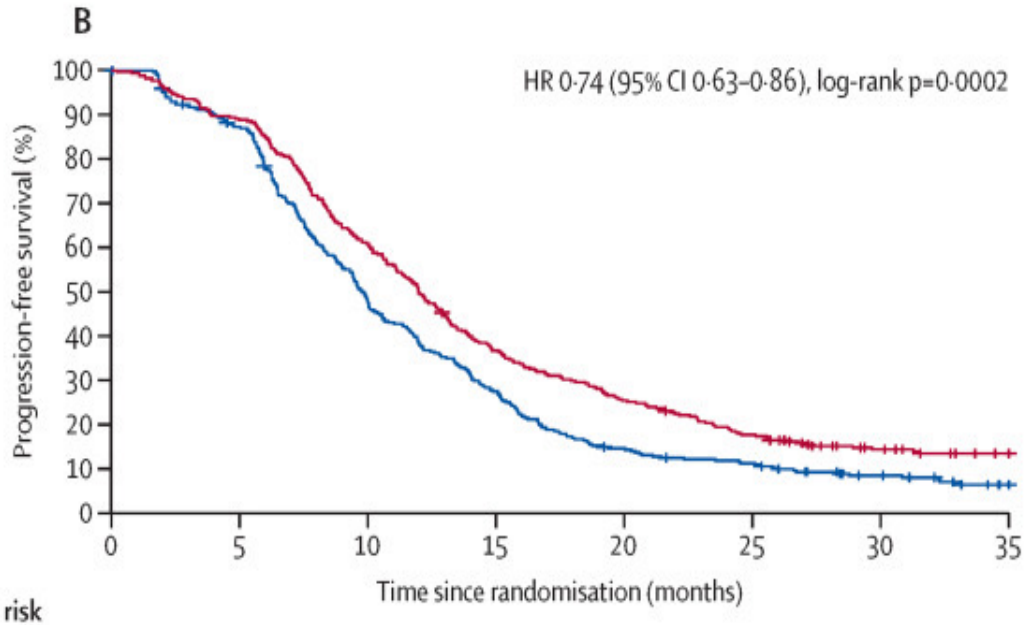


Number at risk (number censored)								
Control group	340 (0)	319 (5)	259 (6)	188 (6)	114 (7)	76 (10)	45 (25)	23 (38)
Experimental group	339 (0)	314 (0)	280 (0)	209 (1)	162 (2)	117 (4)	66 (30)	39 (47)

ORR: 62% vs 50%

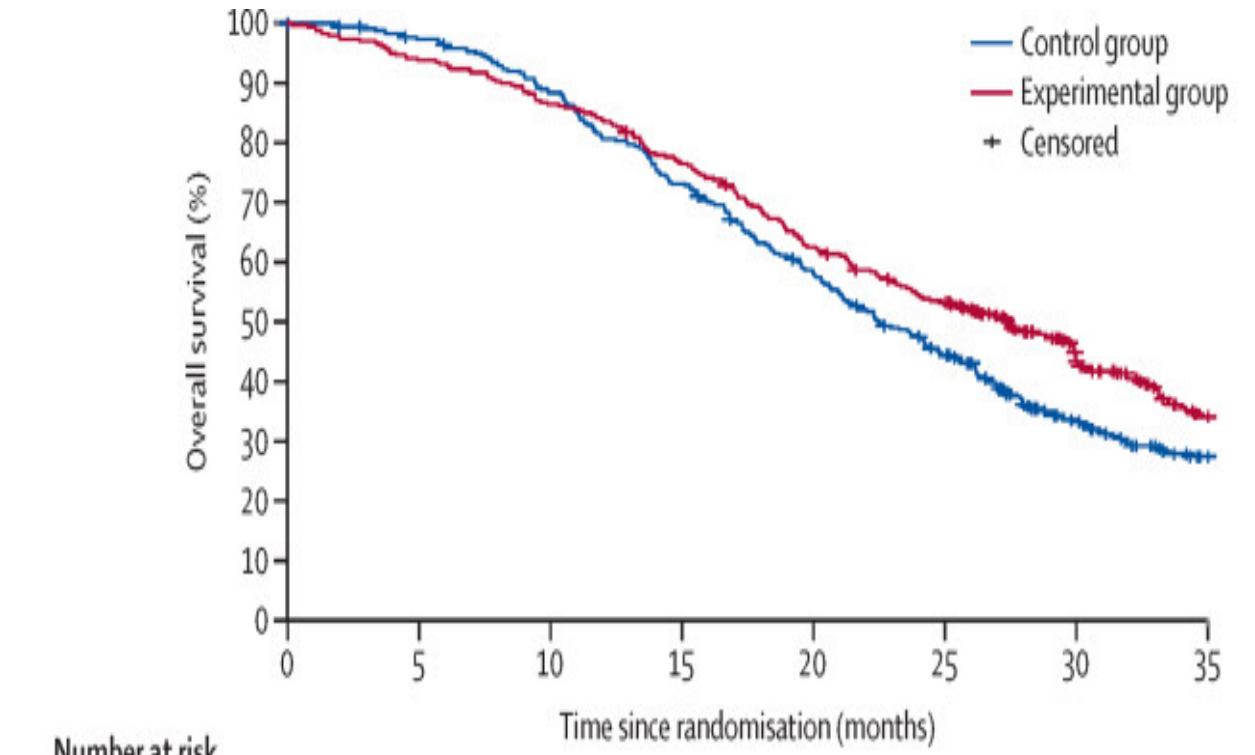
PFS 2

Median PFS2: 19.2 vs 16.4 months



Number at risk (number censored)								
Control group	340 (0)	292 (5)	160 (6)	91 (6)	47 (7)	35 (8)	19 (16)	7 (24)
Experimental group	339 (0)	301 (0)	206 (0)	123 (1)	85 (1)	58 (2)	36 (14)	25 (23)

TRIBE 2: Overall Survival



Median OS: 27.4 vs 22.5 months (p=0.03)

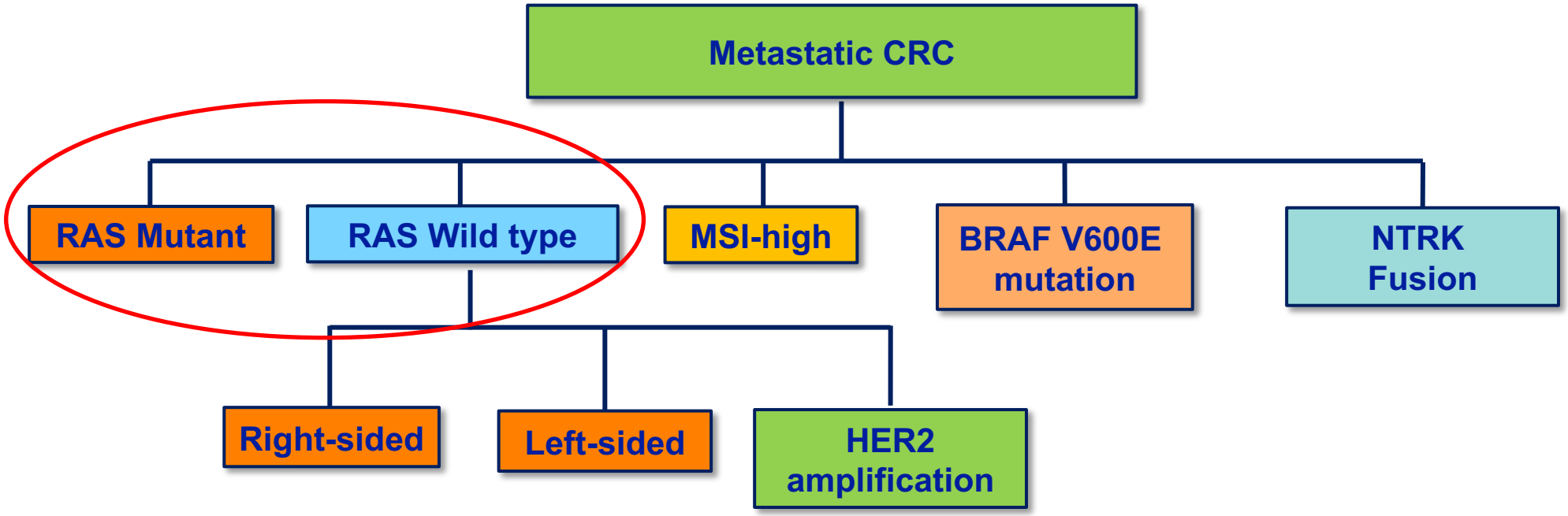
Expense
Increase incidence of grade 3/4 AEs:
Neurotoxicity
Stomatitis
Diarrhea
Neutropenia

Treatment related deaths: 2.3% vs 1%

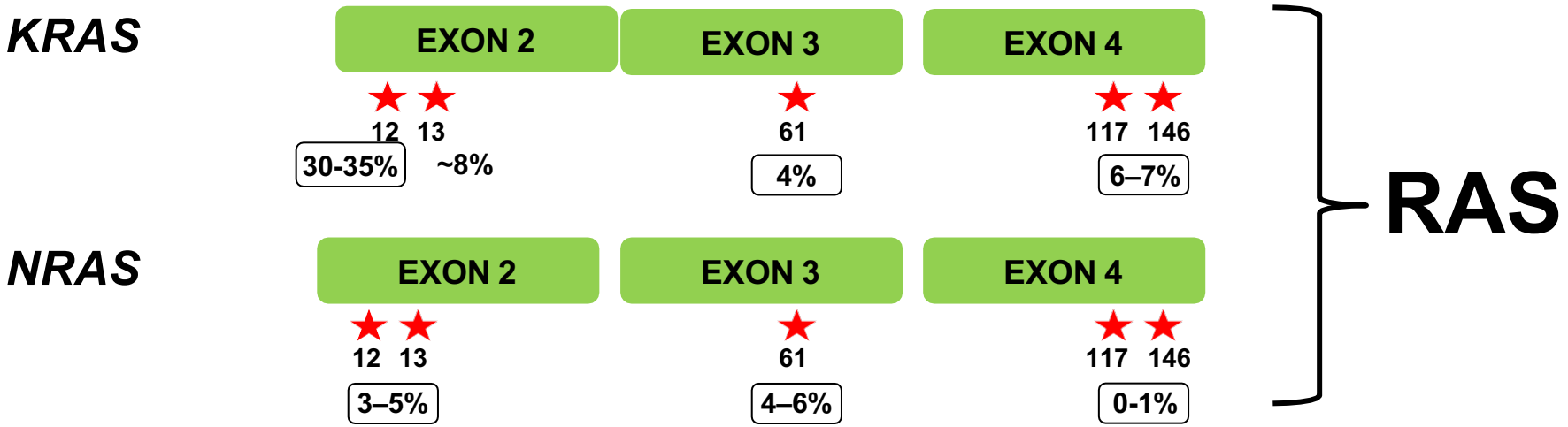
First Line *non-biomarker* driven treatment

- TRIBE and TRIBE 2 trials confirm the survival benefit of treatment intensification
  - 4 months in TRIBE
  - 5 months in TRIBE 2
  - All subgroups seem to benefit
- Higher PFS, RR, R0 resection rate
- TRIBE 2 allowed maintenance therapy and sequencing should not be a concern
- For patients with excellent performance status, FOLFOXIRI + bevacizumab should be preferred first line option

Can Biomarker Drive Treatment Decision?



