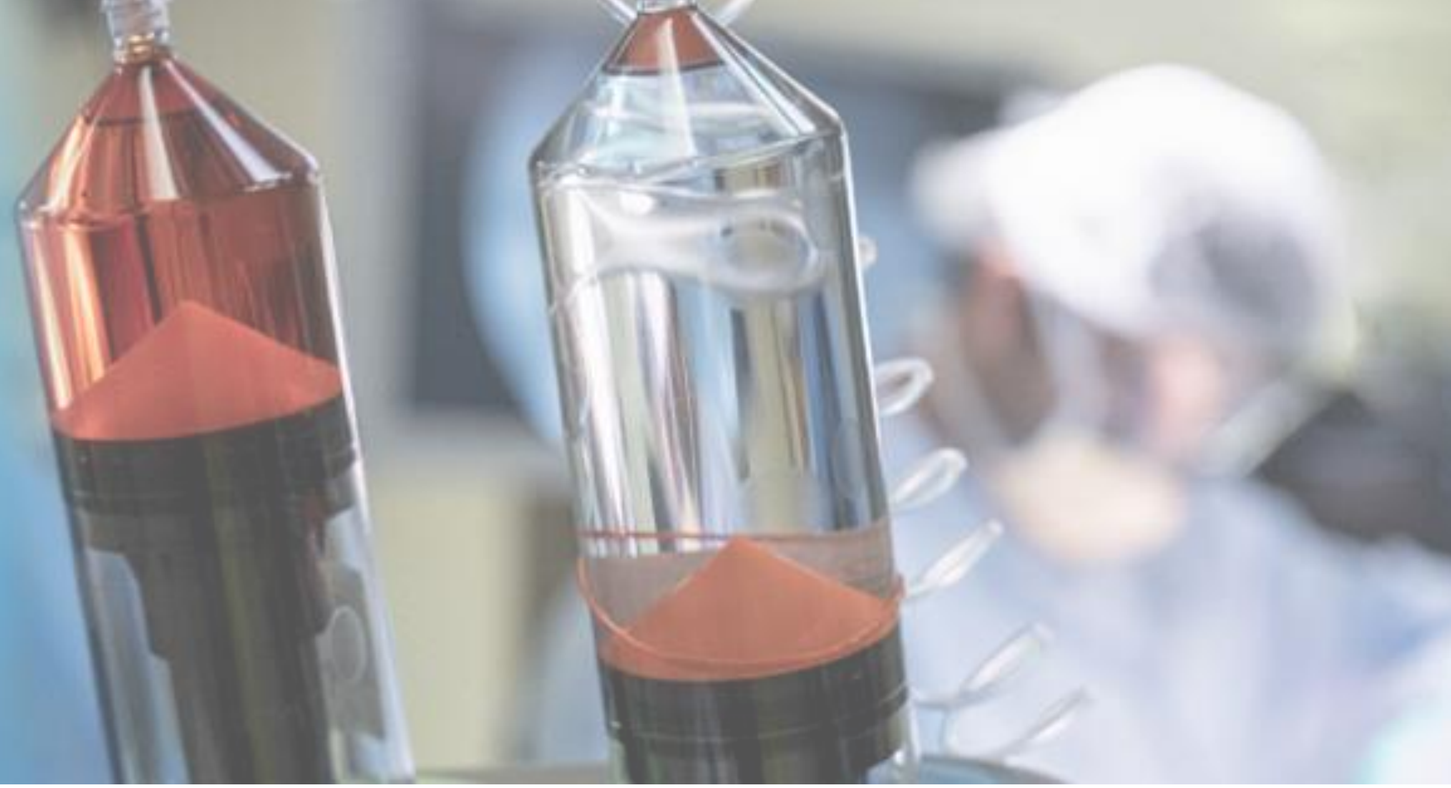
First U.S. PIPAC Training Workshop



Systemic Treatment for Peritoneal Carcinomatosis

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Disclosures

- On the Speakers Bureau for Bristol Myers Squibb, Eisai, Lilly, and MSD.
- Consultant for Amgen, and AstraZeneca.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their products and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Paclitaxel and Oxaliplatin will be addressed.

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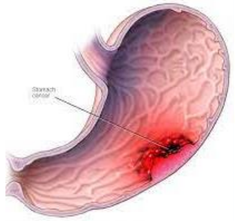
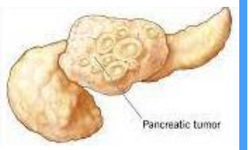
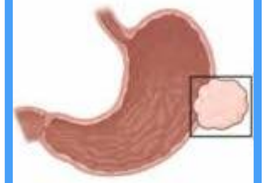
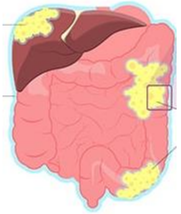
Peritoneal Carcinomatosis

- Peritoneal carcinomatosis (PC) is a heterogeneous disease.

	Ovarian	Colorectal	Gastric	Pancreatic	GIST	Mesothelioma	Appendiceal
							
Propensity for extra-peritoneal spread	/	/			/	/	/
5yrs OS for stage 4 cancer	30.8%	15.1%	5.9%	3.1%	53%	65%	15-85%

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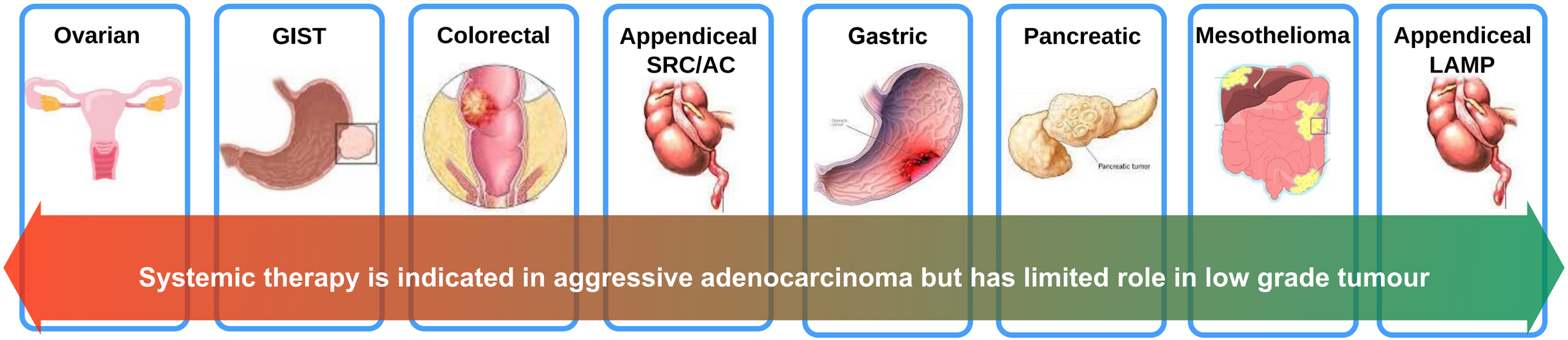
Role and selection of systemic chemotherapy

- Selection of systemic therapy is dependent on origin of the primary cancer and the histology/molecular subtype.
- Susceptibility to systemic therapy and propensity of extra-peritoneal spread influence the relative importance of systemic therapy in the management of PC.



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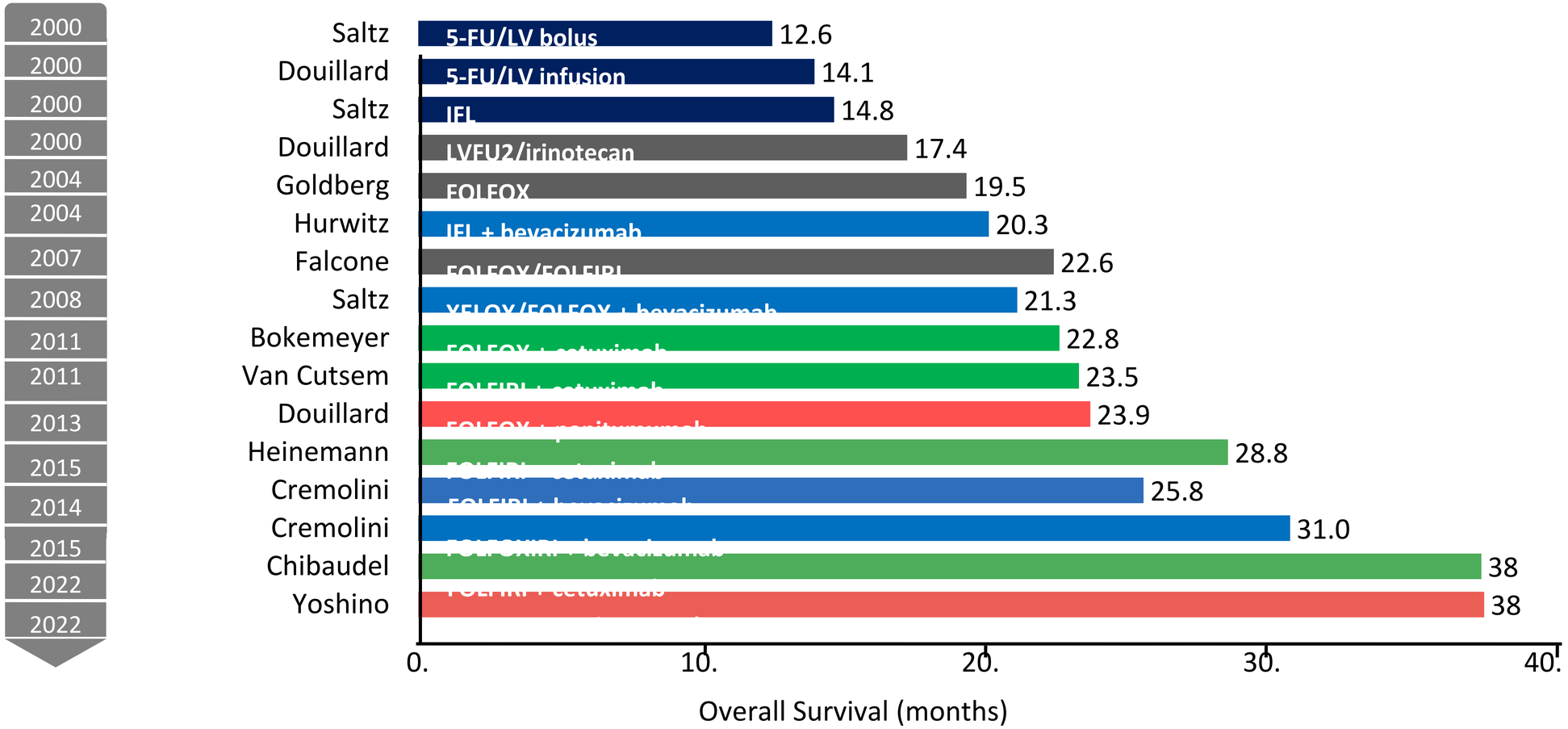
Median OS observed in 1L mCRC trials



Saltz. NEJM. 2000; Douilliard. Lancet. 2000; Goldberg. J Clin Oncol. 2004; Hurwitz. NEJM. 2004; Saltz. J Clin Oncol. 2008; Falcone. J Clin Oncol. 2007; Bokemeyer. Ann Oncol. 2011; Van Cutsem. J Clin Oncol. 2011; Douilliard. NEJM 2013; Heinemann. Lancet Onc 2014; Cremolini. Lancet Onc 2015; Chibaudel. ASCO 2022; Yoshino. ASCO 2022

