The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

A CME/MOC- and NCPD-Accredited Event

Saturday, October 22, 2022
7:30 AM – 5:30 PM ET

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Agenda

Module 1 — Lung Cancer: *Drs Langer and Lovly*

Module 2 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs LaCasce and Smith*

Module 3 — Prostate and Bladder Cancers: *Drs Morgans and Yu*

Module 4 — Renal Cell Carcinoma: *Prof Powles*

Module 5 — Multiple Myeloma: *Dr Usmani*

Module 6 — Hepatobiliary Cancers: *Dr Abou-Alfa*

Agenda

Module 7 — Breast Cancer: *Drs Goetz and Krop*

Module 8 — Endometrial Cancer: *Dr Westin*

Module 9 — Ovarian Cancer and PARP Inhibitors: *Dr O'Malley*

Module 10 — Gastrointestinal Cancers: *Drs Messersmith and Strickler*

Module 11 — Melanoma: *Prof Long*

Gastrointestinal Cancers Faculty

Wells A Messersmith, MD
Chief Medical Officer, Cancer Center
Associate Director of Clinical Services
University of Colorado Cancer Center
Aurora, Colorado

John Strickler, MD
Associate Professor
Duke University
Durham, North Carolina

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Gastrointestinal Cancers Agenda

MODULE 1: Immunotherapy for Gastroesophageal Cancers; PARP Inhibitors in Pancreatic Cancer

MODULE 2: HER2-Positive Gastroesophageal and Colorectal Cancer; Role of Circulating Tumor DNA/Minimal Residual Disease in Colorectal Cancer

MODULE 3: Colorectal Cancer in Younger Patients; Tumor Microbiome

MODULE 4: Neoadjuvant Therapy for Microsatellite Instability-High Gastroesophageal and Colorectal Cancer

MODULE 5: Novel Agents in Pancreatic Cancer

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Upper GI and PARPi in Pancreatic Cancer

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Recent Studies in Gastroesophageal and Gastric Cancer

Wells Messersmith, MD
Professor and Head, Medical Oncology
Chief Medical Officer, Oncology Services

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 1, 2021 VOL. 384 NO. 13

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

R.J. Kelly, J.A. Ajani, J. Kuzdzal, T. Zander, E. Van Cutsem, G. Piessen, G. Mendez, J. Feliciano, S. Motoyama, A. Lièvre, H. Uronis, E. Elimova, C. Grootscholten, K. Geboes, S. Zafar, S. Snow, A.H. Ko, K. Feeney, M. Schenker, P. Kocon, J. Zhang, L. Zhu, M. Lei, P. Singh, K. Kondo, J.M. Cleary, and M. Moehler, for the CheckMate 577 Investigators*

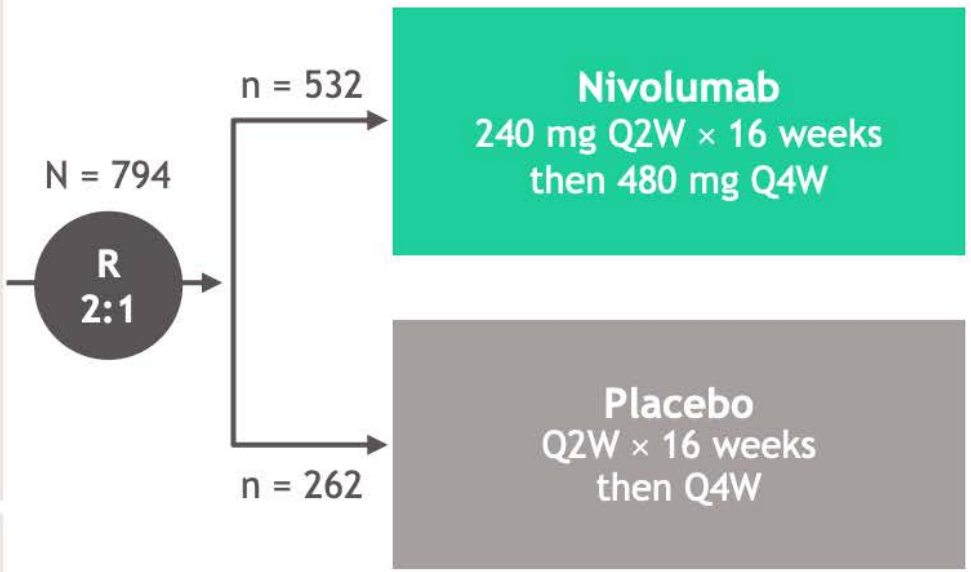
Checkmate-577 Design

Key eligibility criteria

- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

Stratification factors

- Histology (squamous vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])



Total treatment duration of up to 1 year[d]

Primary endpoint:

- DFS[e]

Secondary endpoints:

- OS[f]
- OS rate at 1, 2, and 3 years

- Median follow-up was 24.4 months (range, 6.2-44.9)[g]
- Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)

[a]ClinicalTrials.gov number, NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a pre-specified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]Time from randomization date to clinical data cutoff (May 12, 2020).