RAS mutations



CALGB/SWOG 80405: Biological agent and Tumor sidedness

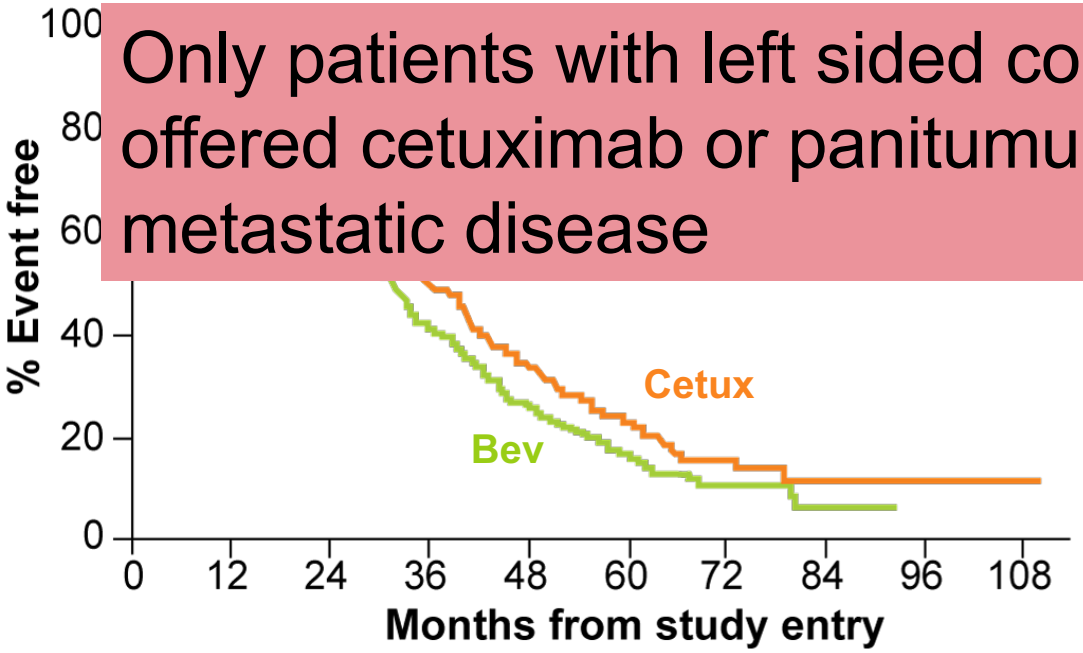
Left-sided primary

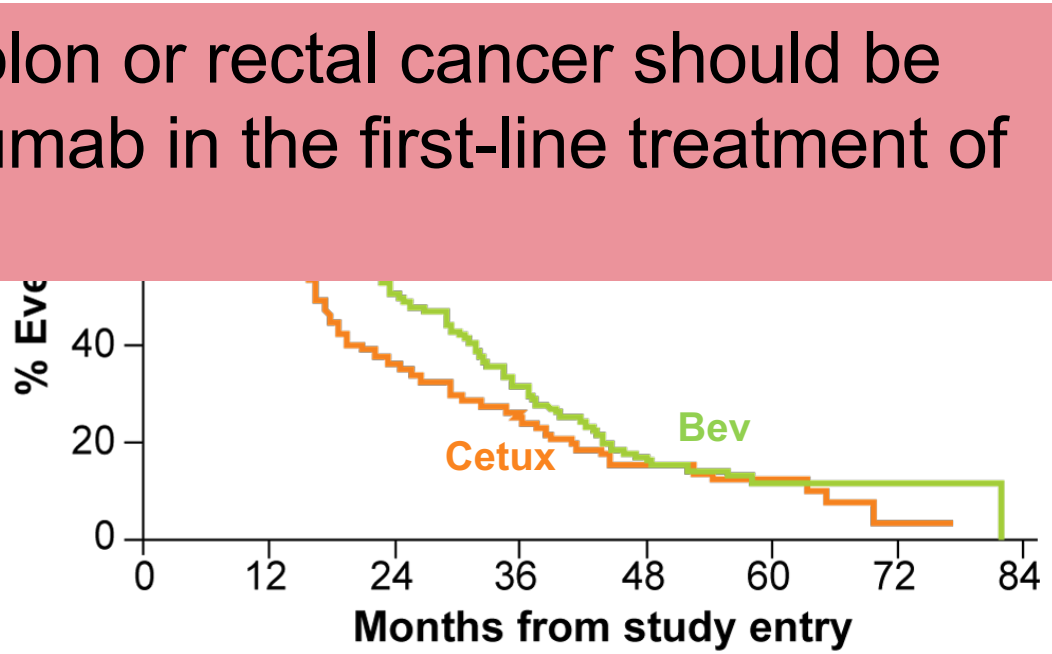
Agent	N	Median	HR	*p*-value
Bevacizumab	356	31.4	0.817	0.018
Cetuximab	376	36.0		

Right-sided primary

Agent	N	Median	HR	*p*-value
Bevacizumab	150	24.2	1.269	0.065
Cetuximab	143	16.7		

Only patients with left sided colon or rectal cancer should be offered cetuximab or panitumumab in the first-line treatment of metastatic disease