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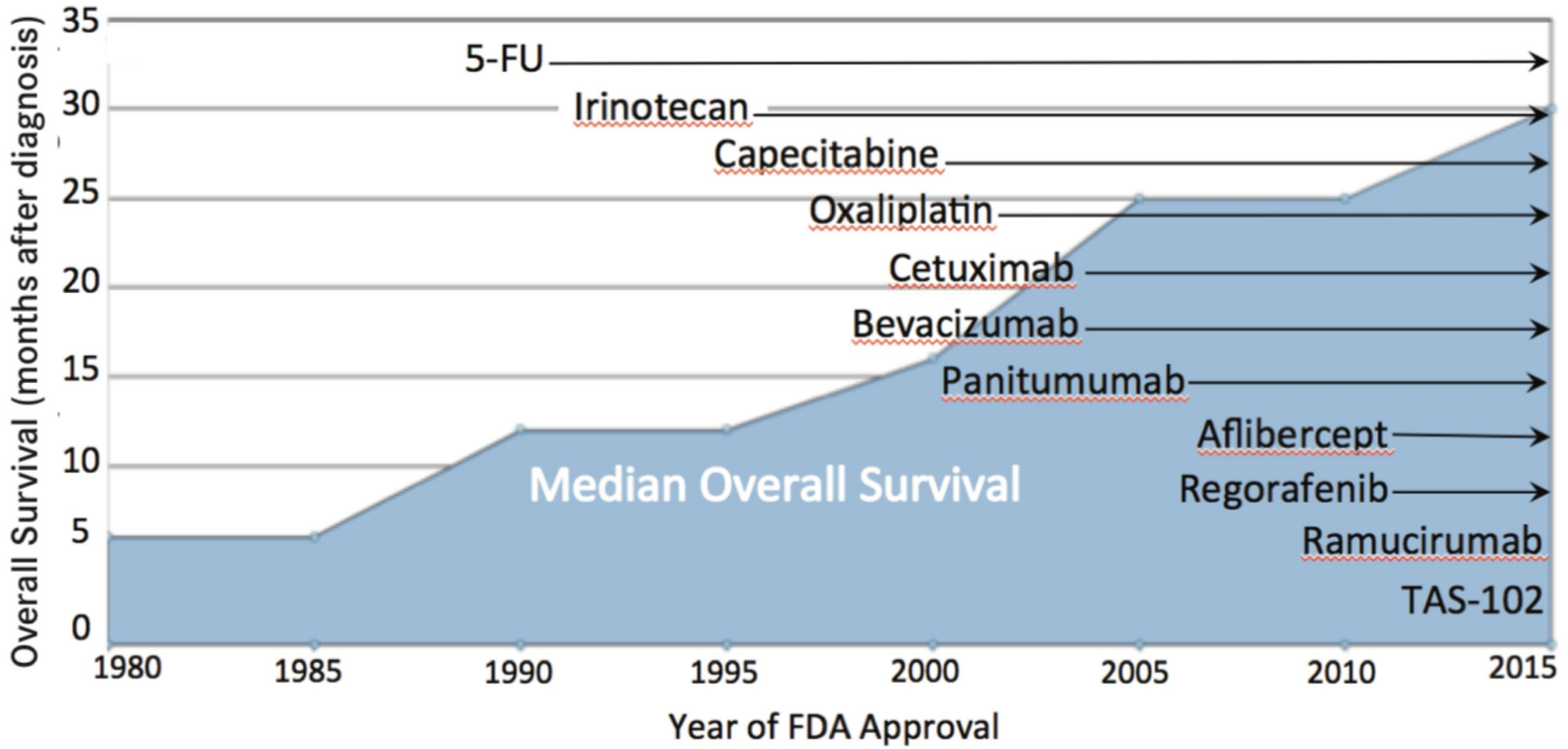
Improved survival associated with increased treatment options beyond 1L



5-FU indicates fluorouracil; CRC, colorectal cancer; TAS-102, trifluridine + tipiracil.

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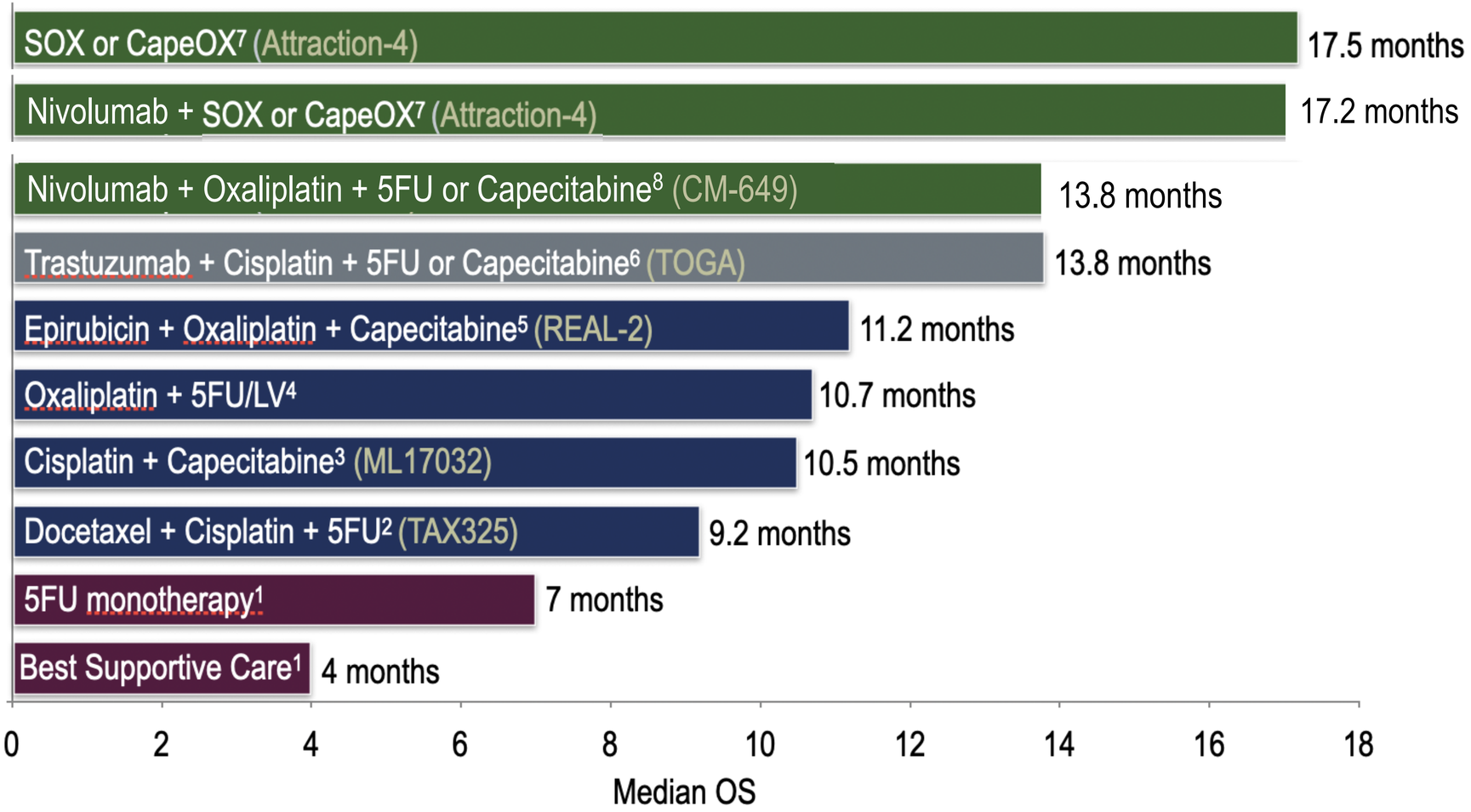
Mody et al. AJHO 2017

Median OS observed in 1L Gastric Cancer trials



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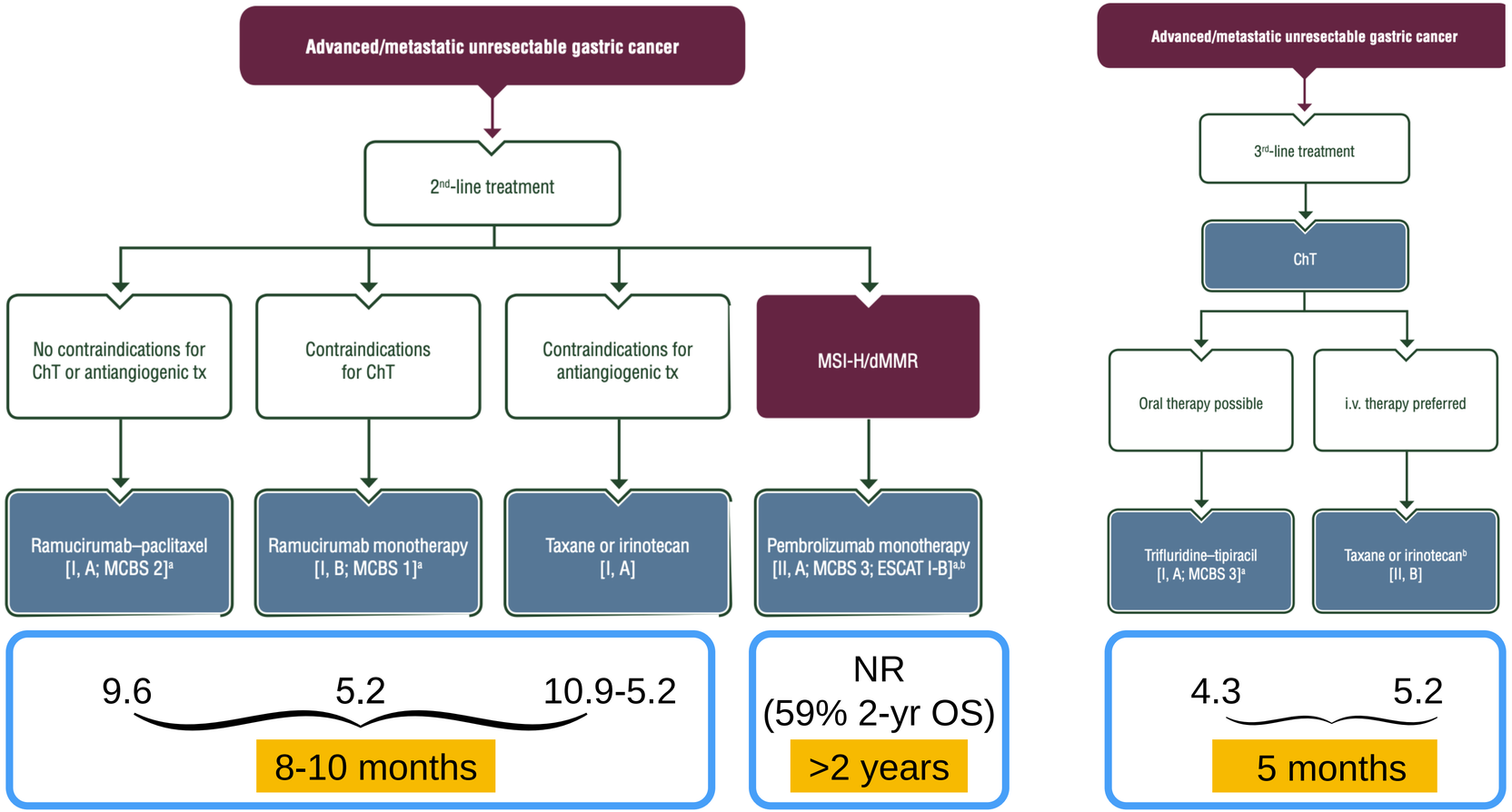
Wagner A, et al. JCO 2006. van Cutsem E, et al. J Clin Oncol 2006. Kang YK et al, Ann Oncol 2009. Al Batran SE, et al. J Clin Oncol 2008. Cunningham D, et al. N Engl J Med 2008. Bang YJ, et al. Lancet 2010. Kang YK N, et al. Lancet 2022; Janjigian YY et al. Lancet 2021

Improved survival associated with increased treatment options beyond 1L: ESMO clinical practice guideline