Kelly, NEJM 2021

Checkmate-577 baseline characteristics

Baseline characteristics

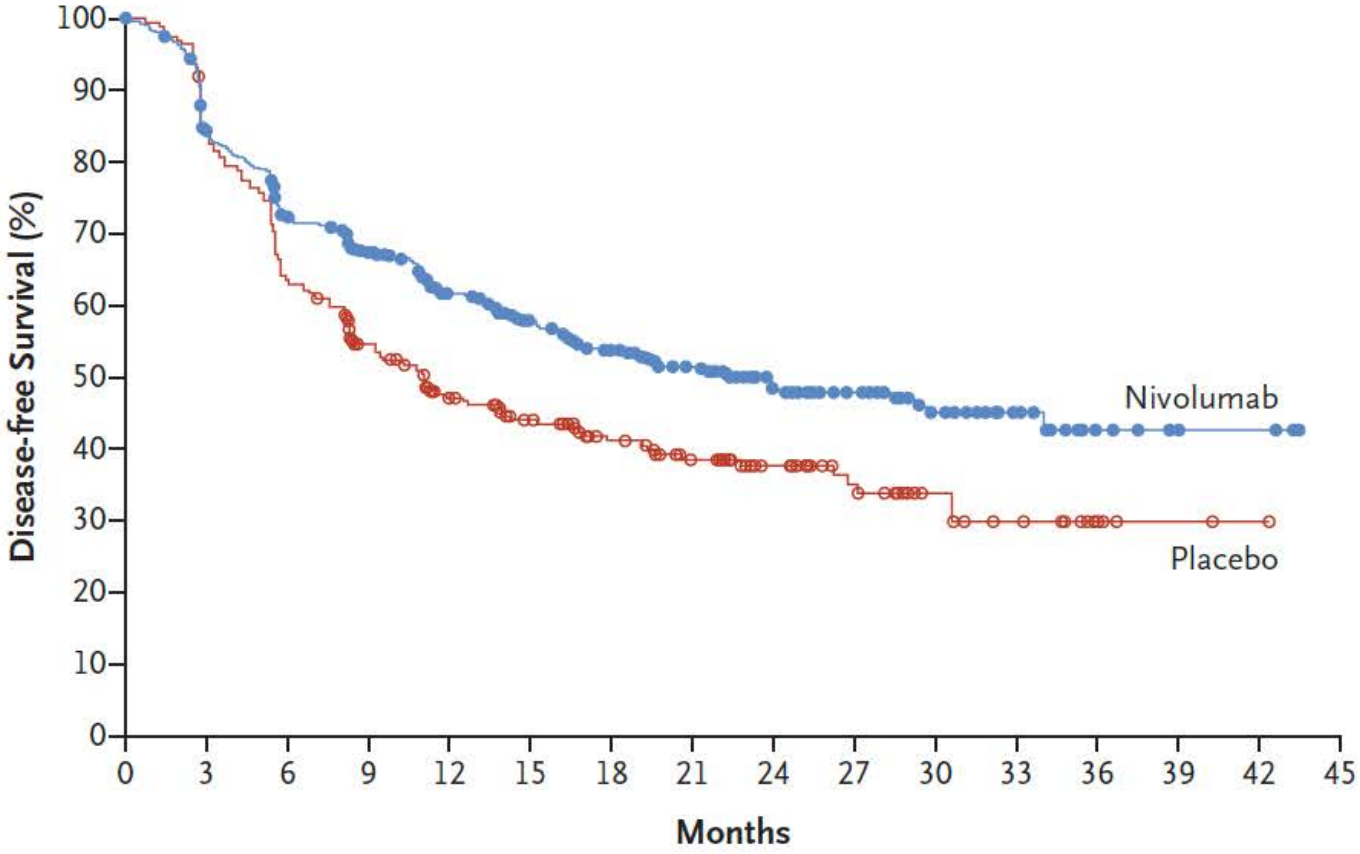
	Nivolumab (n = 532)	Placebo (n = 262)
Median age (range), years	62.0 (26-82)	61.0 (26-86)
Male, %	84	85
Race,[a] %		
White	81	82
Asian	16	13
ECOG PS, %		
0	58	60
1	42	40
Disease stage at initial diagnosis, %		
II	34	38
III	66	62
Tumor location, %		
EC	60	59
GEJC	40	41
Histology, %		
Squamous cell carcinoma	29	29
Adenocarcinoma	71	71
Pathologic lymph node status ≥ ypN1, %	57	58
Tumor cell PD-L1 expression,[b] %		
≥ 1%	17	15
< 1%	70	75
Indeterminate/nonevaluable	13	10

[a]Other races not shown; [b]Tumor cell PD-L1 expression determined from surgical specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako).

Kelly, NEJM 2021

Checkmate-577: Disease-Free Survival

A Disease-free Survival in the Overall Population



No. at Risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

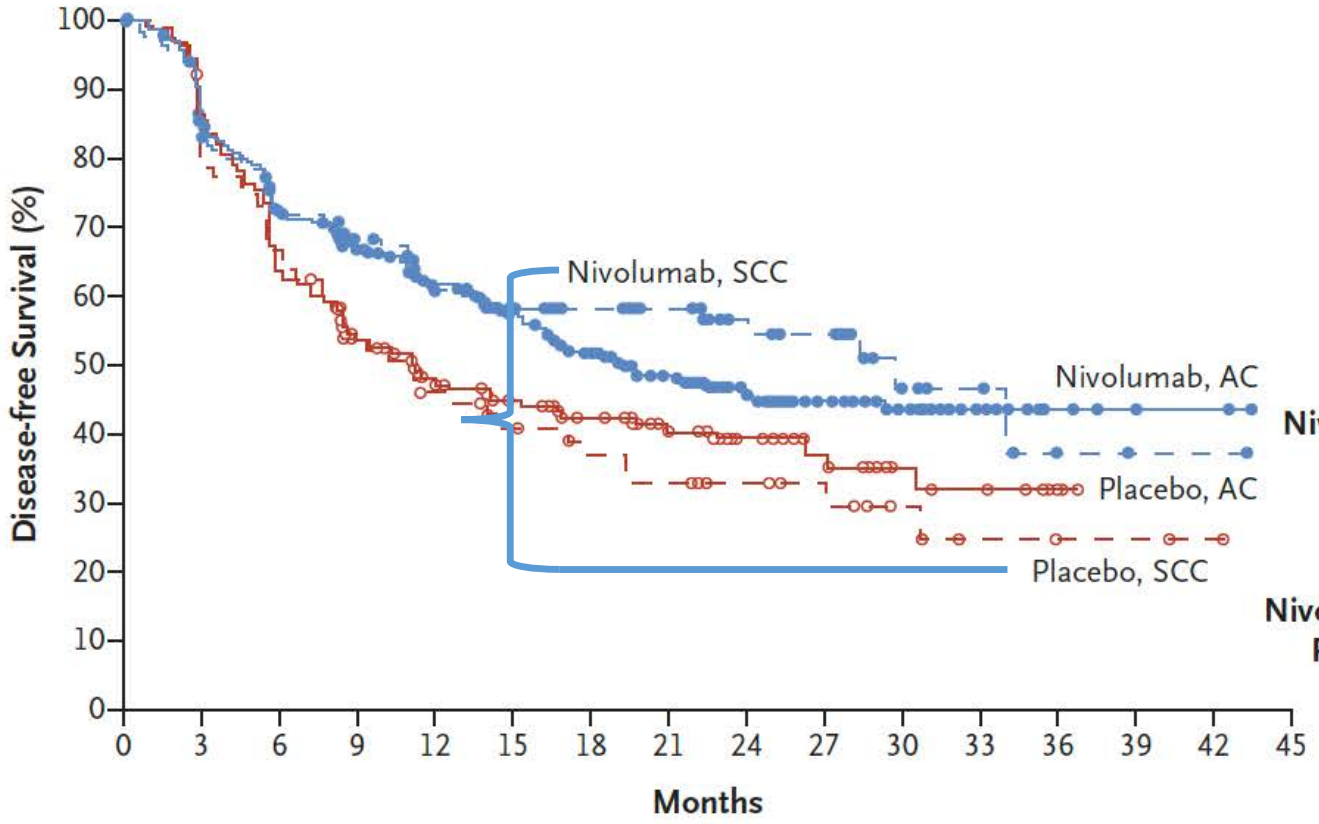
	No. of Patients	Median Disease-free Survival
		mo (95% CI)
Nivolumab	532	22.4 (16.6–34.0)
Placebo	262	11.0 (8.3–14.3)