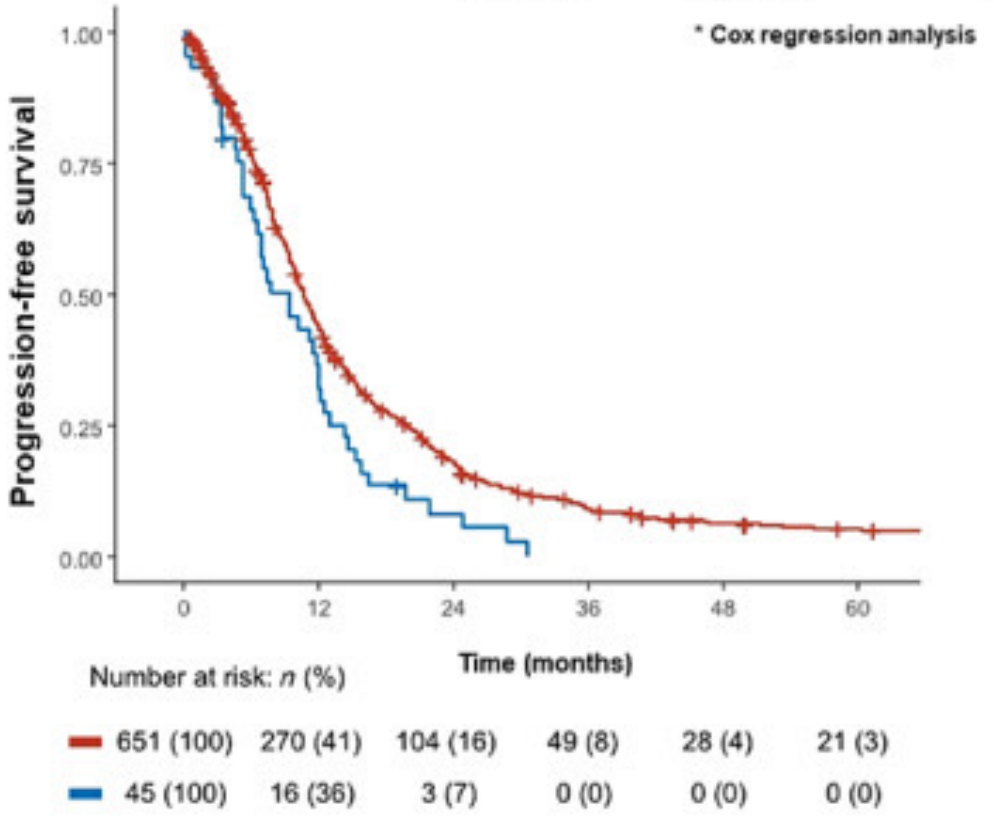




KRAS G12C: Poor Prognostic Marker

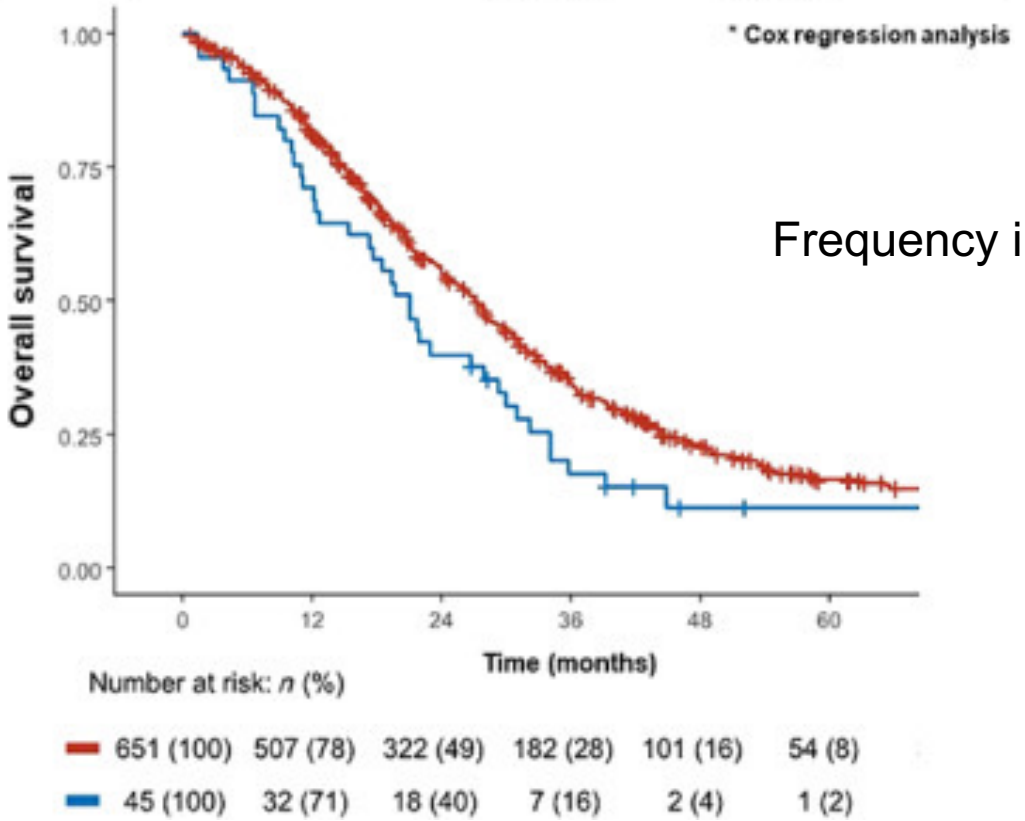
A

KRAS exon2 mutant	*n*	Median (95% CI) (months)	HR vs Other KRAS mutation subtypes (95% CI)	*p* value*
Non-G12C mutations	651	10.8 (10.1-11.5)	Reference	
G12C mutations	45	9.4 (6.4-12.0)	1.47 (1.08-2.01)	.015



B

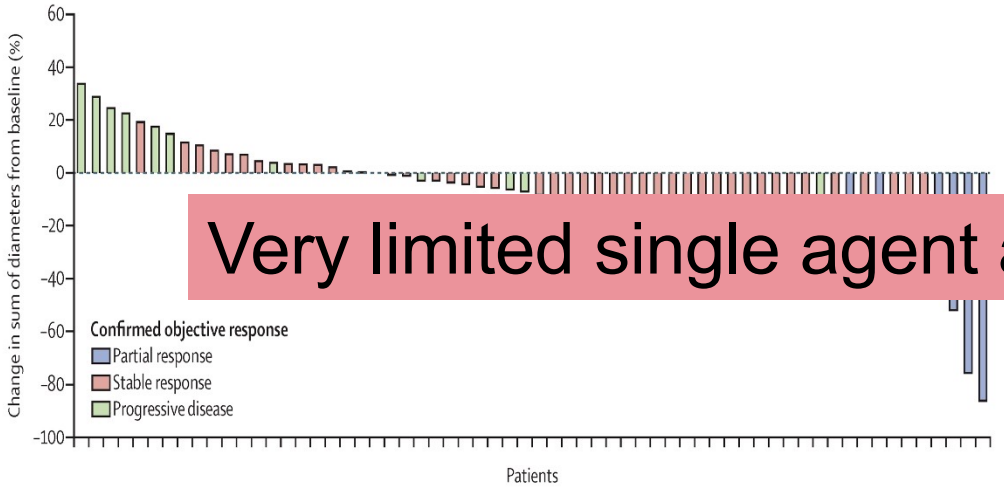
KRAS exon2 mutant	*n*	Median (95% CI) (months)	HR vs Other KRAS mutation subtypes (95% CI)	*p* value*
Non-G12C mutations	651	27.3 (24.8-28.9)	Reference	
G12C mutations	45	21.1 (12.8-27.9)	1.50 (1.08-2.08)	.015



Frequency in CRC: 3.1%

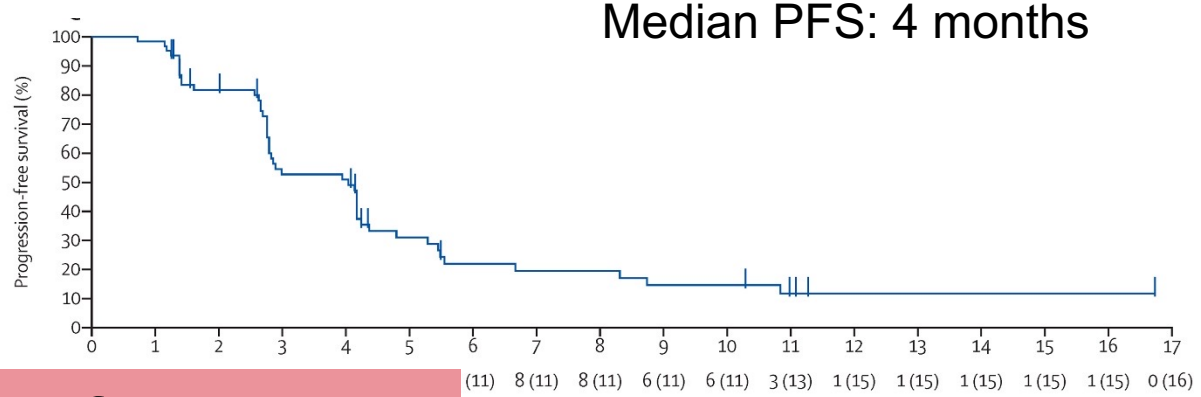
CODEBREAK-100: Sotorasib

RR: 9.7%

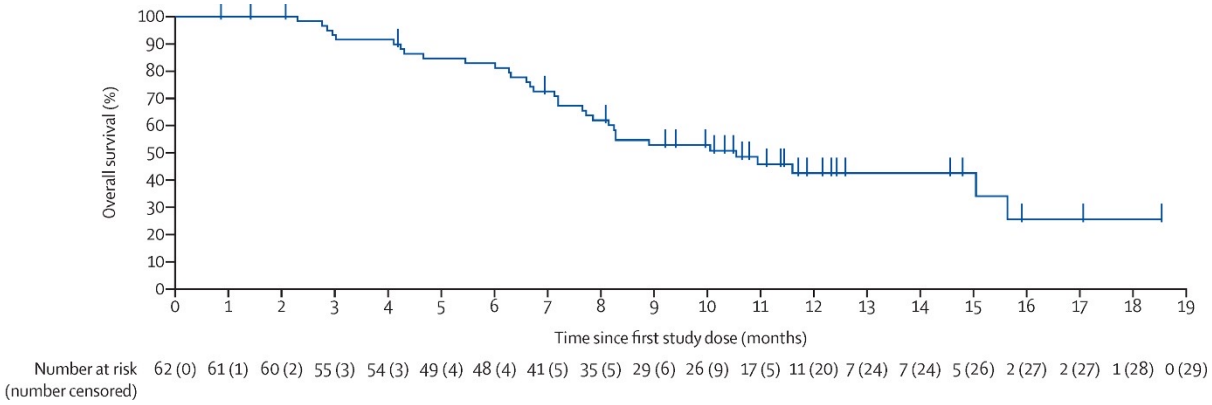


Very limited single agent activity of sotorasib

Median PFS: 4 months



Median OS: 10.7 months

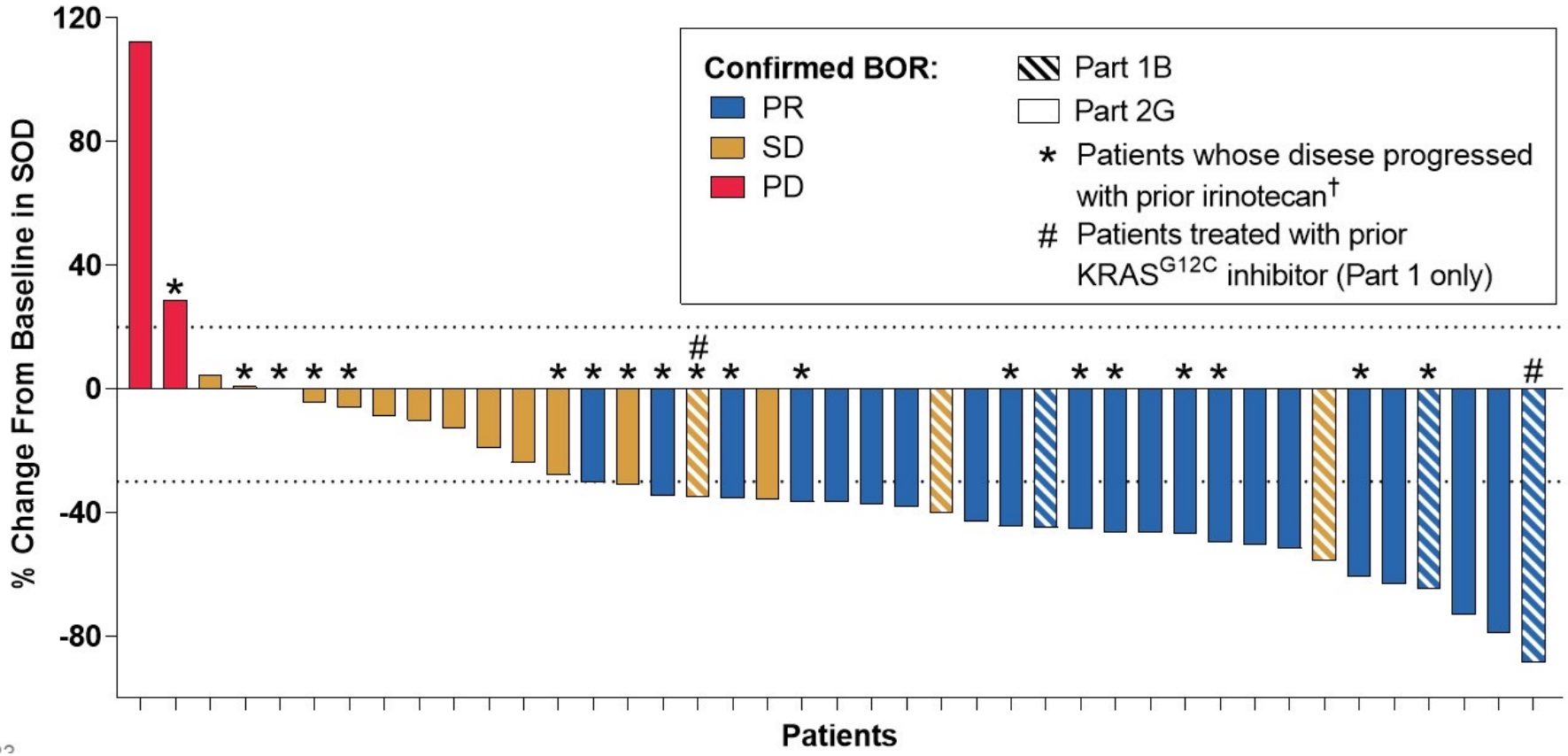


CODEBREAK 101

Response rates:

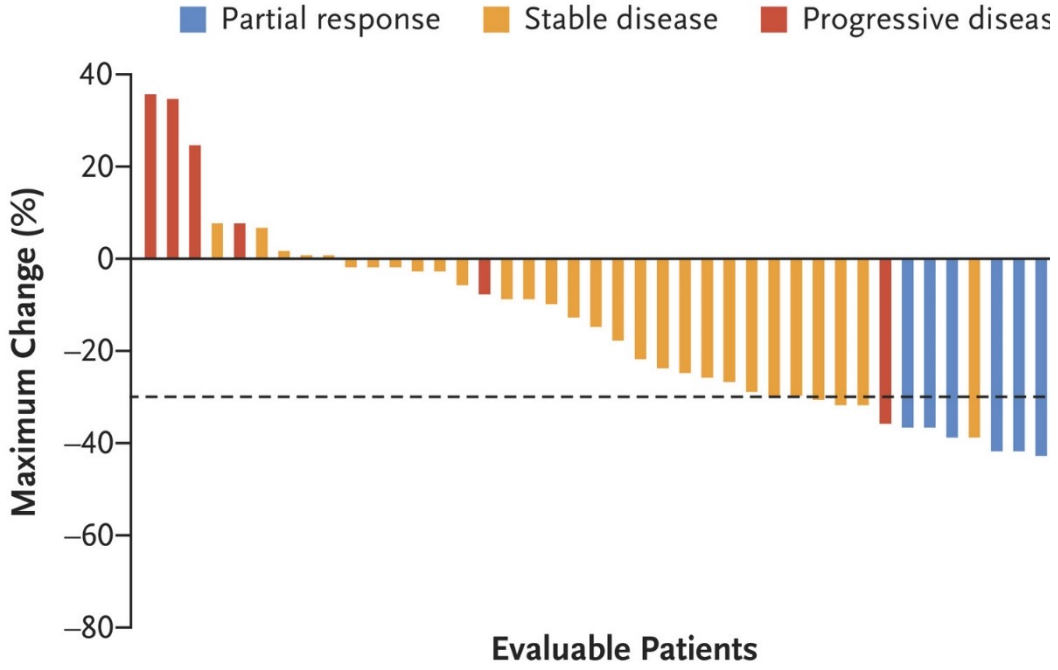
Sotorasib + panitumumab: 26.9%

Sotorasib + panitumumab + FOLFIRI: 55%

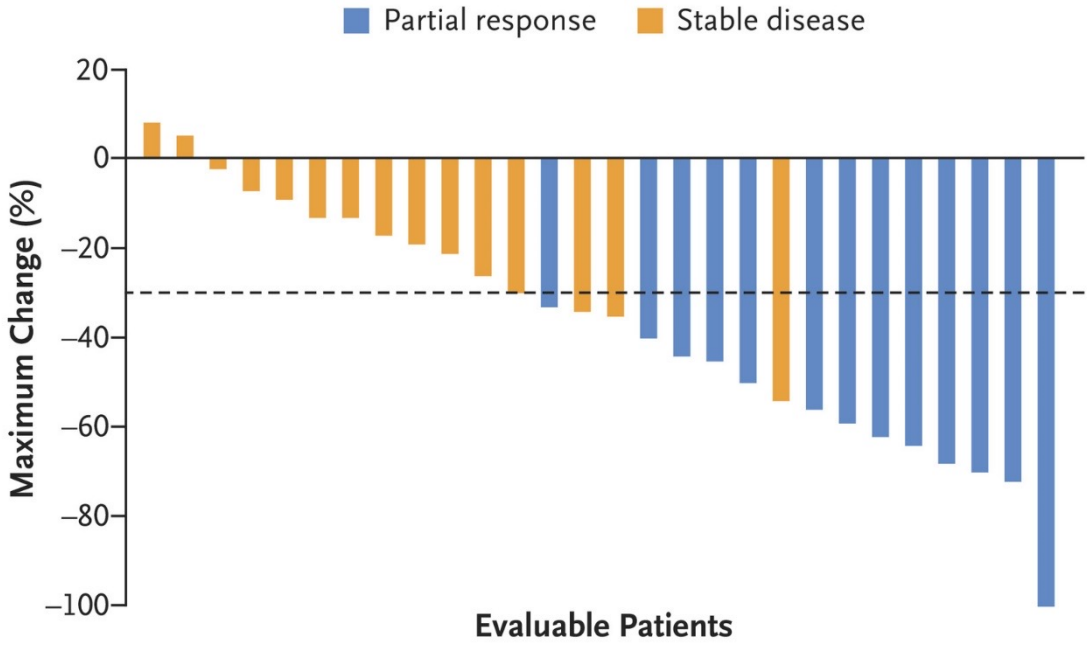


KRYSTAL-1: Adagrasib

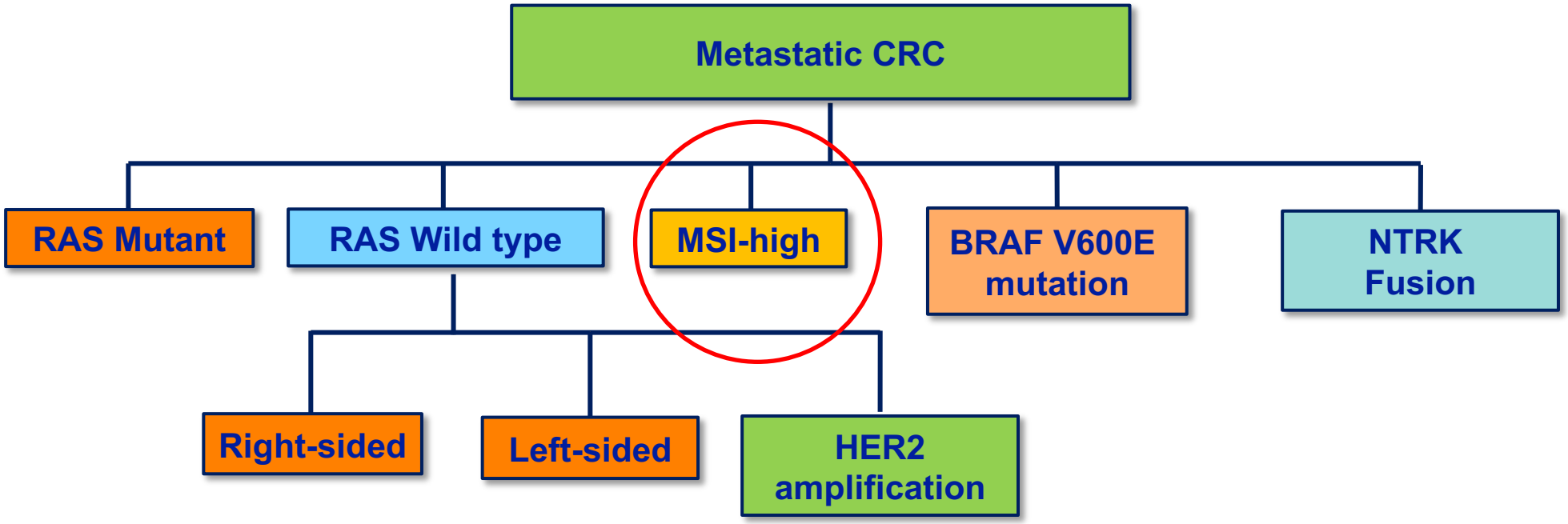
Single Agent Adagrasib
Response Rates: 19%
Disease control rate: 86%