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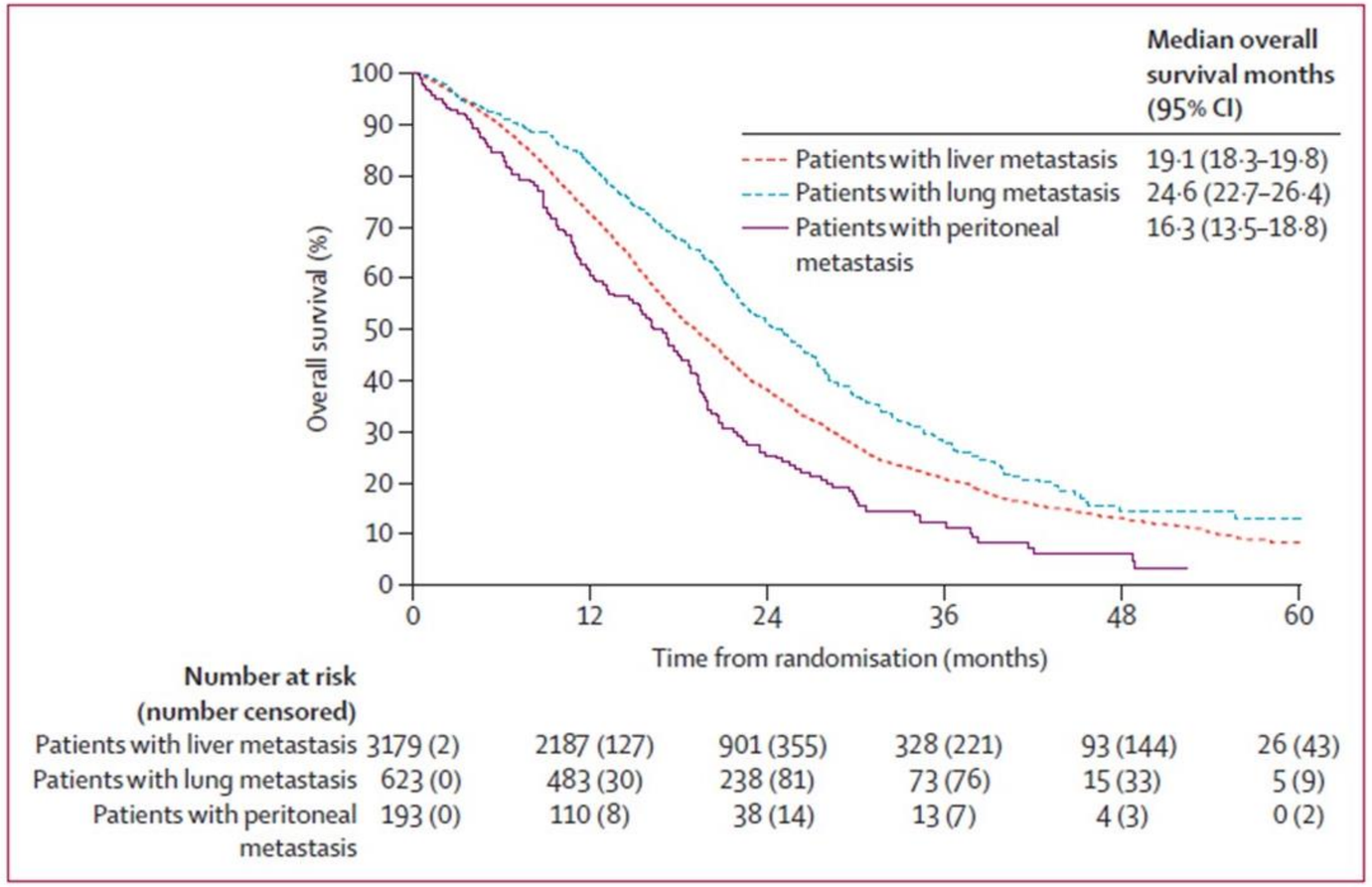
Lordick F et al. Ann Onc 2022; Chao J et al. JAMA Oncol 2021

Systemic therapy in peritoneal metastases



- Peritoneal metastases from CRC have worse prognosis in pool analysis of 14 phase 3 randomised trials done between 1997 and 2008
- But worse prognosis is not = no benefit

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Franko et al. Lancet Oncol 2016

Role of systemic therapy is becoming more important

Population-based survival of patients with peritoneal carcinomatosis from colorectal origin in the era of increasing use of palliative chemotherapy

- 395 exclusive CP (44%)
- 3 Periodes :
  - 1995-1999 : (5FU/FA)
  - 2000-2005 : (5FU/FA; oxaliplatin & CPT11)
  - 2005-2008 : (5FU/FA; oxaliplatin. CPT11; bevacizumab; cetuximab)

Median survival
Patients without other distant metastases

12 Months

14 Months

19 Months

- Median survival without chemotherapy is <6 months.

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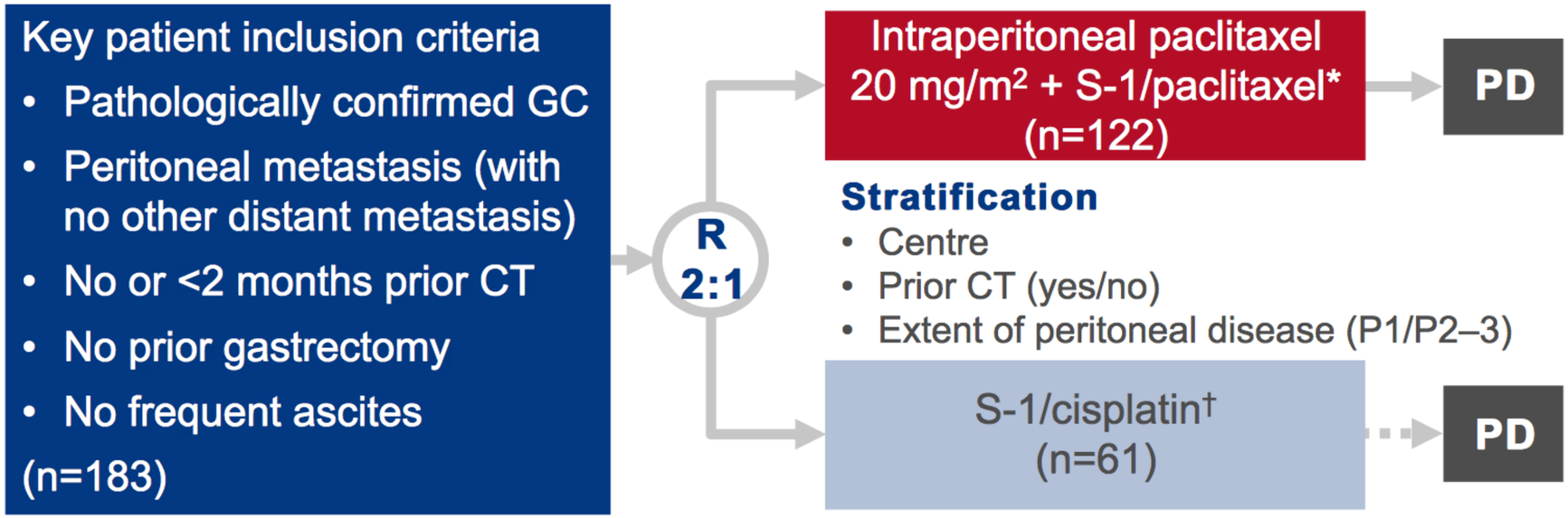
Klaver et al. Ann Oncol 2011

Intraperitoneal paclitaxel in AGC with peritoneal metastases: PHOENIX-GC

Study objective

- To investigate the efficacy and safety of intraperitoneal paclitaxel + S-1/paclitaxel vs S-1/cisplatin in patients with GC and peritoneal metastasis



PRIMARY ENDPOINT(S)

- OS

SECONDARY ENDPOINTS

- ORR
- Safety

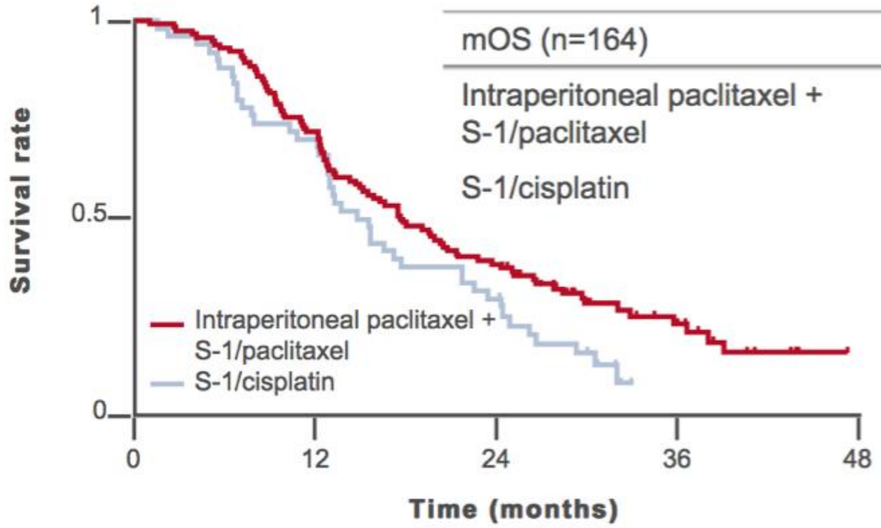
*Paclitaxel 50 mg/m² IV d1+8 + S-1 80 mg/m²/d d1–14, q3w;
†Cisplatin 60 mg/m² IV d8 + S-1 80 mg/m²/d d1–21, q5w.

Ishigami et al. J Clin Oncol 2016; 34 (suppl): abstr 4014

Intraperitoneal paclitaxel in AGC with peritoneal metastases: PHOENIX-GC

Key results

OS



mOS (n=164)	Time (months)	95% CI
Intraperitoneal paclitaxel + S-1/paclitaxel	17.7	14.7, 21.5
S-1/cisplatin	15.2	12.8, 21.8

*p=0.080

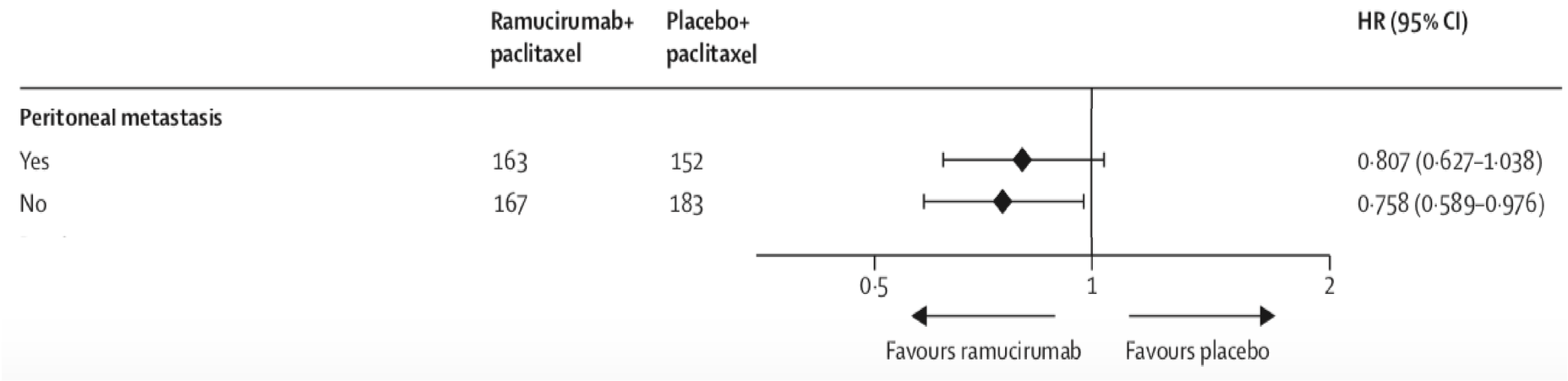
†HR: 0.72 (95% CI 0.49, 1.04); p=0.081

Best response (RECIST v1.1) (in patients with target lesions)	CR	PR	SD	PD	NE	Response rate	Fisher's test
Intraperitoneal paclitaxel + S-1/paclitaxel (n=17)	0	9	4	4	0	53%	p=0.001
S-1/cisplatin (n=5)	0	3	1	0	1	60%	