Hazard ratio for disease recurrence or death, 0.69 (96.4% CI, 0.56–0.86)
P<0.001

Kelly, NEJM 2021

Checkmate-577: DFS by histology

B Disease-free Survival According to Histologic Type



	No. of Patients	Median Disease-free Survival
		mo (95% CI)
Nivolumab, AC	376	19.4 (15.9–29.4)
Placebo, AC	187	11.1 (8.3–16.8)
Hazard ratio for disease recurrence or death, 0.75 (95% CI, 0.59–0.96)		
Nivolumab, SCC	155	29.7 (14.4–NE)
Placebo, SCC	75	11.0 (7.6–17.8)
Hazard ratio for disease recurrence or death, 0.61 (95% CI, 0.42–0.88)		

No. at Risk

Nivolumab, AC	376	305	257	219	178	151	125	99	65	45	32	16	6	3	2	0
Nivolumab, SCC	155	124	106	87	71	61	56	48	27	23	9	6	2	1	1	0
Placebo, AC	187	156	114	92	68	57	47	37	26	18	11	9	3	0	0	0
Placebo, SCC	75	58	49	34	28	23	18	16	12	10	6	3	2	2	1	0

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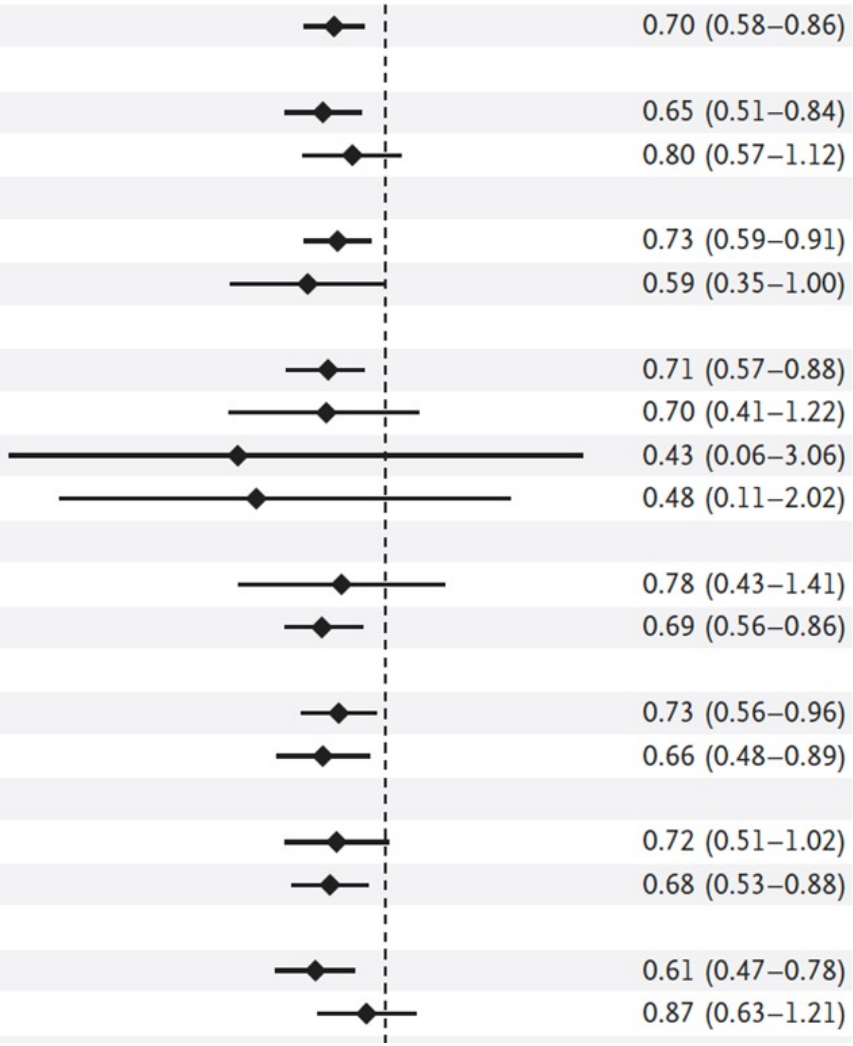
Checkmate-577: Forest Plot

Subgroup	No. of Patients	Median Disease-free Survival (mo)		Unstratified Hazard Ratio (95% CI)
		Nivolumab	Placebo	
Overall	794	22.4	11.0	0.70 (0.58–0.86)
Age				
<65 yr	507	24.4	10.8	0.65 (0.51–0.84)
≥65 yr	287	17.0	13.9	0.80 (0.57–1.12)
Sex				
Male	671	21.4	11.1	0.73 (0.59–0.91)
Female	123	Not reached	11.0	0.59 (0.35–1.00)
Race				
White	648	21.3	10.9	0.71 (0.57–0.88)
Asian	117	24.0	10.2	0.70 (0.41–1.22)
Black	9	14.4	8.3	0.43 (0.06–3.06)
Other	20	Not reached	14.1	0.48 (0.11–2.02)
Region				
Asia	106	24.0	14.3	0.78 (0.43–1.41)
Other	688	21.4	11.0	0.69 (0.56–0.86)
ECOG performance-status score				
0	464	29.4	11.1	0.73 (0.56–0.96)
1	330	17.0	10.9	0.66 (0.48–0.89)
Disease stage at initial diagnosis				
II	278	34.0	13.9	0.72 (0.51–1.02)
III	514	19.4	8.5	0.68 (0.53–0.88)
Tumor location at initial diagnosis				
Esophagus	462	24.0	8.3	0.61 (0.47–0.78)
Gastroesophageal junction	332	22.4	20.6	0.87 (0.63–1.21)



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Checkmate-577: Adverse Events

Treatment-related adverse events with potential immunologic etiology

Select TRAEs,[b,c] n (%)	Nivolumab[a] n = 532		Placebo[a] n = 260	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Endocrine	93 (17)	5 (< 1)	6 (2)	0
Gastrointestinal	91 (17)	4 (< 1)	40 (15)	3 (1)
Hepatic	49 (9)	6 (1)	18 (7)	4 (2)
Pulmonary	23 (4)	6 (1)	4 (2)	1 (< 1)
Renal	7 (1)	1 (< 1)	2 (< 1)	0
Skin	130 (24)	7 (1)	28 (11)	1 (< 1)

- The majority of select TRAEs were grade 1 or 2
- Grade 3-4 select TRAEs occurred in ≤ 1% of patients in the nivolumab arm and there were no grade 5 select TRAEs
- The most common grade 3-4 select TRAEs in the nivolumab arm were pneumonitis (n = 4) and rash (n = 4) (0.8% each); in the placebo arm, these events occurred in 1 patient each (0.4%)

Kelly, NEJM 2021

Example Case: Metastatic disease

- 62-year-old patient presents with dysphagia. EGD reveals a **GEJ mass** – biopsy reveals moderately-differentiated adenocarcinoma, pMMR, Her2 IHC negative, CPS=1.