Adagrasib + cetuximab
Response Rates: 46%
Disease control rate: 100%

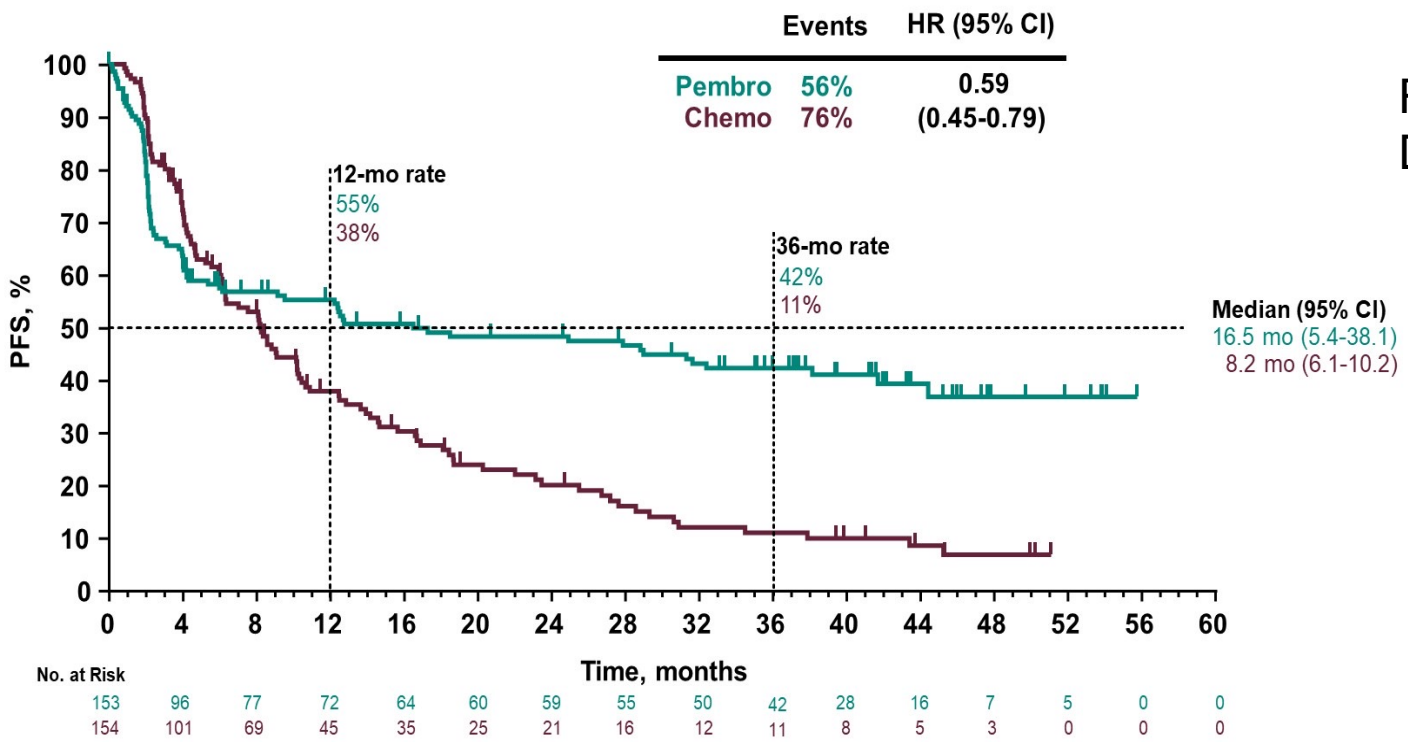


Can Biomarker Drive Treatment Decision?



KEYNOTE-177: Single agent Pembrolizumab

Progression-Free Survival

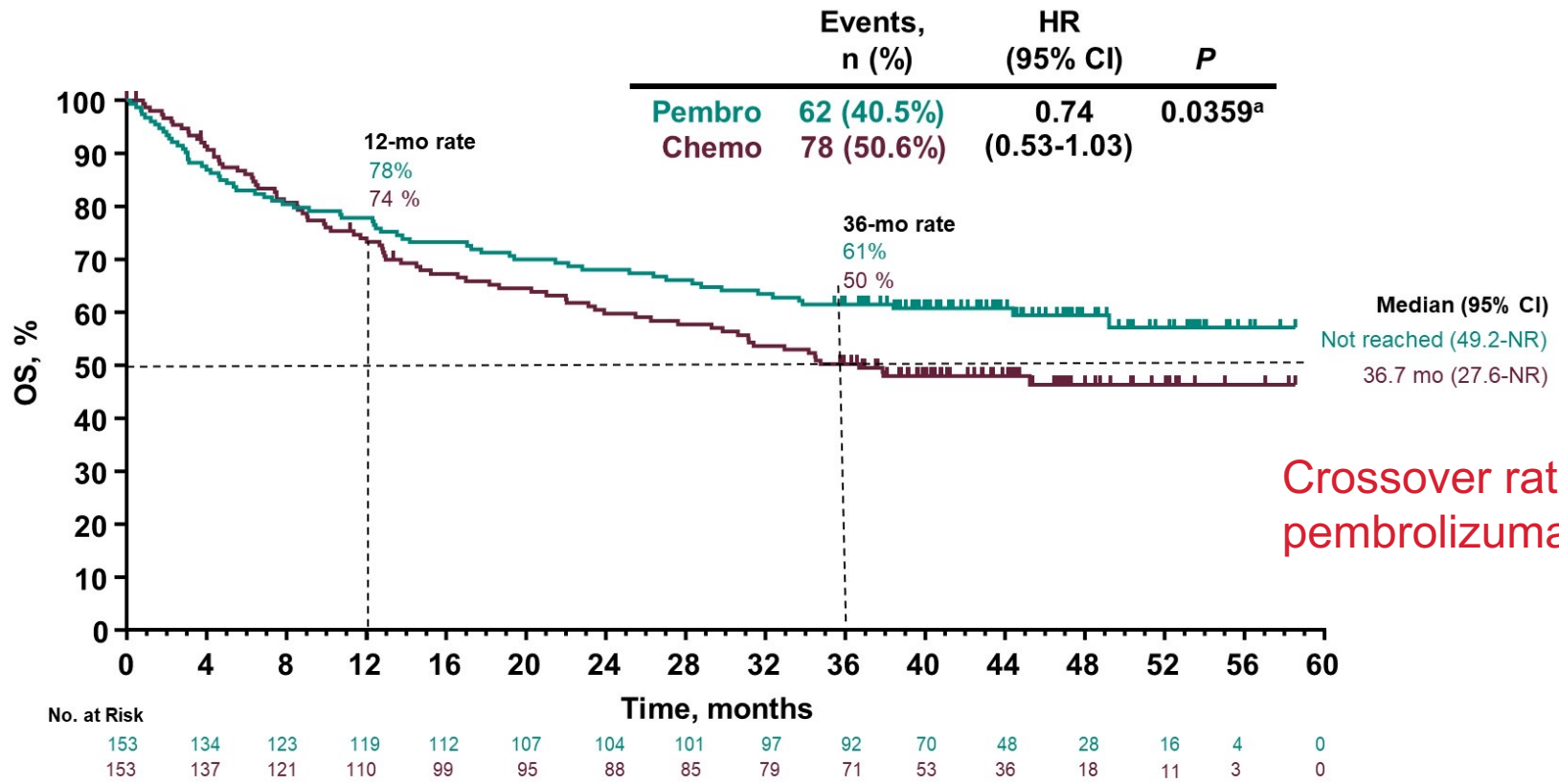


Response rates: 43.8%
Disease control rate: 70.6%

Data cut-off: 19Feb2021.

KEYNOTE-177: Single agent Pembrolizumab

Overall Survival



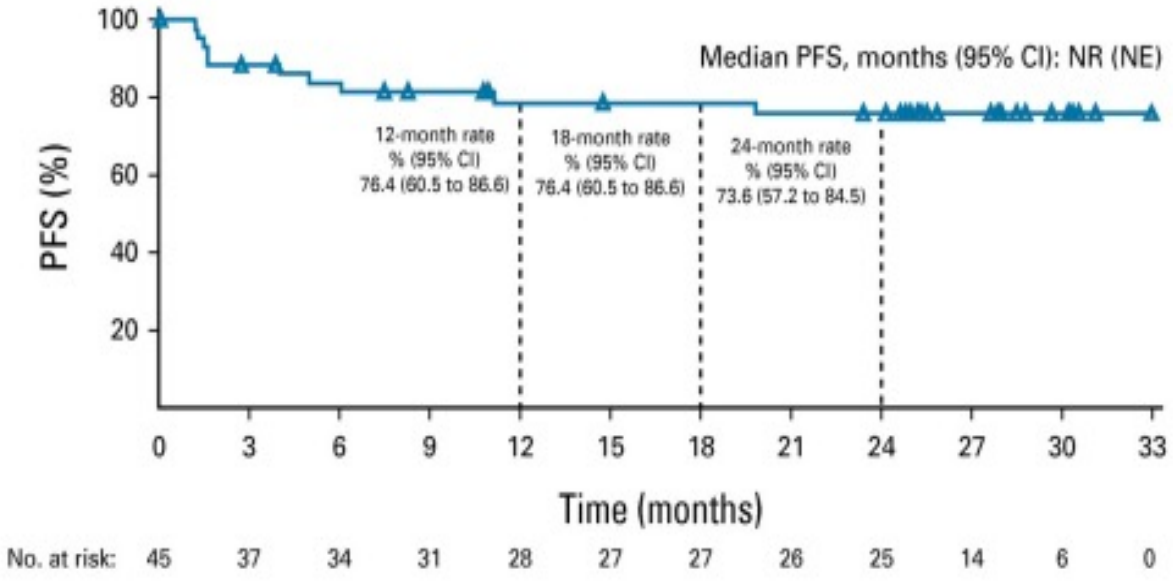
Crossover rate from chemotherapy to pembrolizumab: 36%

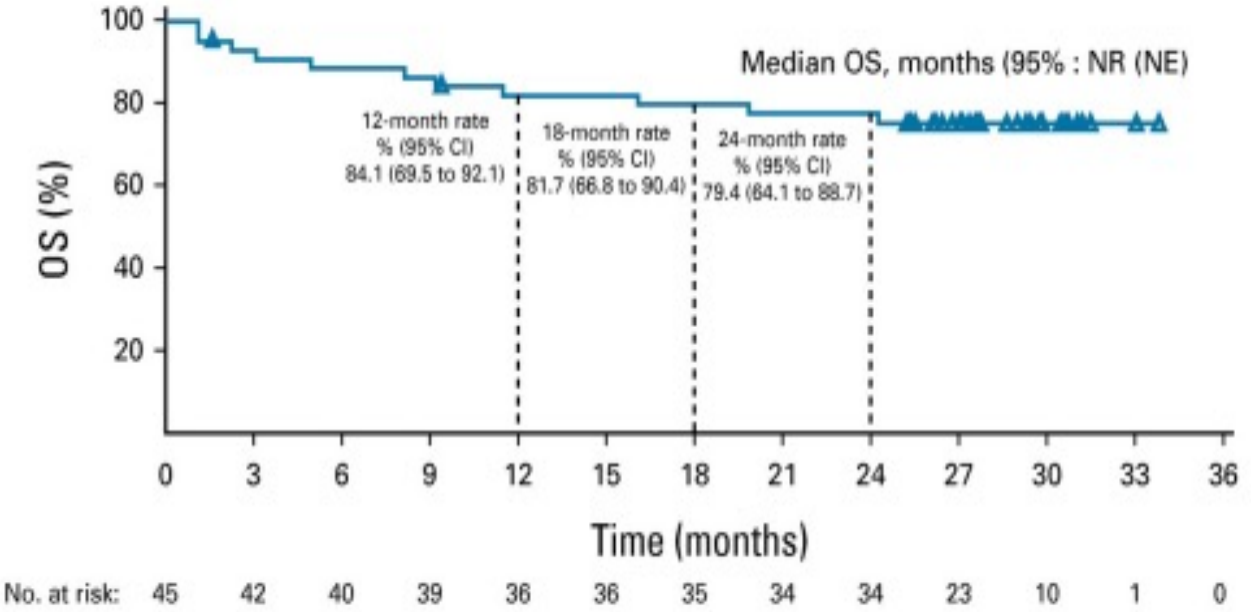
[a]**Pembrolizumab was not superior to chemotherapy for OS as one-sided α > 0.0246. Pre-specified sensitivity analyses to adjust for crossover effect by rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38).** Data cut-off: 19Feb2021.