Ishigami et al. J Clin Oncol 2018

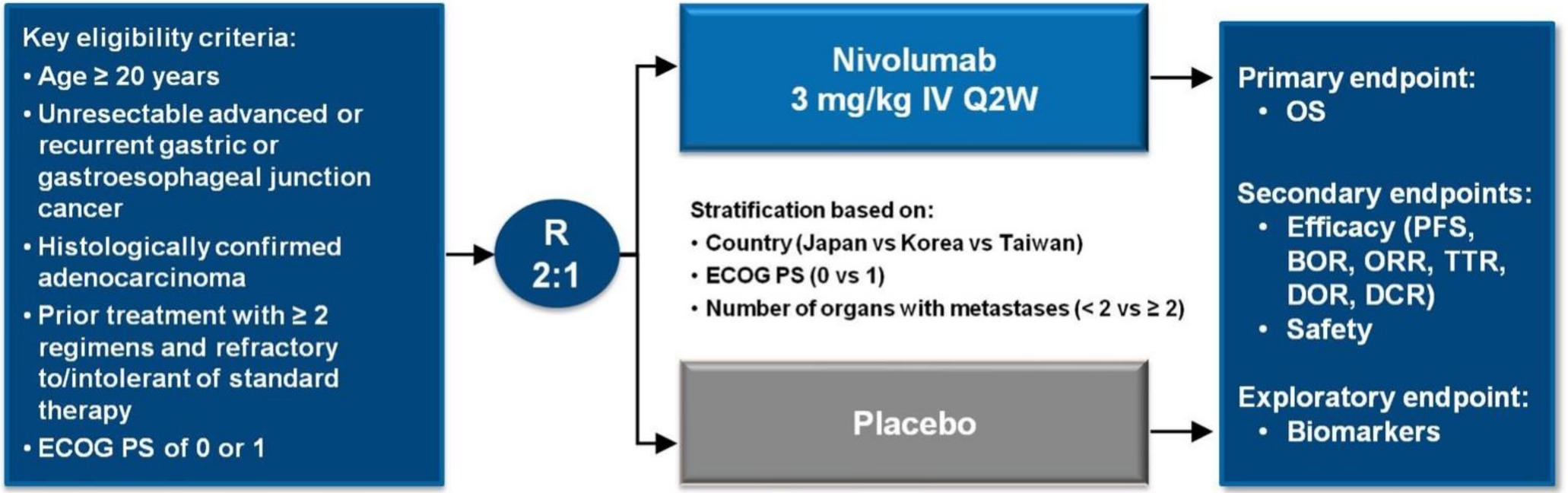
PM in AGC with second-line chemotherapy

Efficacy Parameter	Ram + Paclitaxel	Placebo + Paclitaxel	Odd Rate Hazard Ratio (95% CI)	P-value (Wald's)	Inter-action p-value
Peritoneal metastasis					
Yes	8.0 (6.9, 9.6)	5.7 (4.8, 7.3)	0.811 (0.635, 1.036)	0.0928	0.8891
No	11.3 (9.6, 12.4)	8.7 (7.1, 10.5)	0.816 (0.639, 1.042)	0.1029	



Wilke et al. Lancet 2014

Immunotherapy in AGC



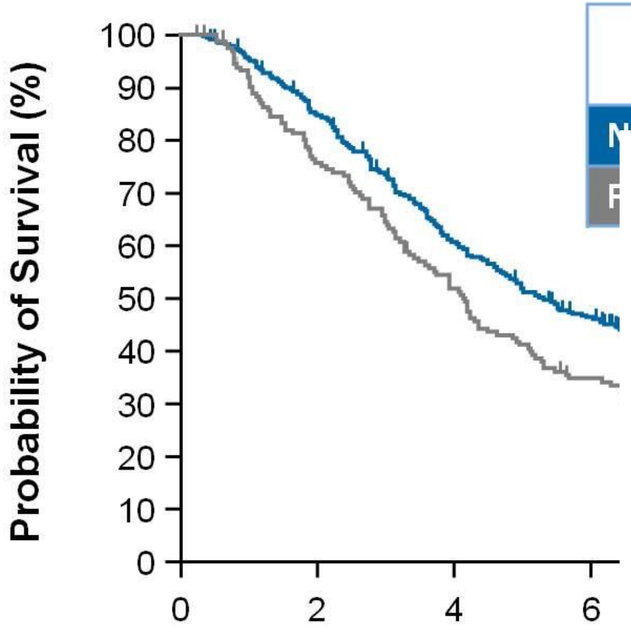
- Patients were permitted to continue treatment beyond initial RECIST v1.1–defined disease progression, as assessed by the investigator, if receiving clinical benefit and tolerating study drug

BOR, best overall response; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV; intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; R, randomization; RECIST, Response Evaluation Criteria In Solid Tumors; TTR, time to tumor response.

Kang YK et al. Lancet 2017

Immunotherapy in AGC

Overall Survival



	Patients, n	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], %
N[illegible]	[illegible]	[illegible]	[illegible]	[illegible][21.1–32.4]
P[illegible]	[illegible]	[illegible]	[illegible]	[illegible][6.2–17.0]
Peritoneal metastasis				
No	178/267	105/121		0·64 (0·50–0·82)
Yes	48/63	36/42		0·74 (0·48–1·15)
Liver metastasis				
No	168/252	115/135		0·64 (0·50–0·81)
Yes	58/78	26/28		0·67 (0·42–1·07)
Measurable lesion				
No	43/62	26/32		0·70 (0·43–1·14)
Yes	183/268	115/131		0·64 (0·51–0·81)
Number of previous regimens‡				
2	47/69	24/29		0·82 (0·50–1·35)
3	98/137	51/62		0·89 (0·63–1·25)
≥4	81/124	66/72		0·44 (0·31–0·61)
Previous treatment with ramucirumab				
No	204/295	123/141		0·66 (0·53–0·82)
Yes	22/35	18/22		0·58 (0·31–1·09)

[illegible].50–0.78)

0 1 2 3

Favours nivolumab Favours placebo

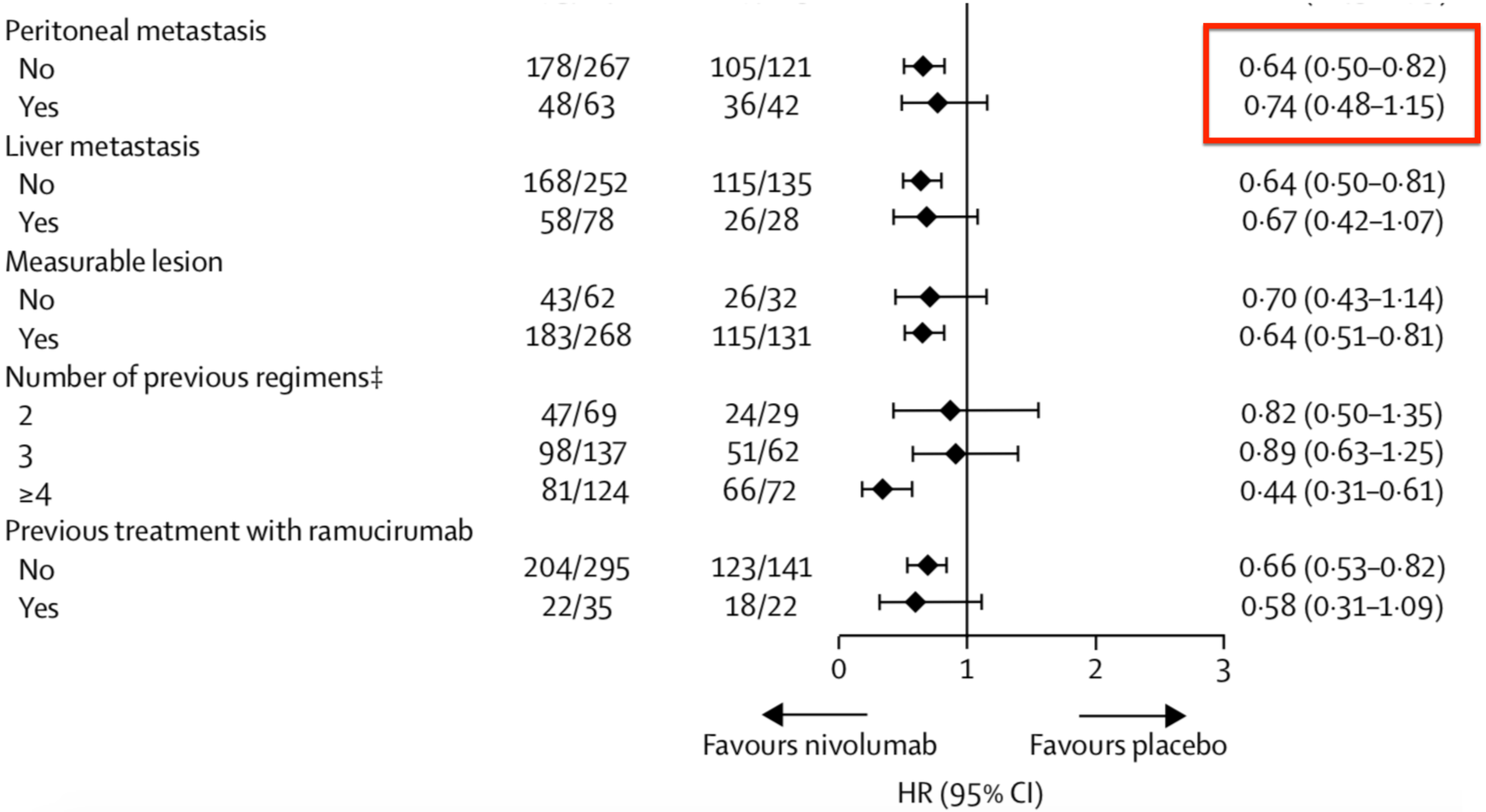
HR (95% CI)

22

At risk:												
Nivolumab	330	275	193	142	95	57	39	19	10	5	3	0
Placebo	163	121	82	53	32	16	10	4	3	3	1	0

Kang YK et al. Lancet 2017

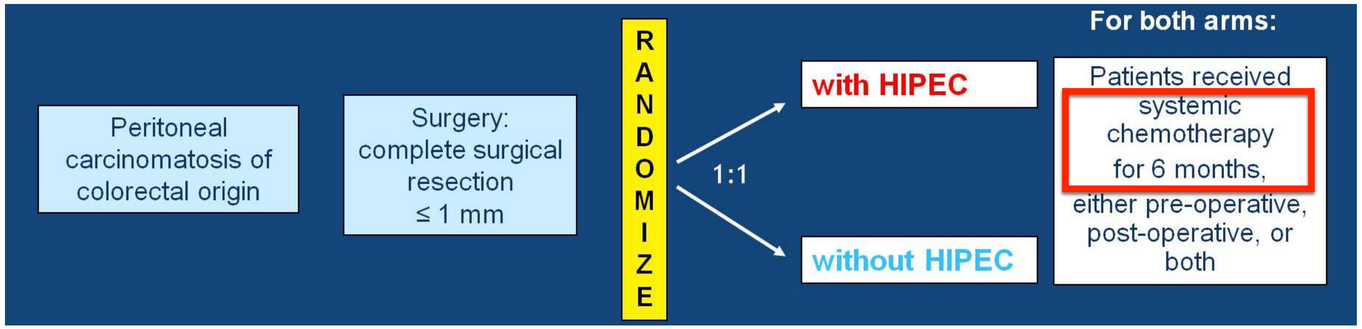
Immunotherapy in AGC



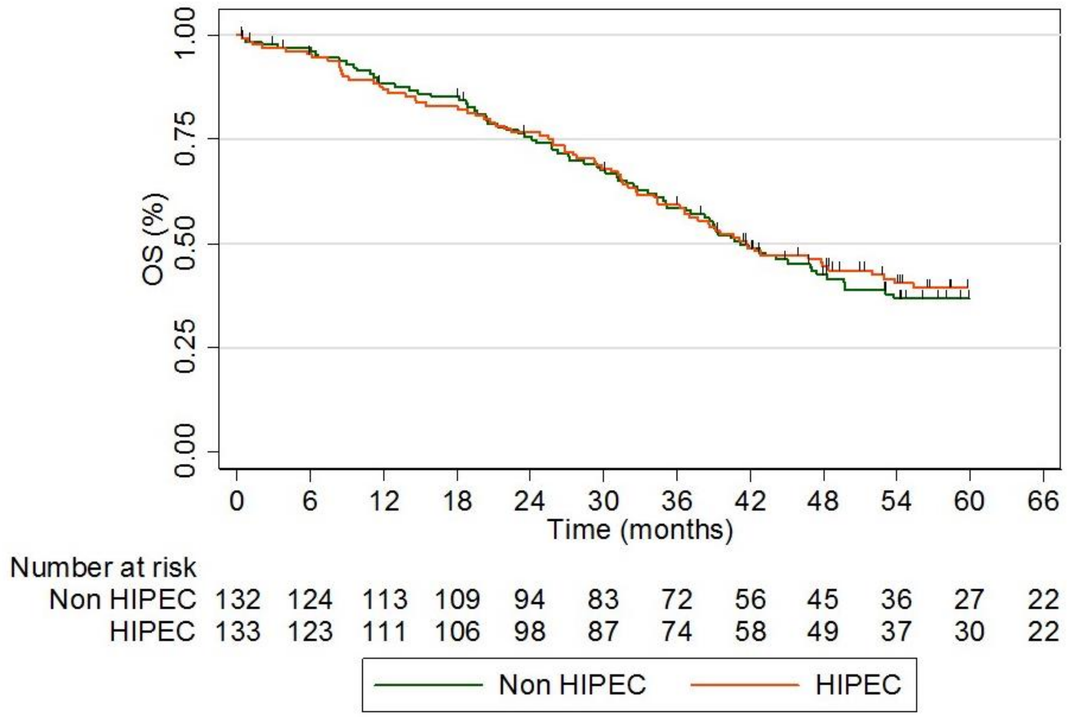
Kang YK et al. Lancet 2017

Changing natural history: cytoreductive surgery in systemic therapy responders

PRODIGE 7 trial



	HIPEC	Non-HIPEC	P-value
Median Survival (months) [95% CI]	41.7 [36.2-52.8]	41.2 [35.1-49.7]	0.995
1-year Survival	86.9%	88.3%	
5-year Survival	39.4%	36.7%	