- CT c/a/p reveals multiple bilobar liver metastases.

- No other medical problems, patient is healthy and works part time.

- ECOG performance status = 1

- What is your initial recommendation for therapy?
  - ECF
  - FOLFOX
  - FOLFOX/Nivo
  - FOLFOX/Pembro

Therapy options in advanced gastric/ esophageal cancers

1st Line	Fluoropyrimidine + platinum
	+Trastuzumab/Pembro (HER-2 positive)
	+Pembro (PD-L1 CPS ≥10)
	+Nivo (PD-L1 CPS ≥5)
2nd Line	Ramucirumab + paclitaxel
	Trastuzumab Deruxtecan (HER-2 positive)
	Pembro (MSI/MMR-D)
	Pembro (PD-L1 CPS ≥10)
3rd Line and beyond	Irinotecan
	Trifluridine/Tipiracil

1. National Comprehensive Cancer Network. Esophageal Cancer Guidelines v4.2021. Available at www.nccn.org. Accessed Sept 15, 2021
2. National Comprehensive Cancer Network. Gastric Cancer Guidelines v4.2021. Available at www.nccn.org. Accessed Sept 15, 2021

Combination chemotherapy results in improved survival

Study	Treatment	No Pts	RR (%)	TTP (mos)	OS (mos)	P-value
Van Cutsem (V325)	CDDP+5FU	224	25	3.7	**8.6**	**0.02**
	Doce+CDDP+5FU	221	37	5.6	**9.2**	
Dank (V306)	CDDP+5FU	163	26	4.2	**8.7**	**NS**
	Irinotecan+5FU/LV	170	32	5.0	**9.0**	
Cunningham (REAL-2)	ECF	263	41	6.2	**9.9**	**0.02**
	EOF	245	42	6.5	**9.3**	
	ECX	250	46	6.7	**9.9**	
	EOX	244	48	7.0	**11.2**	
Kang	CDDP+5FU	137	29	5.0	**9.3**	**NS**
	CDDP+**capecitabine**	139	41	5.6	**10.5**	
Boku (JCDG9912)	5FU	234	9	2.9	**10.8**	**NS**
	CDDP+**irinotecan**	236	38	4.8	**12.3**	
	S-1	234	28	4.2	**11.4**	
Narahara (SPIRITS)	**S-1**	150	31	4.0	**11.0**	**0.036**
	CDDP+**S-1**	148	54	6.0	**13.0**	
Ajani (FLAGS)	CDDP+5-FU	508	31.9	5.5	**7.9**	**0.0198**
	CDDP+**S-1**	521	29.1	4.8	**8.6**	

Courtesy of S. Kim, Colorado

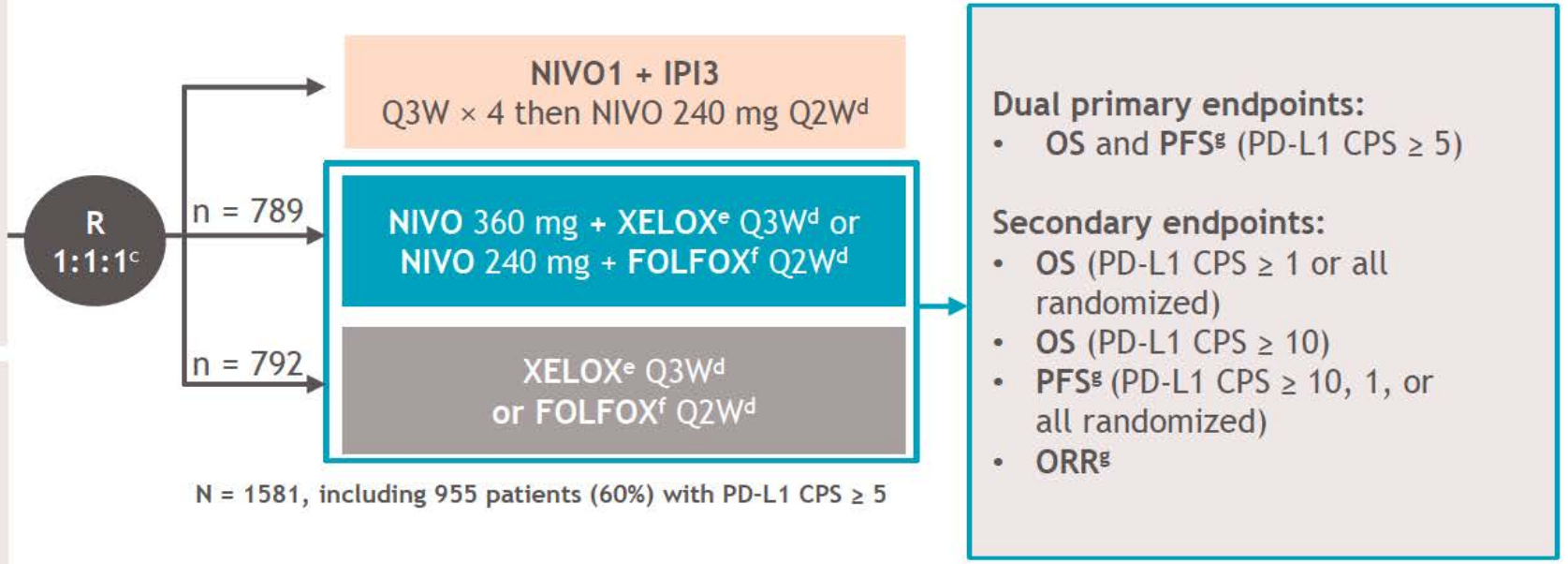
CheckMate 649: 1L Chemoimmunotherapy in gastric and GEJ

CheckMate 649 study design

- CheckMate 649 is a randomized, open-label, phase 3 study[a]

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/ esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0-1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)