CHECKMATE 142: Ipilumumab + Nivolumab

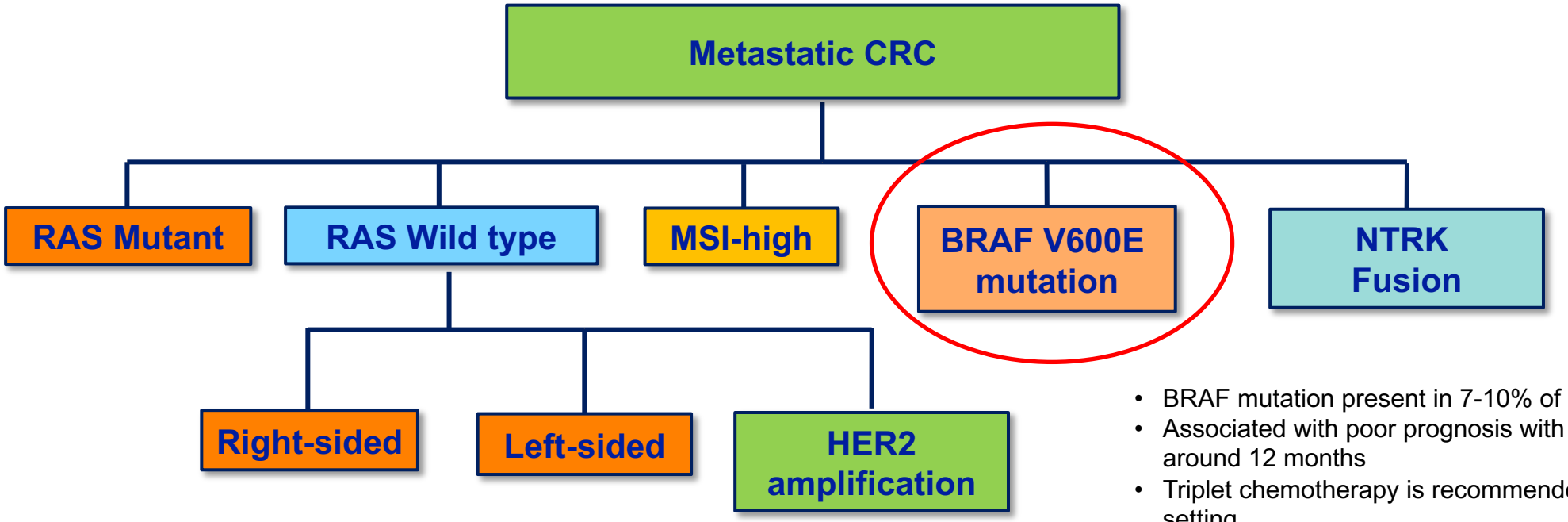
Response rate: 64%
Disease control rate: 84%

Expense: Increase toxicities (compared to single agent pembrolizumab)



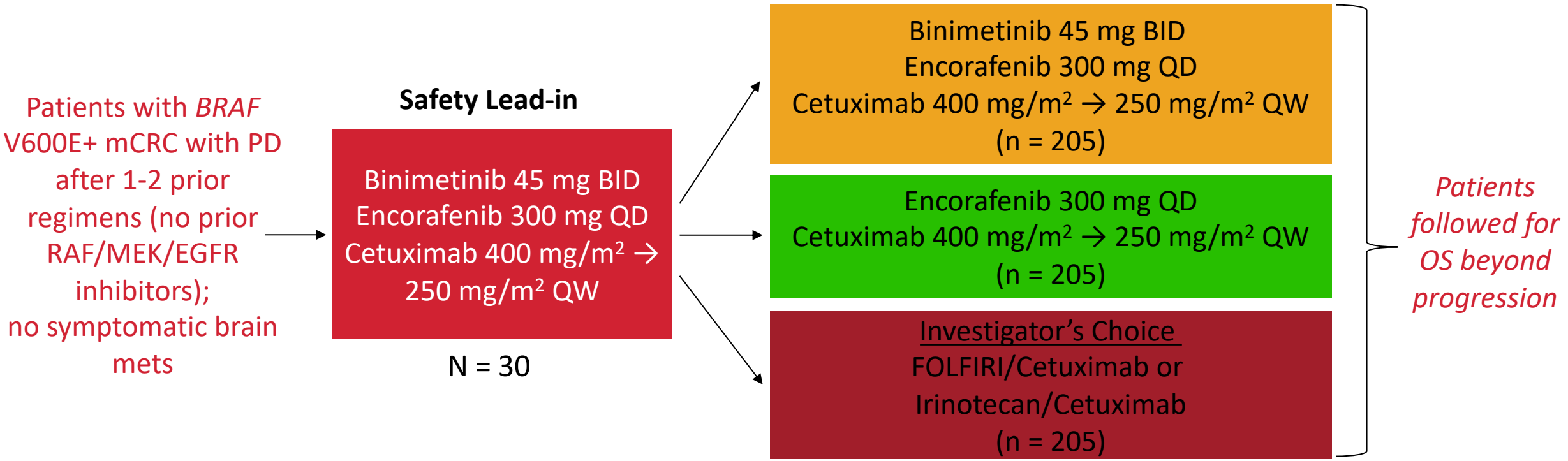


Can Biomarker Drive Treatment Decision?



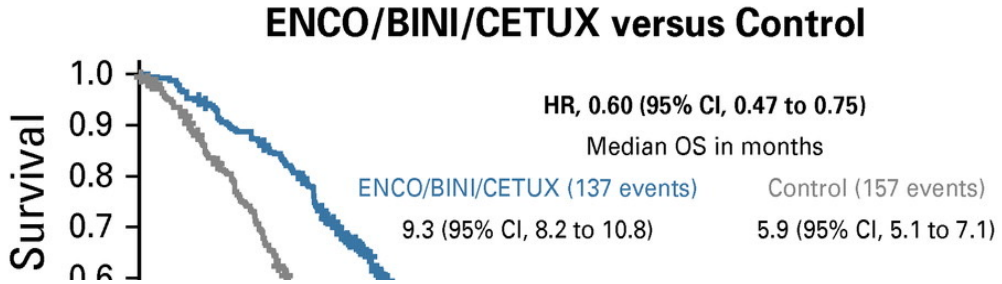
- BRAF mutation present in 7-10% of CRC
- Associated with poor prognosis with median OS around 12 months
- Triplet chemotherapy is recommended in first line setting

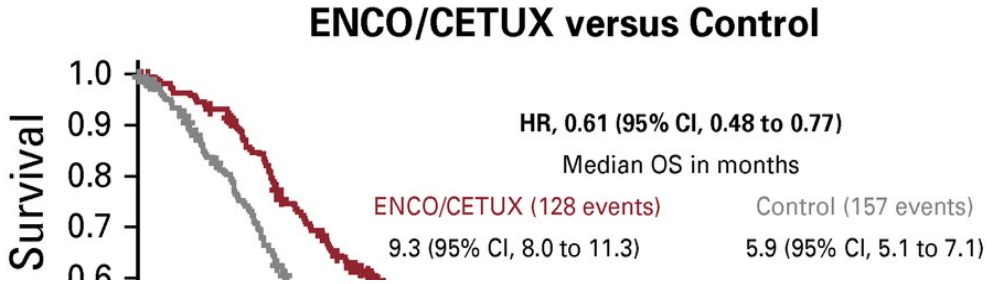
BEACON Trial: 2nd Line or later



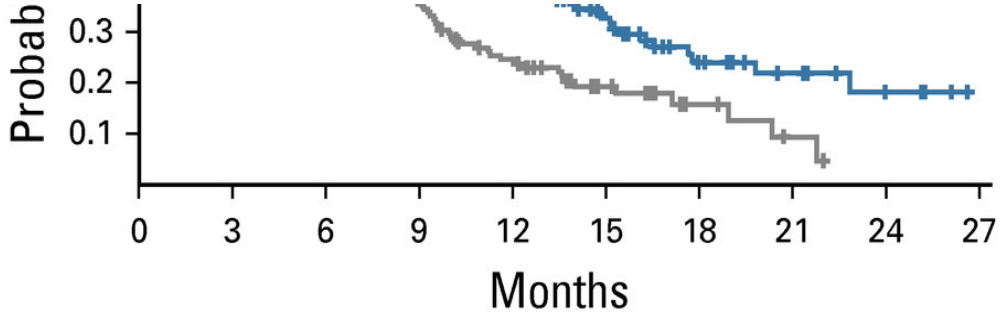
BEACON Trial

Response rates:
Triplet therapy: 26%
Doublet therapy: 20%



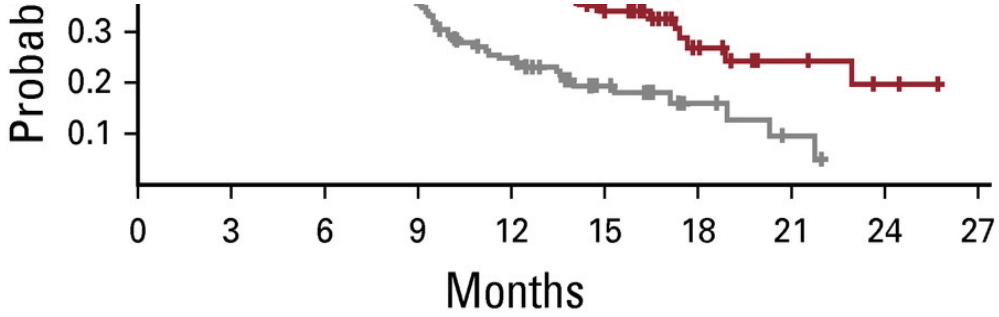


FDA Approved Encorafenib + Cetuximab for mCRC



Number of patients at risk

ENCO/BINI/CETUX	224	198	157	89	56	33	15	9	4	0
Control	221	166	98	54	33	15	6	2	0	0