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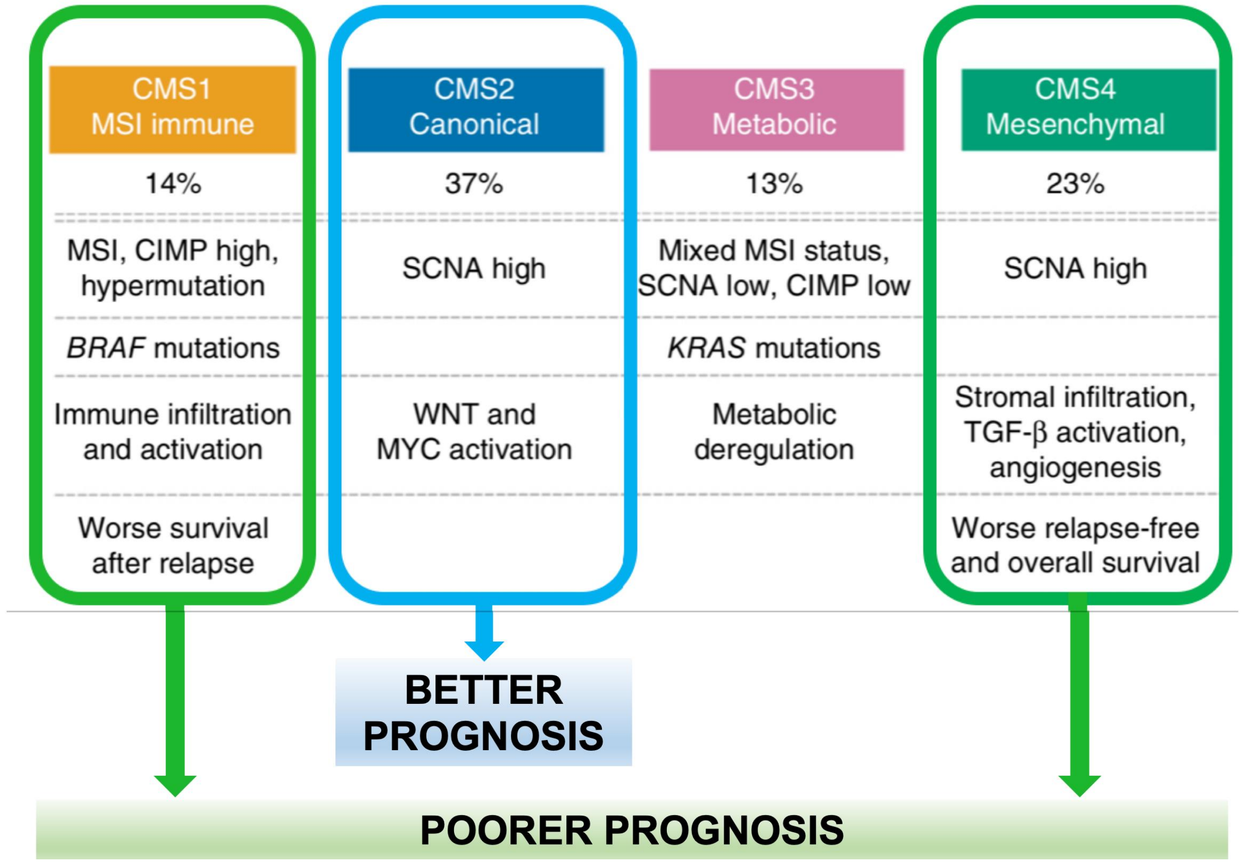
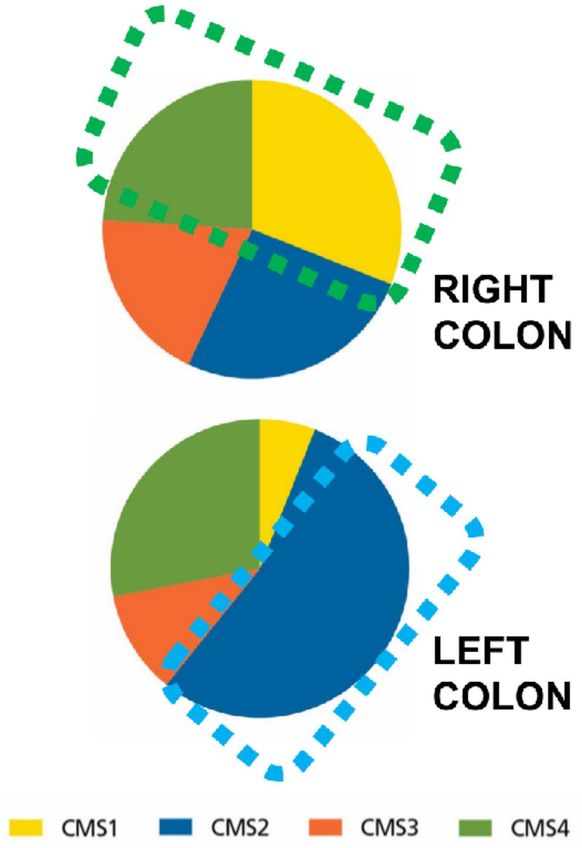
Quenet et al. Lancet Oncol 2021

Molecular subtypes in CRC: Heterogeneous disease





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Gunny et al. Nat Med 2015; Lee et al. JNCCN 2017

Actionable molecular subtypes in CRC

BRAF

HER2

RAS

NTRK1

MSI

Gene	Alteration	Prevalence	ESCAT	References
KRAS *NRAS*	Mutations (resistance biomarker)	44% 4%	Not applicable	Van Cutsem E, et al. *J Clin Oncol.* 2015[79] Douillard J-Y, et al. *N Engl J Med.* 2013[80] Sorich M, et al. *Ann Oncol.* 2015[81]
BRAF^{V600E}	Mutations	8.5%	IA	https://doi.org/10.1093/annonc/mdw235 Kopetz S, et al. *N Engl J Med.* 2019[82]
	MSI-H	4%—5%	IA	Overman M, et al. *Lancet Oncol.* 2017[83] Le DT, et al. *J Clin Oncol.* 2020[84]
NTRK1	Fusions	0.5%	IC	Demetri G, et al. *Ann Oncol.* 2018[85] Doebele RC, et al. *Lancet Oncol.* 2020[50]
ERBB2	Amplifications	2%	IIB	Meric-Bernstam F, et al. *Lancet Oncol.* 2019[86] Sartore-Bianchi A, et al. *Lancet Oncol.* 2016[87]

Mosele et al. Ann Oncol 2020

Immune checkpoint inhibitors in CRC

THE STRAITS TIMES WORLD LOG IN ST SUBSCRIBE

A cancer trial's unexpected result: Remission in every patient

PUBLISHED 6 JUN 2022, 6:19 AM SGT

NEW YORK (NYTIMES) - It was a small trial, just 18 rectal cancer patients, every one of whom took the same drug.

But the results were astonishing. The cancer vanished in every single patient, undetectable by physical exam, endoscopy, positron emission tomography scans, or MRI scans.

Dr Luis Diaz Jr of Memorial Sloan Kettering Cancer Centre, an author of a paper published on Sunday (June 5) in the New England Journal Of Medicine describing the results, which were sponsored by drug company GlaxoSmithKline, said he knew of no other study in which a treatment completely obliterated a cancer in every patient.

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Immune checkpoint inhibitor in 1L dMMR/MSI-H mCRC

KEYNOTE 177: Registration trial in 1L dMMR/MSI-H mCRC

Phase 3 Trial of Pembrolizumab vs Chemotherapy in Patients With MSI-H/dMMR Metastatic CRC

Patients (N≈307):

- Locally confirmed MSI-H/dMMR metastatic CRC
- No prior systemic therapy for metastatic disease
- ECOG PS 0 or 1
- Life expectancy ≥3 mo
- No active autoimmune disease or brain metastases

R 1:1

- Pembrolizumab 200 mg IV Q3W (n = 153)
- Investigator's choice of SOC chemotherapy mFOLFOX6 or FOLFIRI alone or in combination with Bevacizumab or Cetuximab (n = 154)

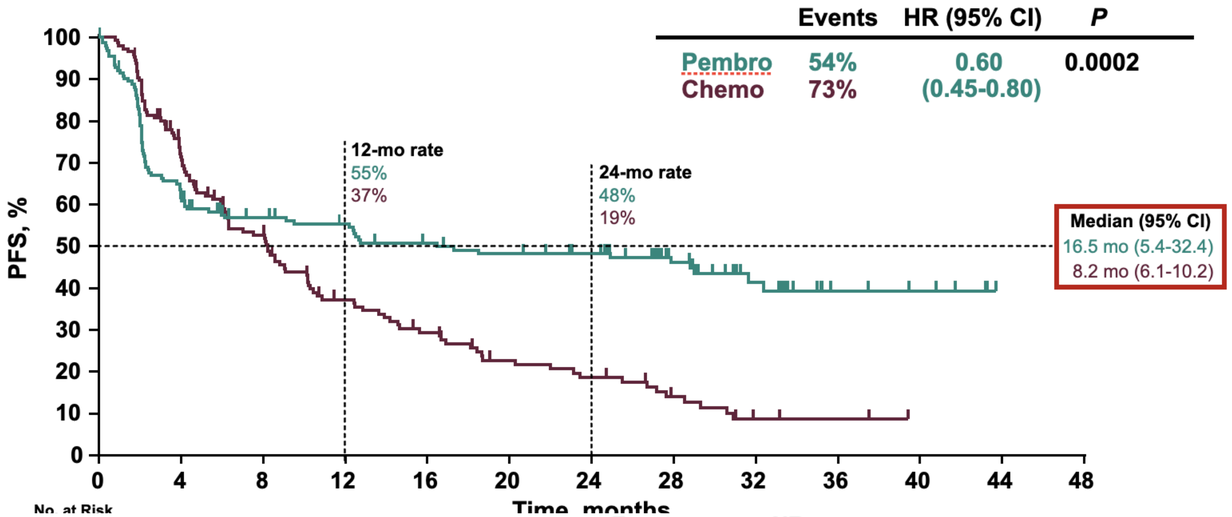
Optional: Pembrolizumab 200 mg IV Q3W

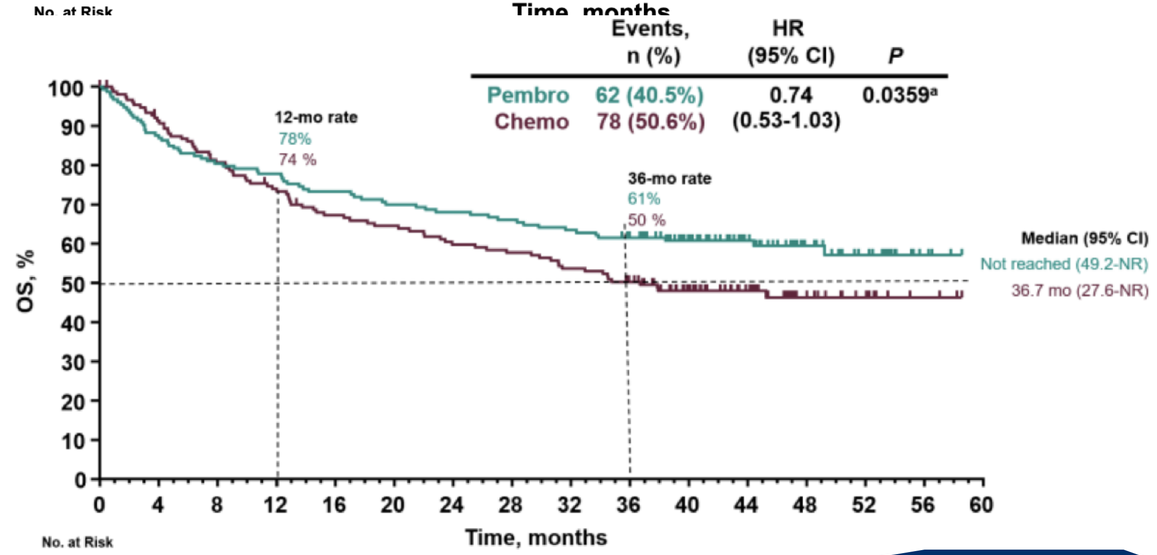
Continue until:

- 35 cycles (~2 y)
- Disease progression
- Intolerable toxicity
- Withdrawal of consent

Primary Endpoints	Select Secondary Endpoints
PFS, OS	ORR

Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR





- Pembrolizumab provided a clinically meaningful and statistically significant improvement in PFS versus chemotherapy in patients with MSI-H mCRC
- OS endpoint not met statistically but clear clinical benefit
- Responses were more durable with pembrolizumab versus chemotherapy
  - Overall response rate: 43.8% vs 33.1% (P = 0.0275)
  - Median duration of response: not reached vs 10.6 months
- Improved safety profile with pembrolizumab versus chemotherapy

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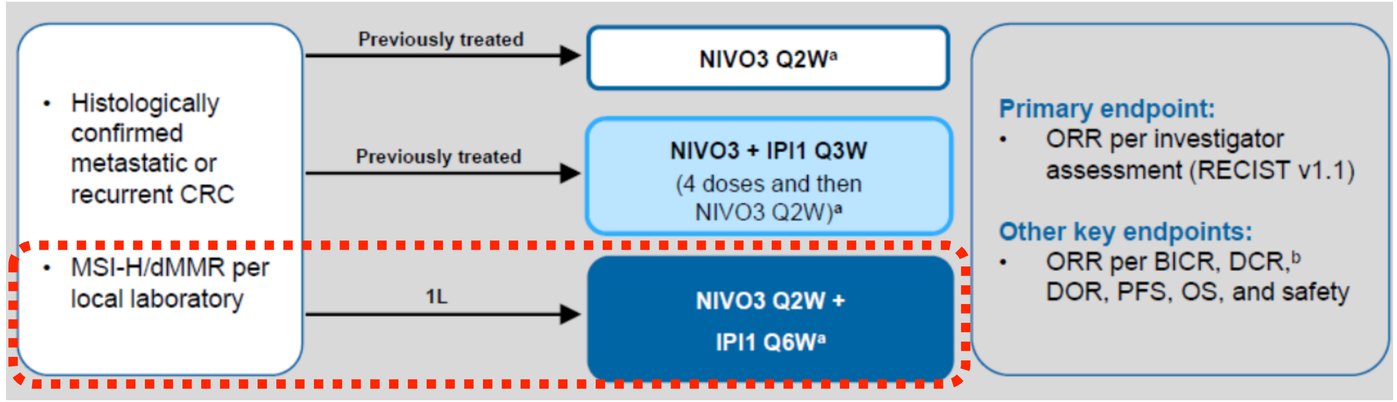
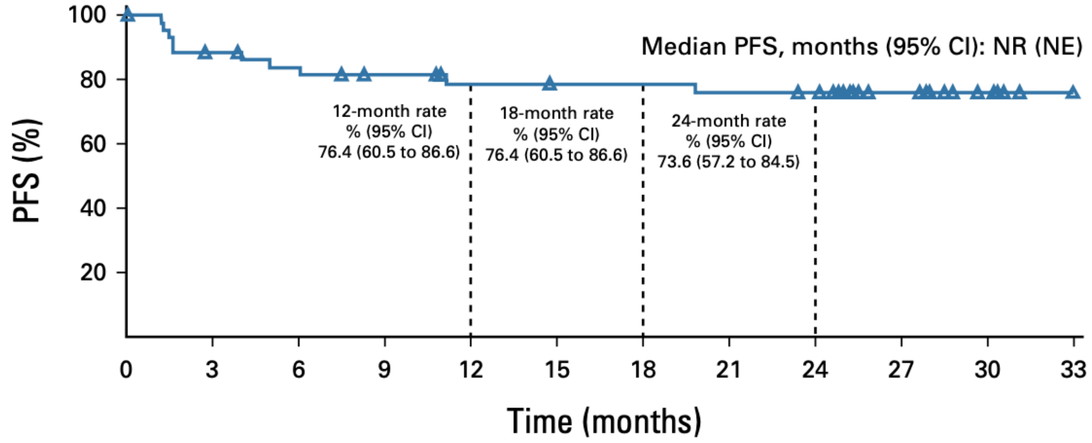
Andre et al. NEJM 2020; Diaz et al, Lancet Oncol 2022

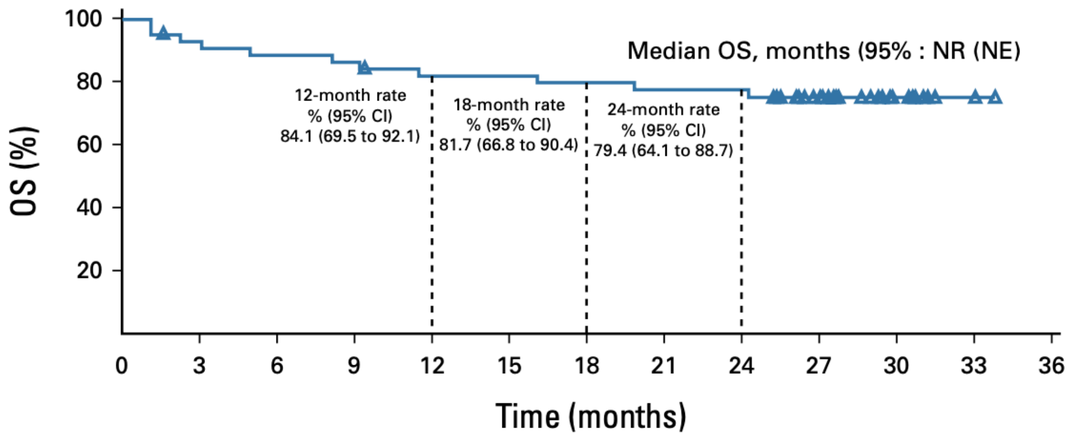
Immune checkpoint inhibitor in 1L dMMR/MSI-H mCRC

CHECKMATE 142: Role of dual PD-1/CTLA-4 inhibition in 1L dMMR/MSI-H mCRC



	Investigator Assessed	BICR Assessed
Best overall response,[c] No. (%)		
CR	6 (13)	11 (24)
PR	25 (56)	17 (38)
SD	7 (16)	8 (18)
PD	6 (13)	7 (16)
Not determined	1 (2)	2 (4)
DCR,[d] No. (%)	38 (84)	35 (78)





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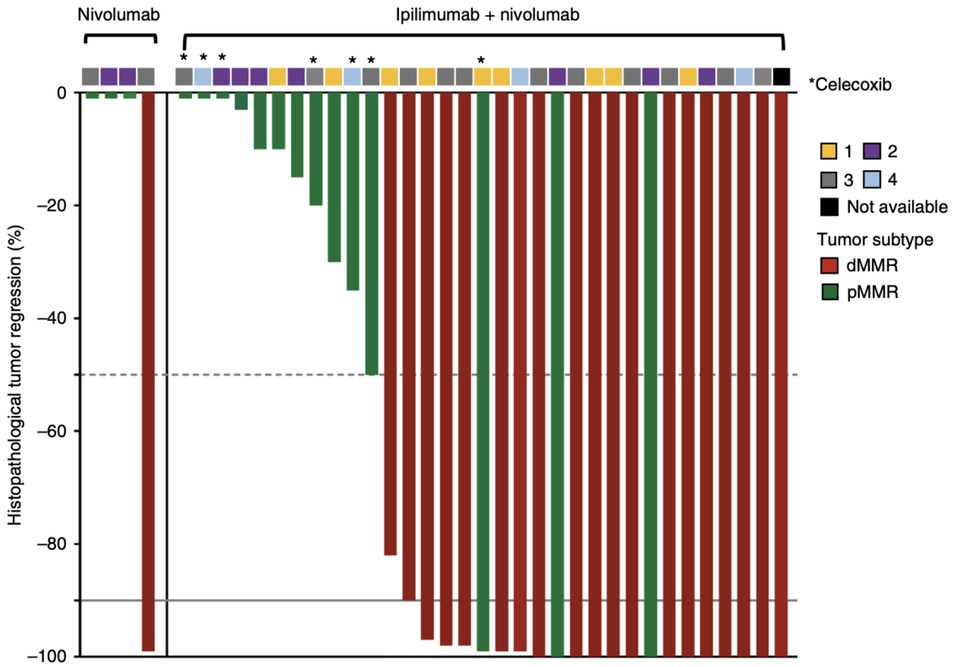
- confirmatory randomized phase III study (CheckMate 8HW, ClinicalTrials.gov identifier: NCT04008030) is underway

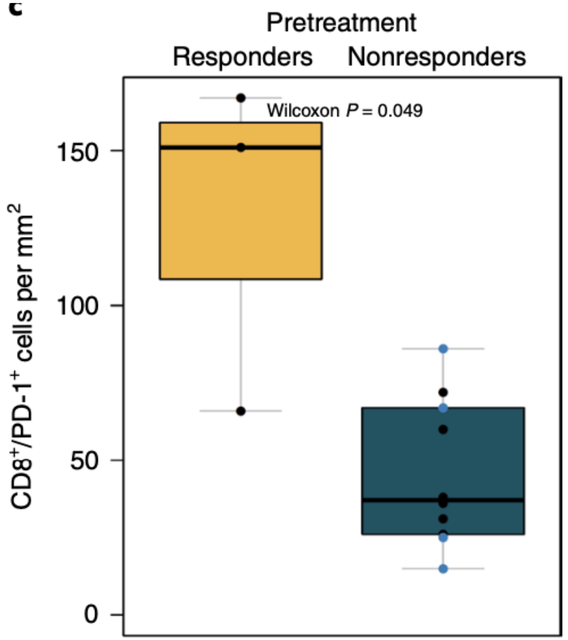
Andre et al. NEJM 2020; Diaz et al, Lancet Oncol 2022

Immune checkpoint inhibitors in neoadjuvant setting

NICHE study: 20 dMMR and 15 pMMR early-stage colon cancer were given 2 doses of nivolumab every 2 weeks and 1 dose of ipilimumab, followed by surgical resection



- All 20 patients with dMMR disease achieved pathologic response, and of those, 12 achieved pathologic complete response
- 4 of 15 patients with pMMR achieved pathologic response, and none achieved pathologic complete response