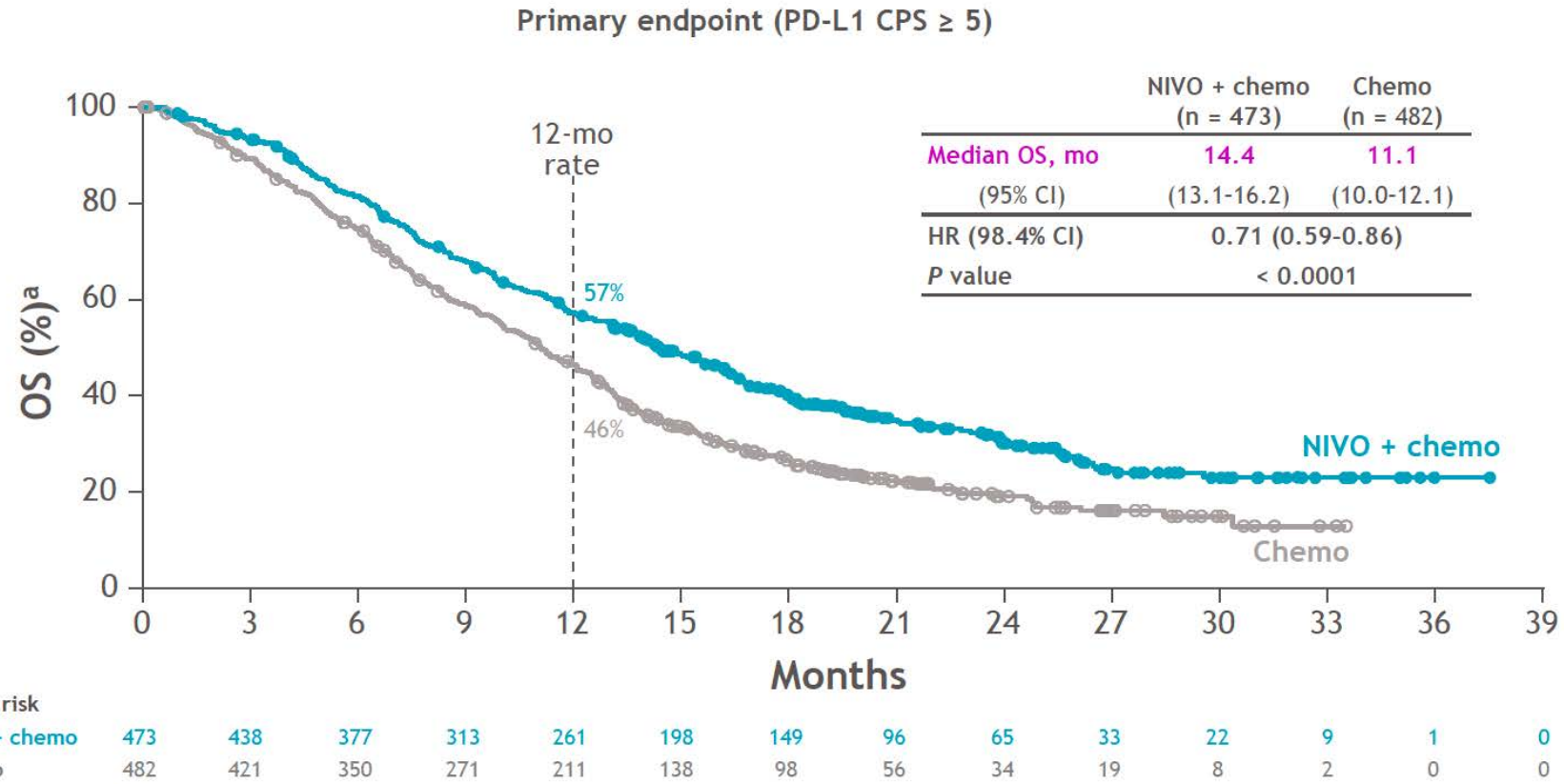


- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]

Janjigian, Lancet 2021

CheckMate 649: 1L Chemoimmunotherapy

Overall survival



- Superior OS, 29% reduction in the risk of death, and a 3.3-month improvement in median OS with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5

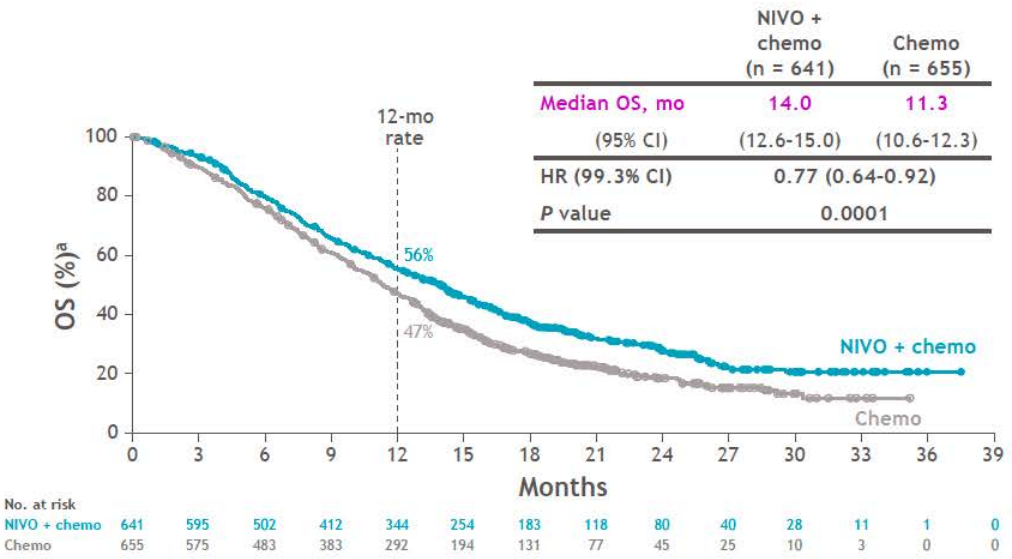
[a]Minimum follow-up 12.1 months.