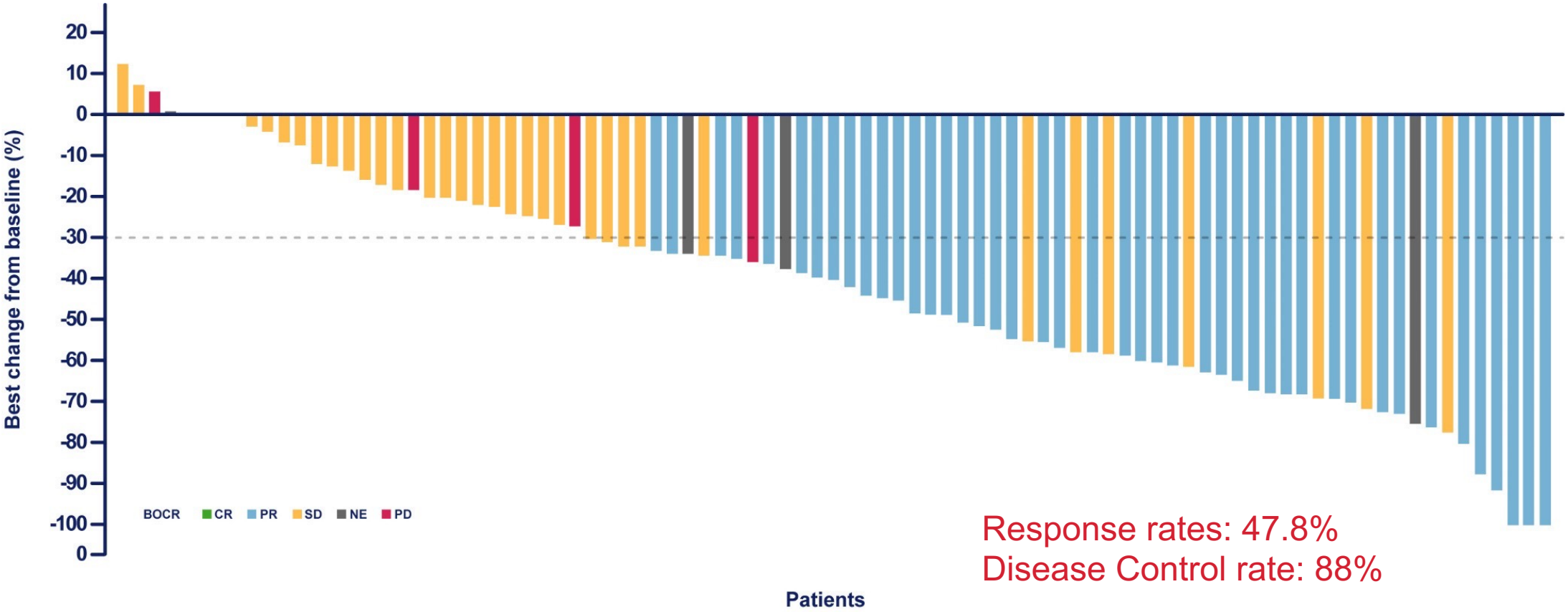


Number of patients at risk

ENCO/CETUX	220	197	143	83	47	28	13	7	2	0
Control	221	166	98	54	33	15	6	2	0	0

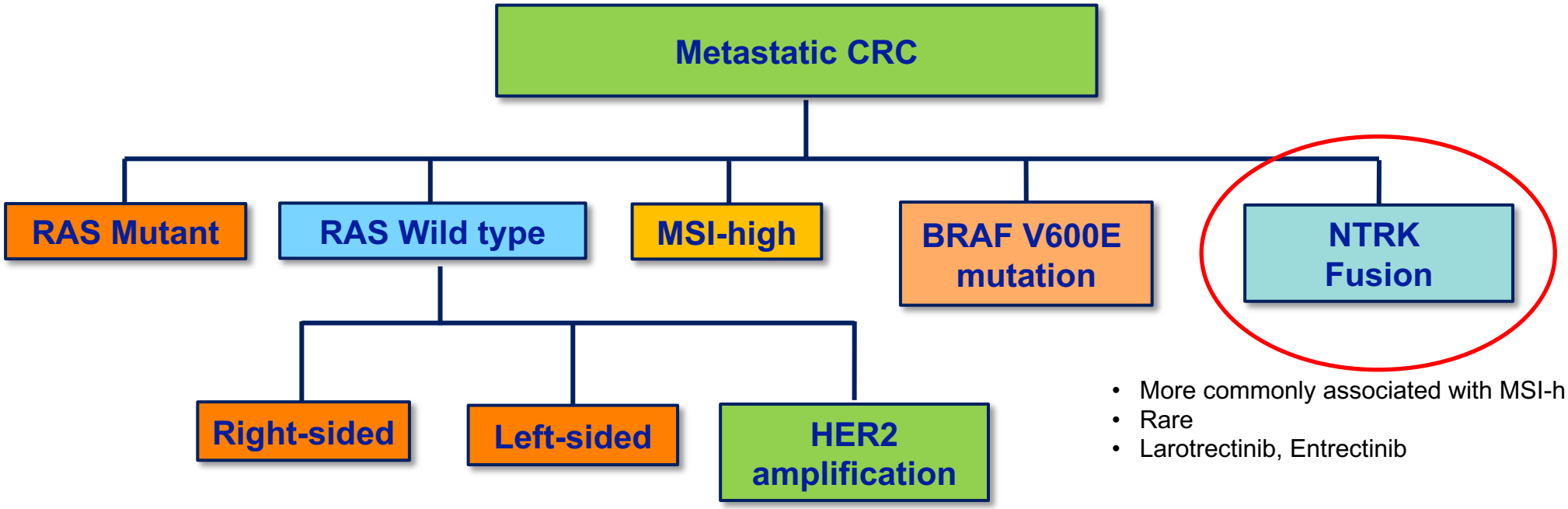
ANCHOR Trial: 1st line

Encorafenib + binimetinib + cetuximab



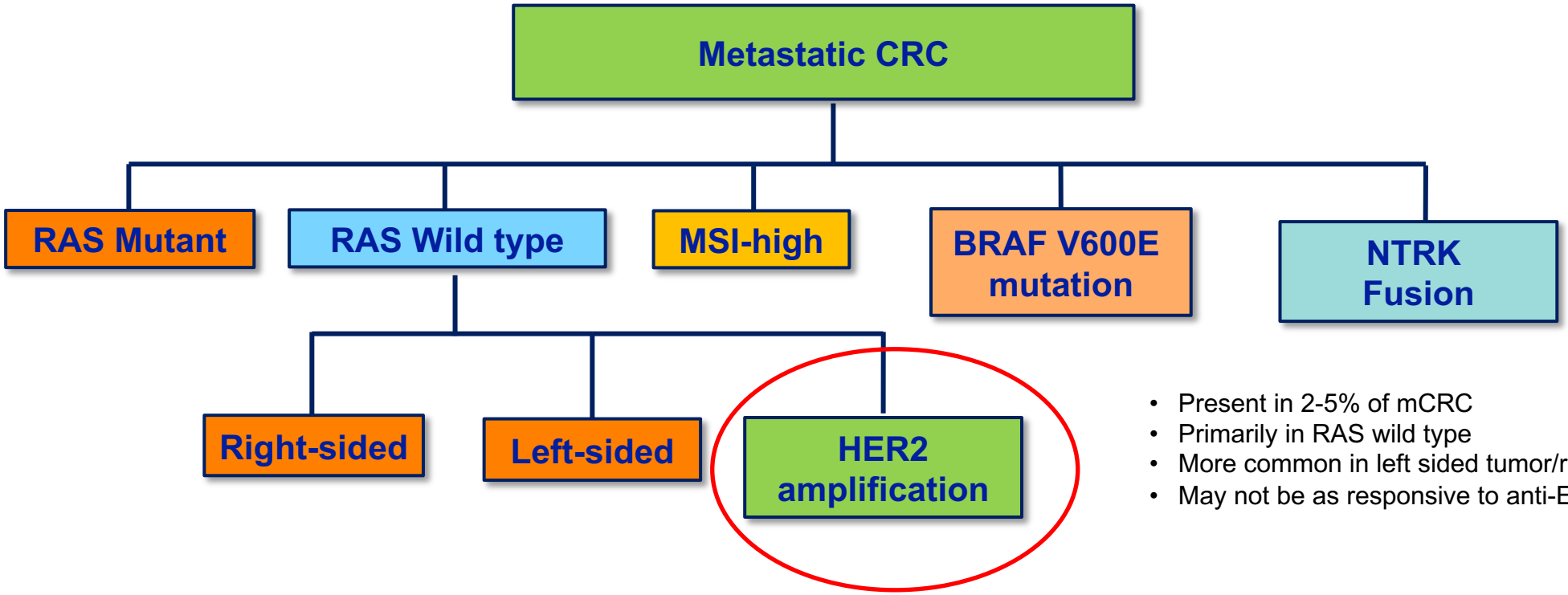
Response rates: 47.8%
Disease Control rate: 88%

Can Biomarker Drive Treatment Decision?



- More commonly associated with MSI-h tumors
- Rare
- Larotrectinib, Entrectinib

Can Biomarker Drive Treatment Decision?