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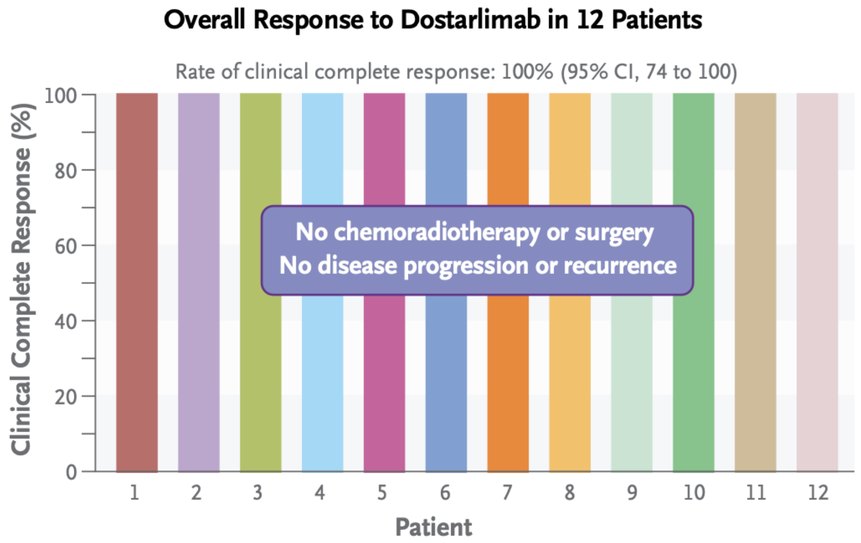
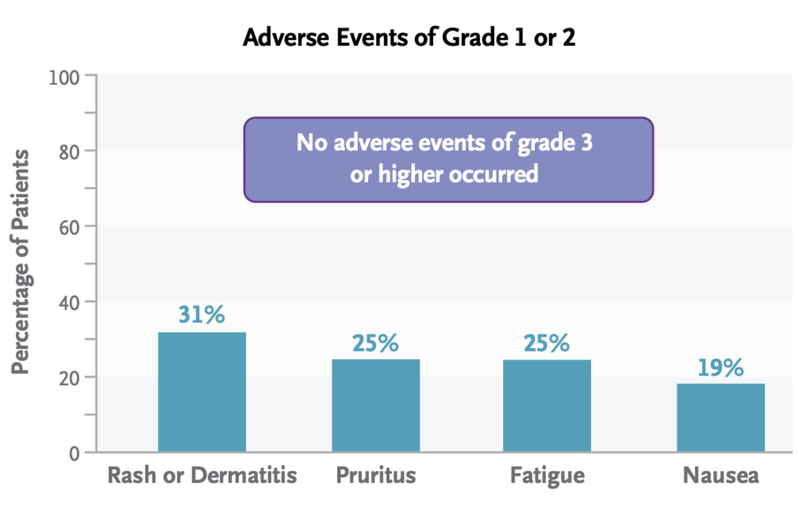
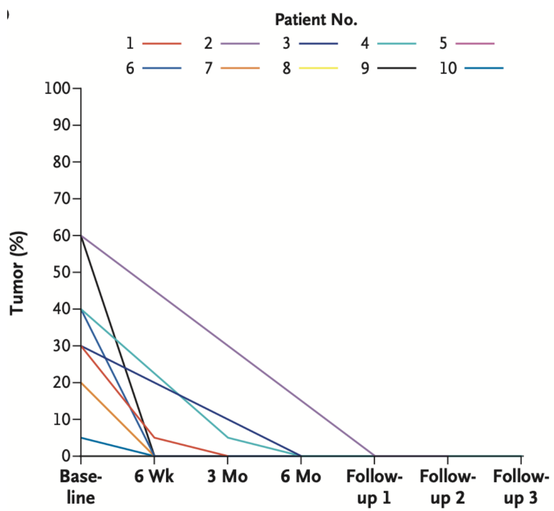
Chalabi et al. Nat Med 2020

Immune checkpoint inhibitors in neoadjuvant setting

Phase 2 dostarlimab: 12 dMMR early-stage rectal cancer were given 6 months of dostarlimab every 3 weekly







- Neoadjuvant checkpoint inhibitors are associated with high cCR.
- Path toward organ preservation in a subset of patients that historically have had poorer responses to systemic chemotherapy.

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Cercek et al. NEJM 2022

Immune checkpoint inhibitors in pMMR/MSS CRC

Author		Drug	N	ORR
Le et al	MSS CRC	Pembrolizumab	18	0%
Overman et al	MSS CRC	Nivolumab + ipilimumab	20	5%
Chung et al	Refractory CRC	Tremelimumab	49	2%
Topialan et al	Refractory CRC	Nivolumab	19	0%

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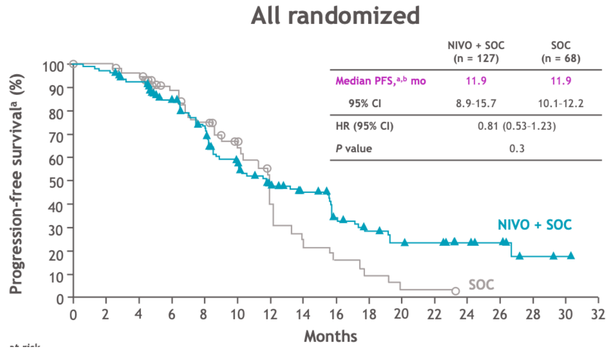
Lee et al, N. Engl. J. Med. 2015; Overman et al, J. Clin. Oncol. 2016; Chung et al, J Clin Oncol. 2010; Topialian et al, N. Engl. J. Med. 2012

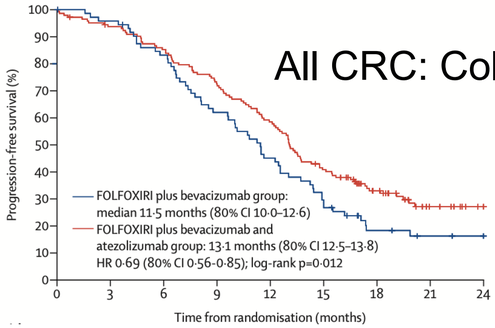
‘Hot’ CRC benefited from immune checkpoint inhibitors + chemo?

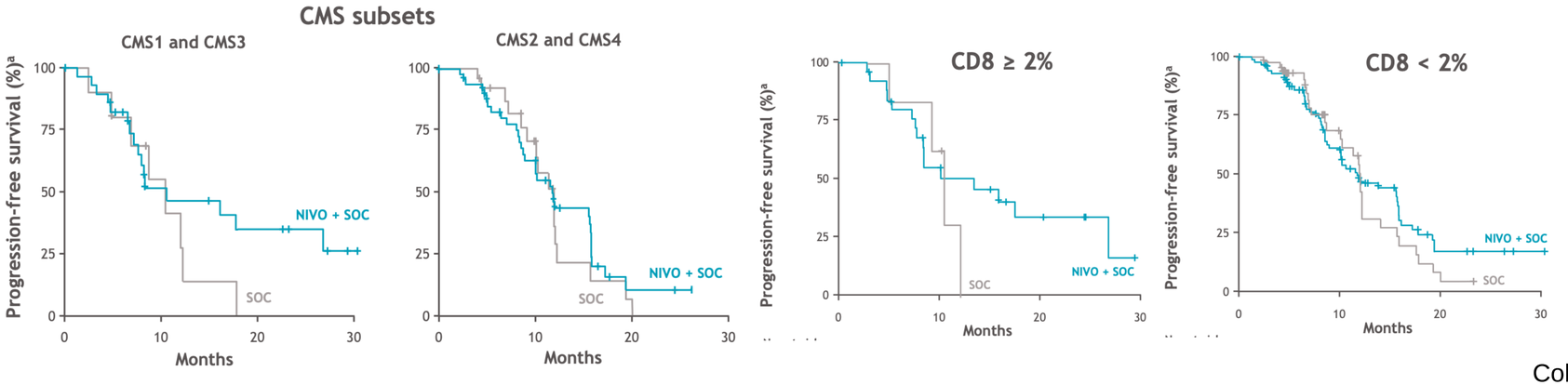
CHECKMATE 9X8

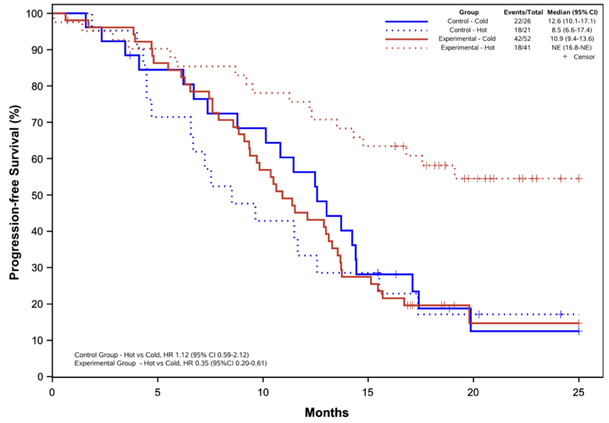


ATEZO-TRIBE

All CRC: Cold + Hot







Cold tumours: pMMR and TMB-low and Immunoscore IC-low tumours;
Hot tumours: dMMR and/or TMB-high and/or Immunoscore IC-high tumours.

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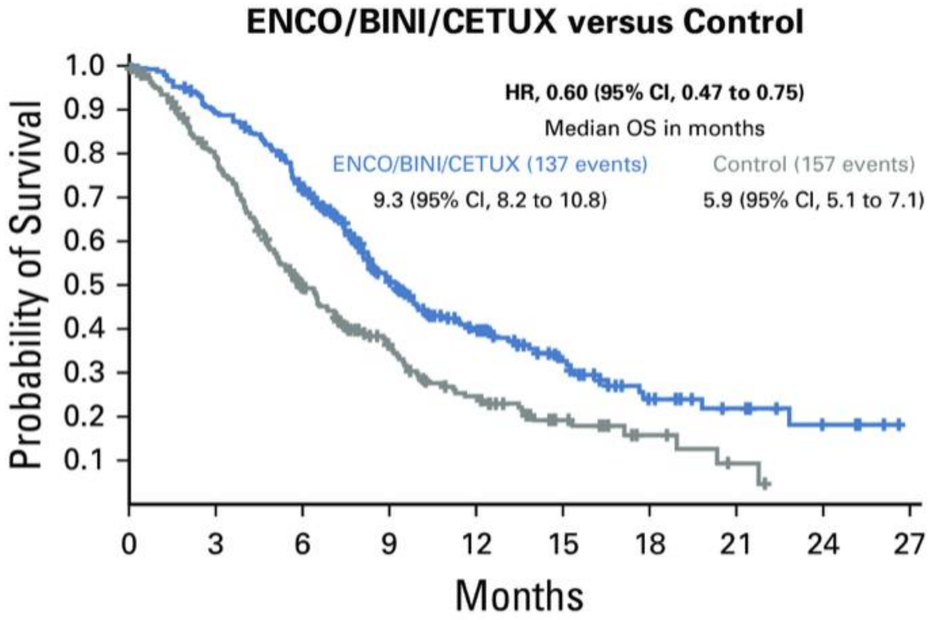
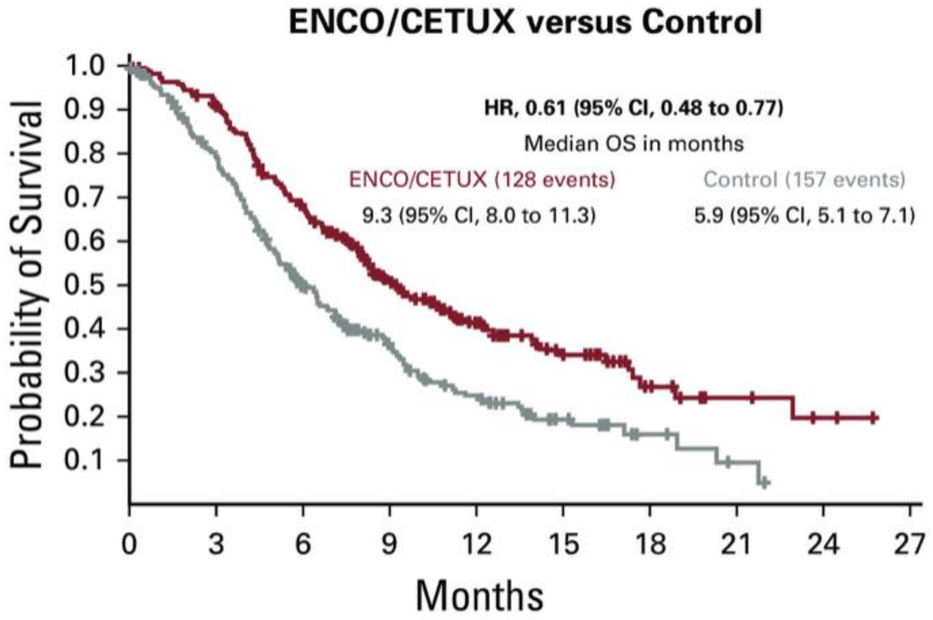
Leinz et al, ASCO-GI. 2022; Antoniotti et al, Lancet Onc. 2022