Janjigian, Lancet 2021

CheckMate 649: 1L Chemoimmunotherapy in gastric and GEJ

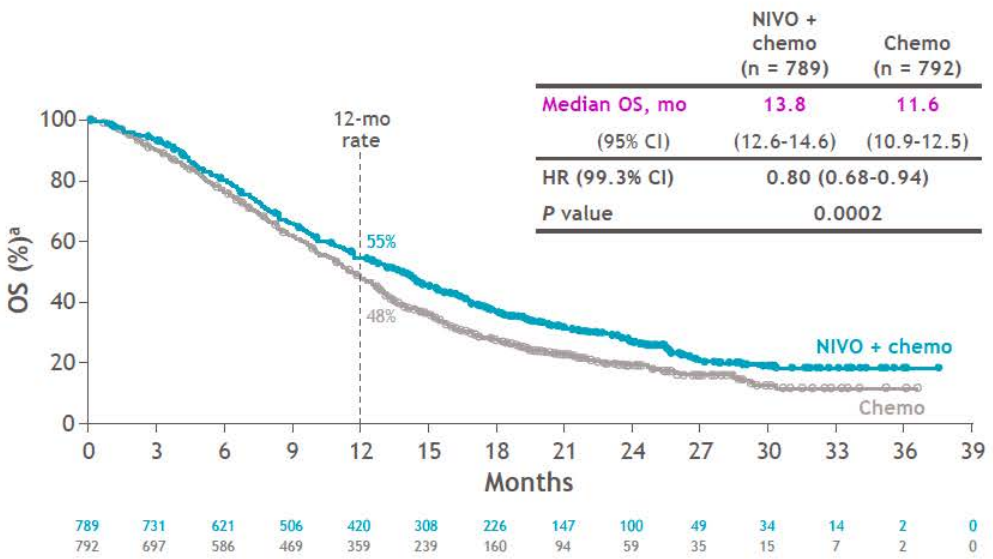
Overall survival

PD-L1 CPS ≥ 1



74% CPS ≥ 5

All randomized



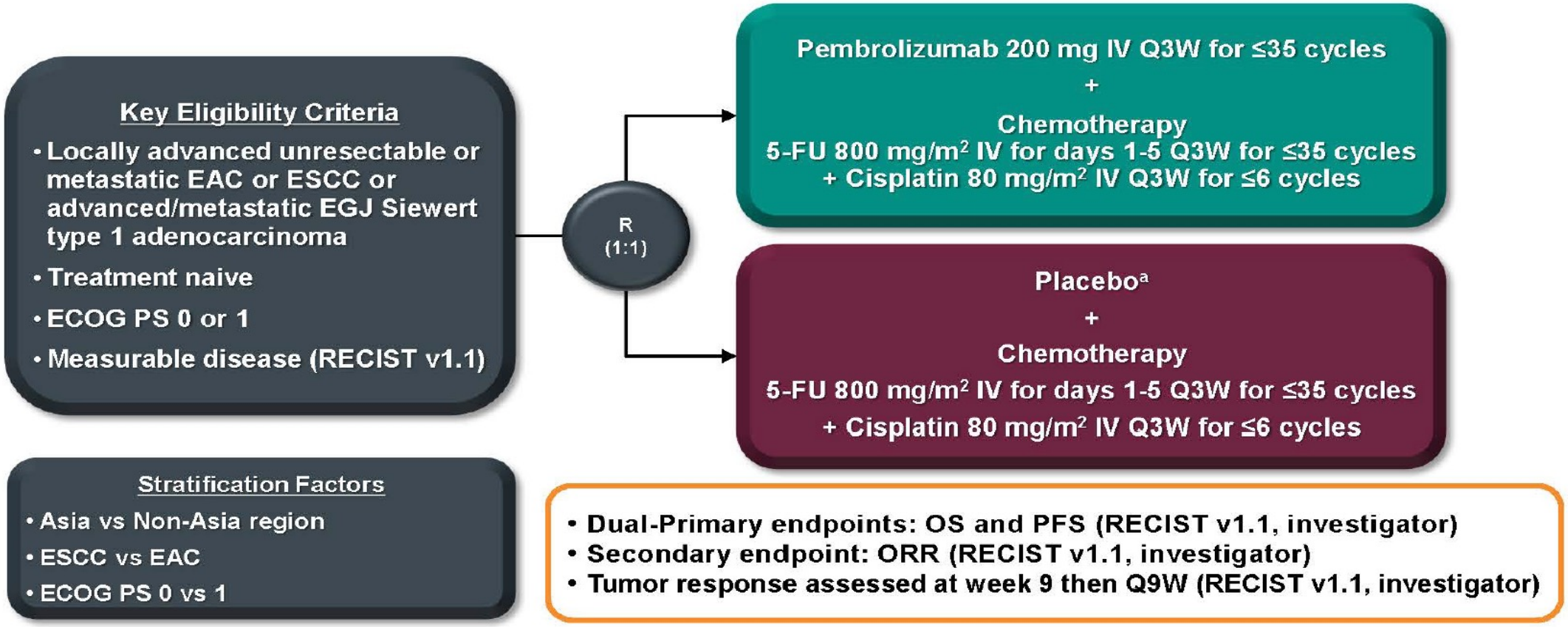
60% CPS ≥ 5

- Superior OS benefit in PD-L1 CPS ≥ 1 and all randomized patients with NIVO + chemo versus chemo

Janjigian, Lancet 2021

Keynote-590: 1L Chemoimmunotherapy

KEYNOTE-590 Study Design (NCT03189719)



Primary end points were
- OS in pts with ESCC PD-L1 combined positive score (CPS) ≥10 tumors
- OS and PFS in ESCC, PD-L1 CPS ≥10, and all pts.

Sun, Lancet 2021

Keynote-590: 1L Chemoimmunotherapy

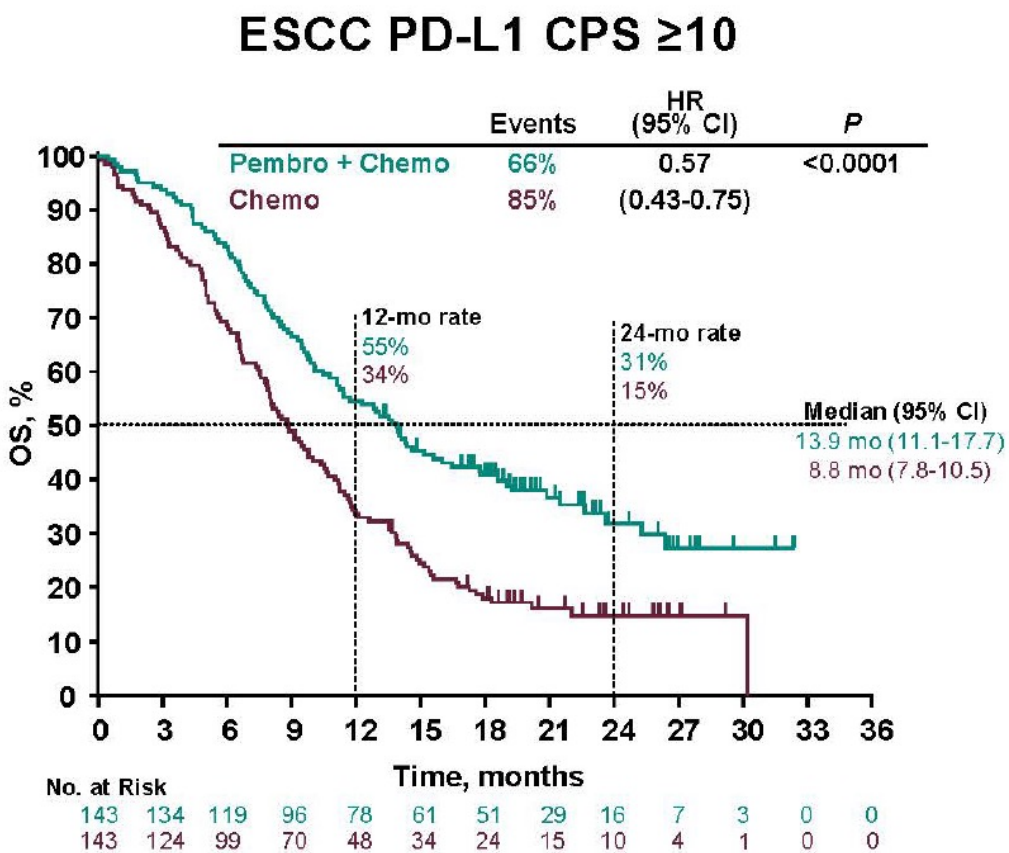
Baseline Characteristics (ITT)