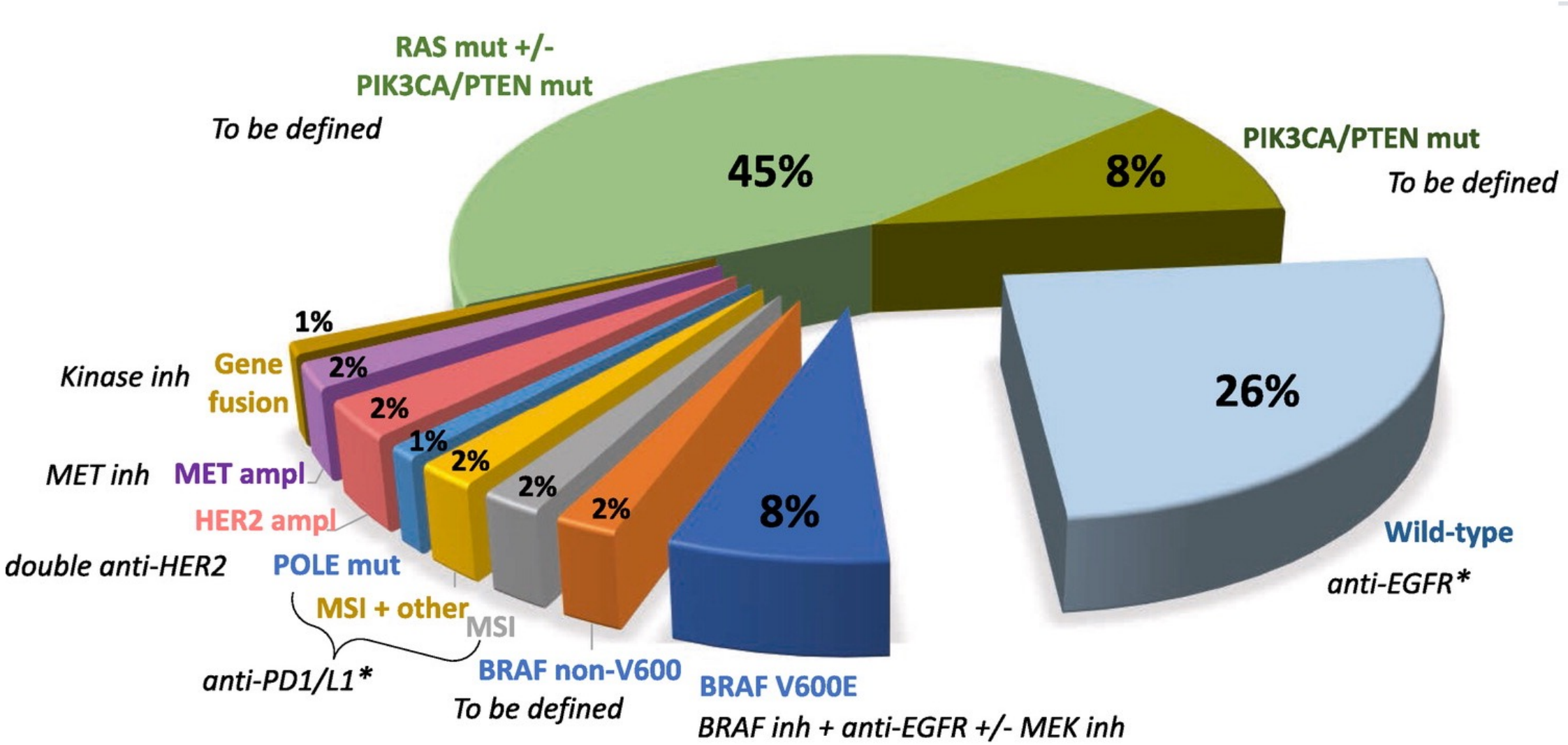
- Present in 2-5% of mCRC
- Primarily in RAS wild type
- More common in left sided tumor/rectum
- May not be as responsive to anti-EGFR therapy

Her-2 Targeted Trials in CRC

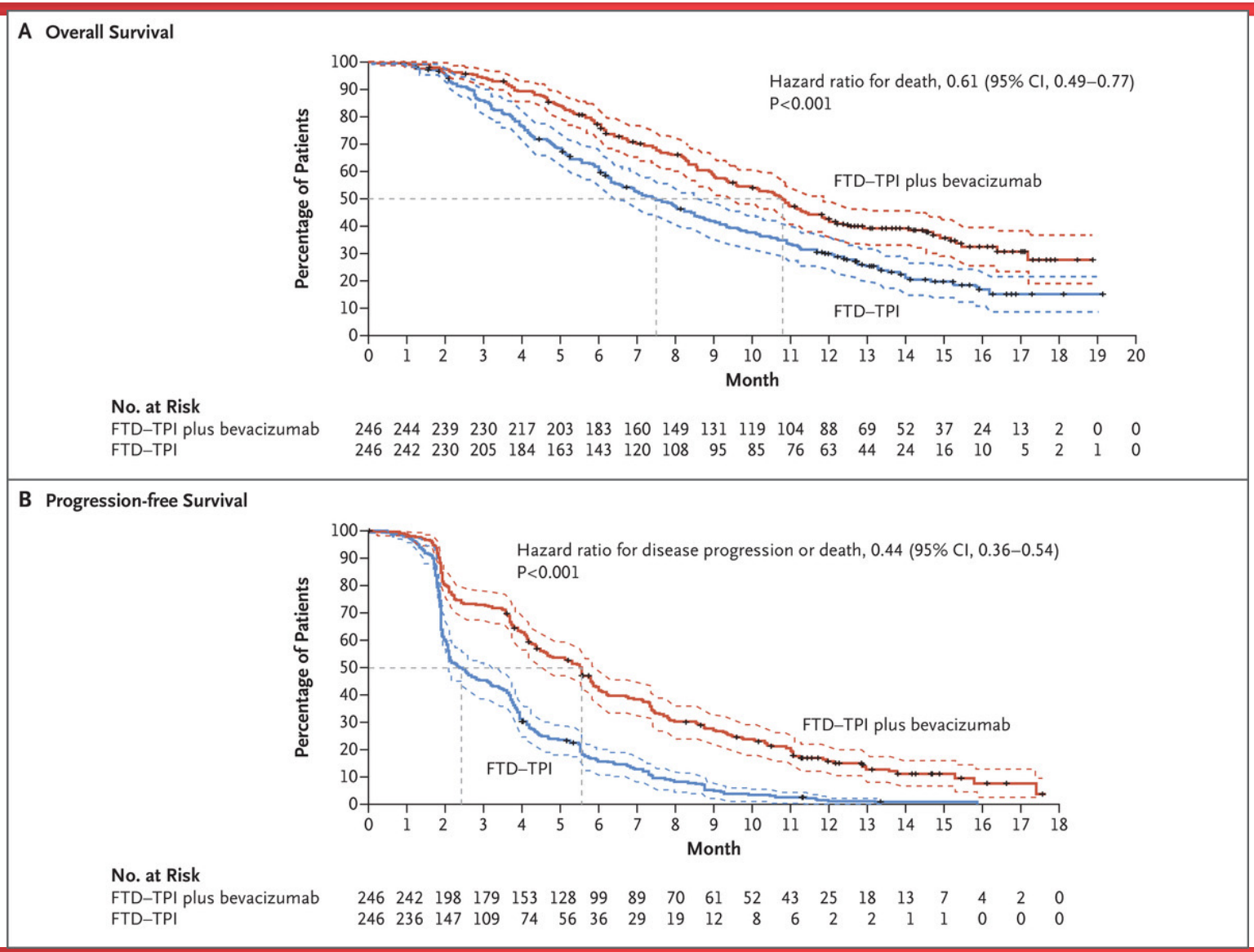
Treatment (Study name)	Strategy	N	ORR (%)	PFS (months)	OS (months)
Trastuzumab + Lapatinib (HERACLES-A)	Ab + TKI	32	28%	4.7	10
Trastuzumab + Pertuzumab (MY PATHWAY-RASwt)	Ab + Ab	43	40%	5.3	14
Pertuzumab + TDM-1 (HERACLES-B)	Ab + ADC	31	9.7%	4.7	10
Trastuzumab + Tucatinib (MOUNTAINEER)	Ab + TKI	84	38.1%	8.2	24.1
Trastuzumab Deruxtecan (DESTINY-CRC02)	ADC	82	37.8%	5.8	13.4

FDA Approved

Biomarker Driven Treatment for Metastatic CRC



SUNLIGHT Trial: Refractory Setting



TAS-102 + bevacizumab vs TAS-102
Median PFS: 5.6 vs 2.4 months
Median OS: 10.8 vs 7.5 months

FDA Approval: 8/2023
Establishes new SOC for refractory disease

	RAS/BRAF WT	KRAS mutant	BRAF mutant	HER2 amp	MSI-H/dMMR
1st line:	FOLFOXIRI + bev FOLFOX + bev FOLFOX + EGFR Ab (left sided)	FOLFOXIRI + bev FOLFOX + bev	FOLFOXIRI + bev	FOLFOXIRI + bev FOLFOX + bev	pembrolizumab Ipilimumab + nivolumab
2nd line:	FOLFIRI + bev	FOLFIRI + bev	EGFR Ab + Encorafenib	FOLFIRI + bev	FOLFOX + bev FOLFOXIRI + bev FOLFOX + EGFR (left sided)
3rd line:	Irinotecan + EGFR Ab	TAS-102 + bev	TAS-102 + bev	Dual anti-HER2 TDXd	FOLFIRI + bev
4th line:	TAS-102 + bev	Regorafenib	Regorafenib	TAS-102 + bev	TAS-102 + bev
5th line:	Regorafenib			Regorafenib	Regorafenib

Conclusions

- Treatment of metastatic CRC has evolved since dawn of century
  - Median OS increased from 6 months to ~36 months
- Biomarker based treatment have increasing utility
- All patients should be tested for:
  - MSI
  - Her-2
  - NGS
- Her-2 , BRAF and KRAS G12C targeted treatments will likely move into first line
- FOLFOXIRI + bevacizumab should be de facto standard for all “fit” patients if there is no specific biomarker
- FOLFOX + EGFR Ab is a reasonable alternative for left sided RAS wild type tumors
- Multidisciplinary approaches required for combining organ directed treatment with systemic therapy
  - Lung
  - Liver
  - Peritoneum