BRAF mut CRC

BEACON: 2L+ BRAF V600E mut CRC with RAF + EGFR inhibition





- BRAF V600E is associated with worse prognosis and a poorer response to anti-EGFR treatment
- Binimetinib addition did not increase overall efficacy but add MEK inhibitor-related toxicities

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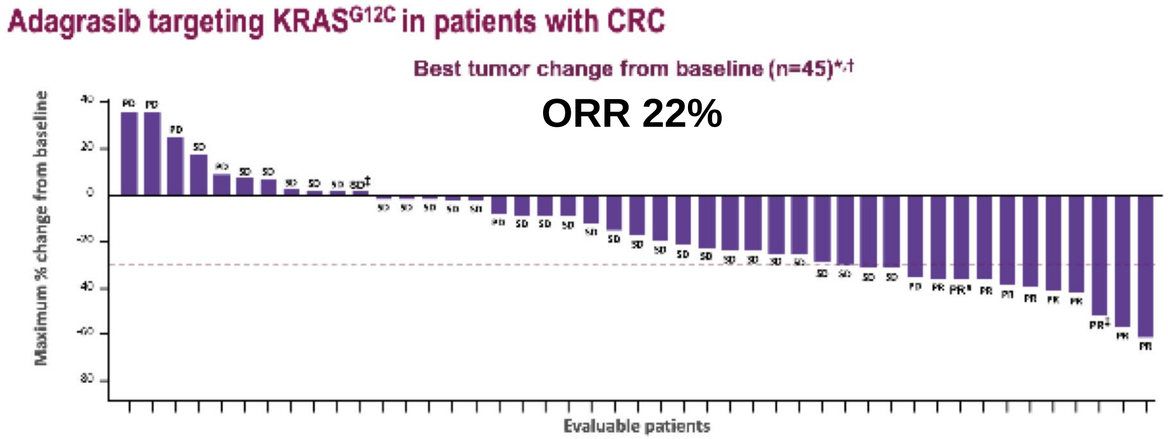
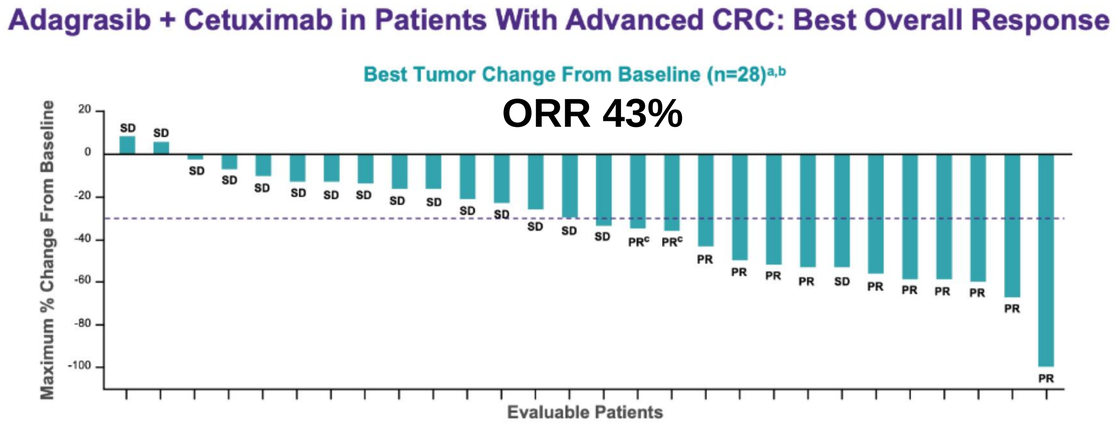
Tabernero et al. J Clin Oncol 2021

RAS mut CRC

KRYSTAL-1 study: KRAS G12C inhibition: Adagrasib +/- cetuximab





- KRAS and NRAS are associated a poorer response to anti-EGFR treatment
- KRAS G12C ~4% of all CRC RAS mut
- Adagrasib covalently bind to the cysteine residue of mutant KRAS G12C and inactivate it

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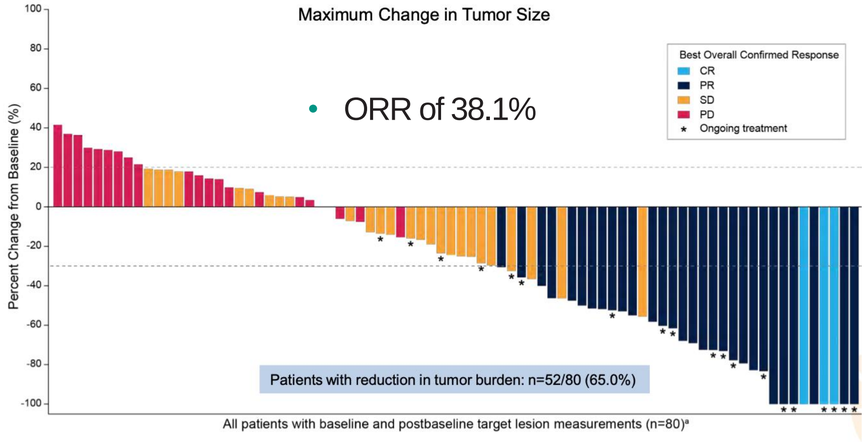
Weiss et al. ESMO 2021

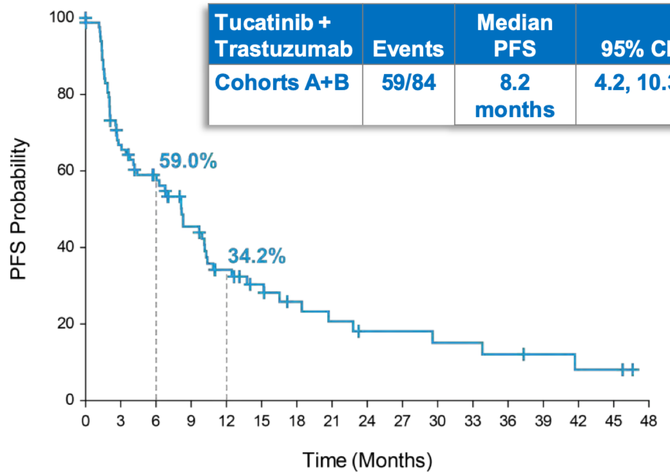
HER2+/ERBB2 amplified CRC

MOUNTAINEER study: 2L+ HER2+ CRC: Tucatinib +/- Trastuzumab

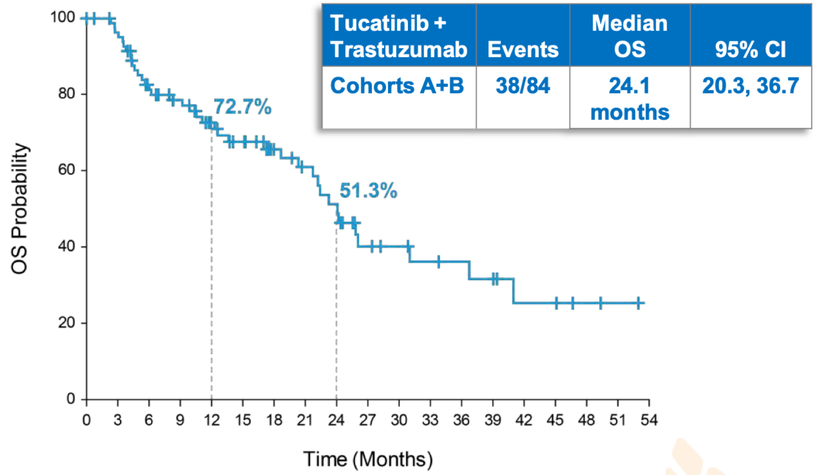
Tucatinib + Trastuzumab: Change in Tumor Size



Progression-free Survival per BICR



Overall Survival



- In chemotherapy-refractory patients with HER2+ mCRC, tucatinib in combination with trastuzumab demonstrated durable and clinically meaningful antitumor activity
  – Confirmed ORR of 38.1%, DOR of 12.4months, median PFS of 8.2 months, and median OS of 24.1 months
- Ongoing phase 3 MOUNTAINEER-03 trial (NCT05253651) will compare tucatinib + trastuzumab + mFOLFOX6 with standard of care

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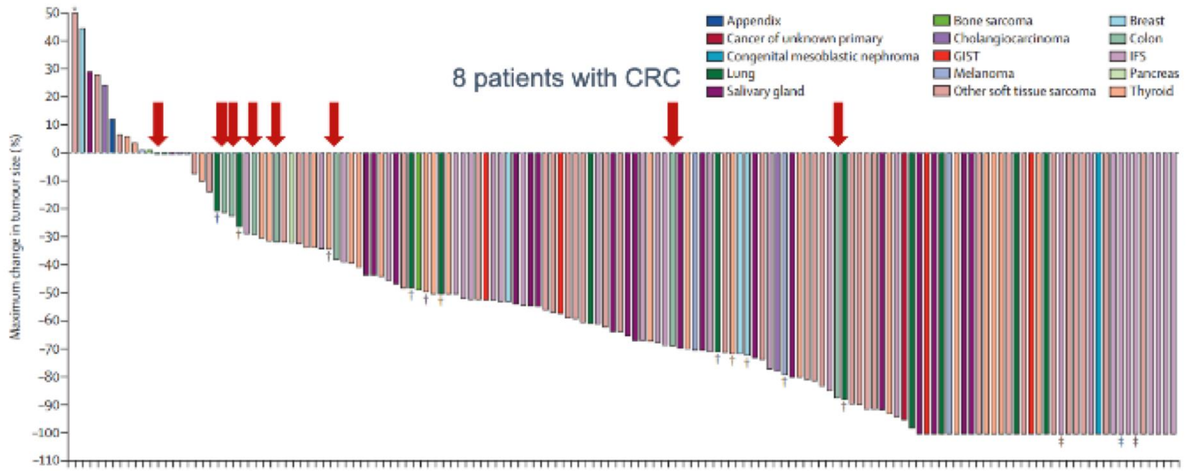
Strickler et al. ESMO WCGIC 2022

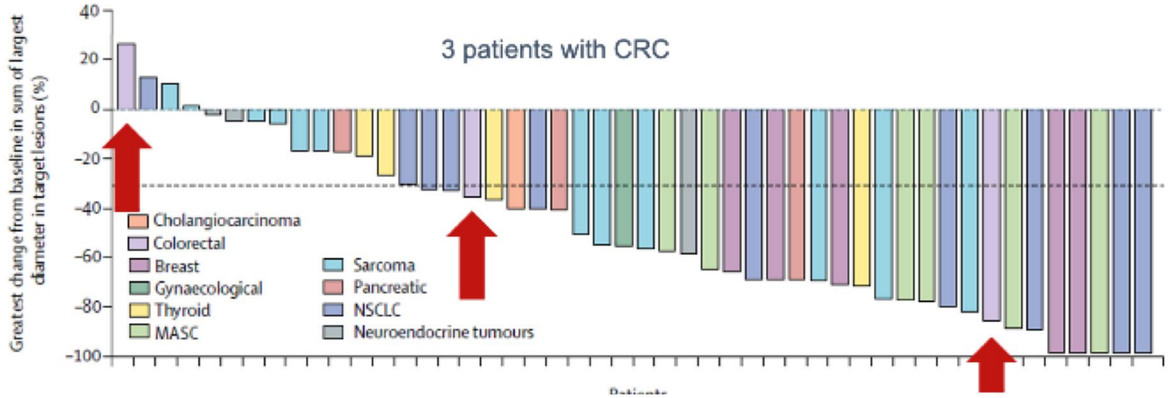
NTRK1 fusion-translocation CRC

Larotrectinib



ORR (all tumor types): 79%
CRC RR: 50%

Entrectinib



ORR (all tumor types): 57%
CRC RR: 67%

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Hong et al. Lancet Oncol 2020; Doebele et al. Lancet Oncol 2020

Conclusions

- Systemic therapy is the cornerstone for treatment for advanced CRC.
- Systemic therapy > Cytoreductive surgery is associated with impressive survival in patients with peritoneal metastases - PRODIGY 7.
- Efficacy of immunotherapy is restricted dMMR/MSI CRC.
- Majority of pMMR/MSS CRC are immune ‘cold’ tumours. A small subset may be immune ‘hot’ tumour.
- BRAF, NTRK1, KRAS G12C, HER2 are promising targets for CRC.

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