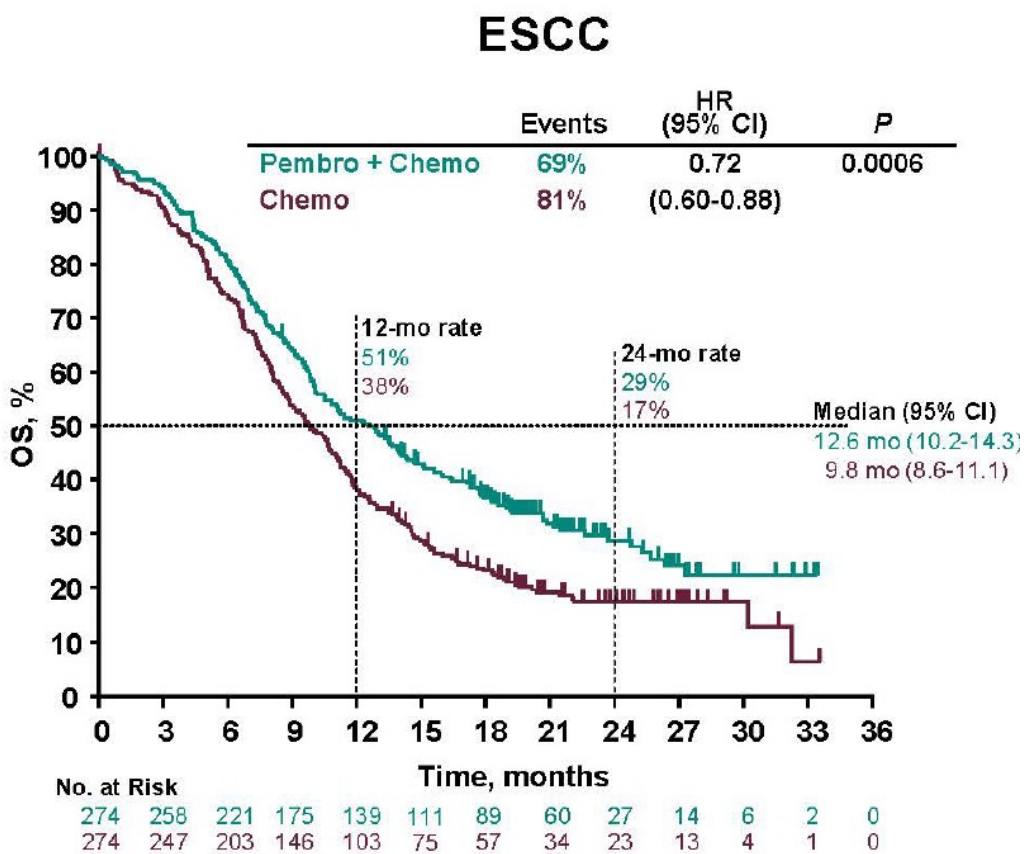
Characteristic, n (%)	Pembro + Chemo N = 373	Chemo N = 376
Median age, years (range)	64.0 (28-94)	62.0 (27-89)
≥65 years	172 (46)	150 (40)
Male	306 (82.0)	319 (84.8)
Asia Region	196 (52.5)	197 (52.4)
ECOG PS 1	223 (59.8)	225 (59.8)
Metastatic disease	344 (92.2)	339 (90.2)
Unresectable/locally-advanced	29 (7.8)	37 (9.8)
Squamous-cell carcinoma	274 (73.5)	274 (72.9)
Adenocarcinoma	99 (26.5)	102 (27.1)
Esophageal	58 (15.5)	52 (13.8)
EGJ	41 (11.0)	50 (13.3)
PD-L1 CPS ≥10[a]	186 (49.9)	197 (52.4)

Sun, Lancet 2021

Keynote-590: OS in SCC

Overall Survival



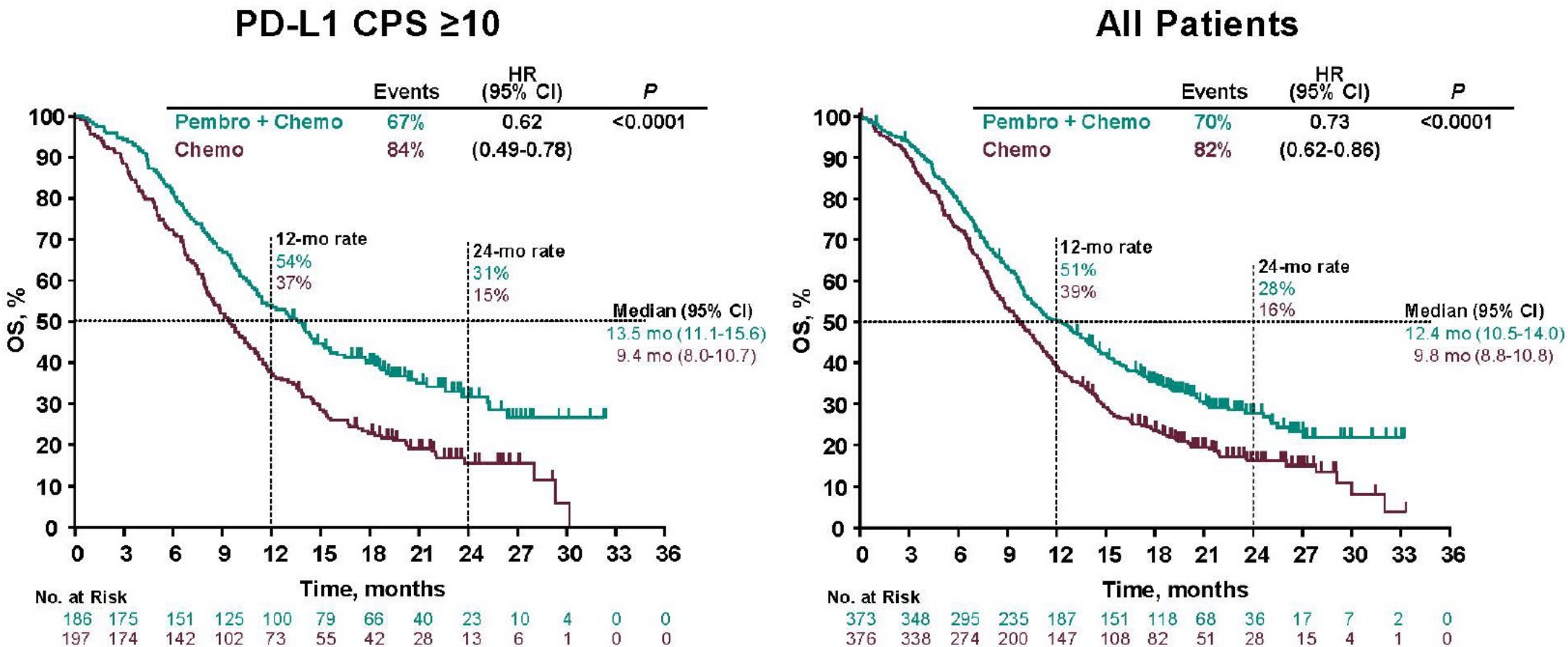


Data cut-off: July 2, 2020

Sun, Lancet 2021

Keynote-590: OS by CPS and All patients

Overall Survival



Sun, Lancet 2021

Questionable PD-L1 Assay Concordance

CPS cutoff	Proportion of samples testing PD-L1 positive, %		*P* value
	22C3	28-8	
≥ 1	49.4	70.3	< .001
≥ 5	13.4	29.1	< .001
≥ 10	7.0	13.7	.004

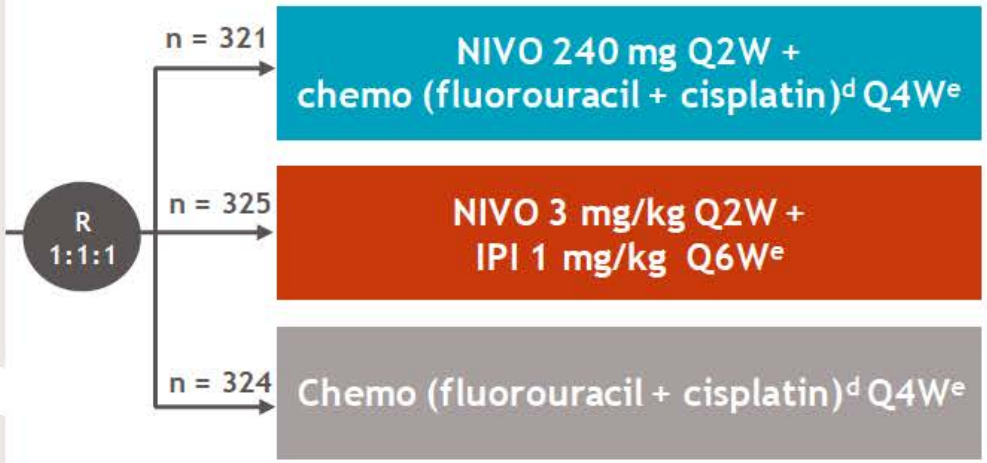
Different results with different antibodies.

Tay, 2022 Annual ASCO Meeting

CheckMate-648: esophageal SCC

Key eligibility criteria
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤ 1 vs ≥ 2)



Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

Exploratory endpoints:
- OS (by tumor cell PD-L1 and PD-L1 CPS)
- DOR[f]
- PFS2[g]
- Safety

- At data cutoff (January 18, 2021), the minimum follow-up was 12.9 months[h]

Chau, ESMO GI 2022

CheckMate-648: esophageal SCC

All randomized	NIVO + chemo (n = 321)	NIVO + IPI (n = 325)	Chemo (n = 324)[a]
Median age, years (range)	64 (40-90)	63 (28-81)	64 (26-81)
Male, %	79	83	85
Asian,[b] %	70	70	70
ECOG PS 1, %	53	54	52
ESCC,[c] %	97	> 99	98
Tumor cell PD-L1 expression,[d] %			
≥ 1%	49	49	48
≥ 5%	37	37	36
≥ 10%	32	32	30
Disease status at study entry, %			
De novo metastatic	57	60	58
Recurrent - locoregional	7	8	8
Recurrent - distant	22	22	19
Unresectable advanced	14	10	16
Number of organs with metastases[e]			
≤ 1	49	49	49
≥ 2	51	51	51
Current or former smoker, %	79	82	79

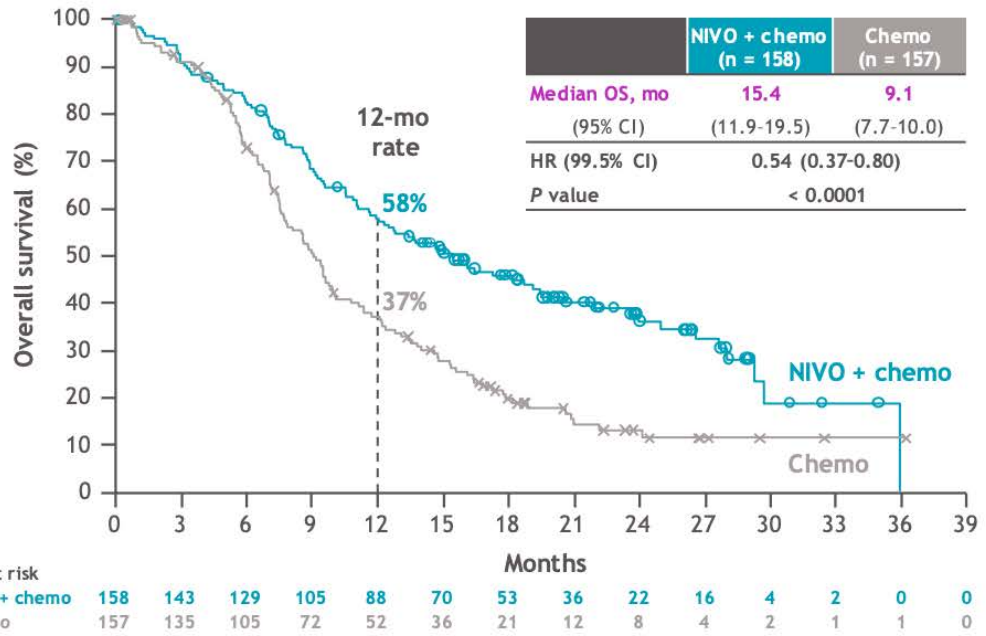
- Of the 906 patients with quantifiable PD-L1 expression at baseline across all three treatment arms, a total of 288 (32%) had both tumor cell PD-L1 ≥ 1% and PD-L1 CPS ≥ 10, and 339 (37%) had both tumor cell PD-L1 < 1% and PD-L1 CPS < 10

Chau, ESMO GI 2022

CheckMate-648: esophageal SCC

Overall survival: NIVO + chemo vs chemo

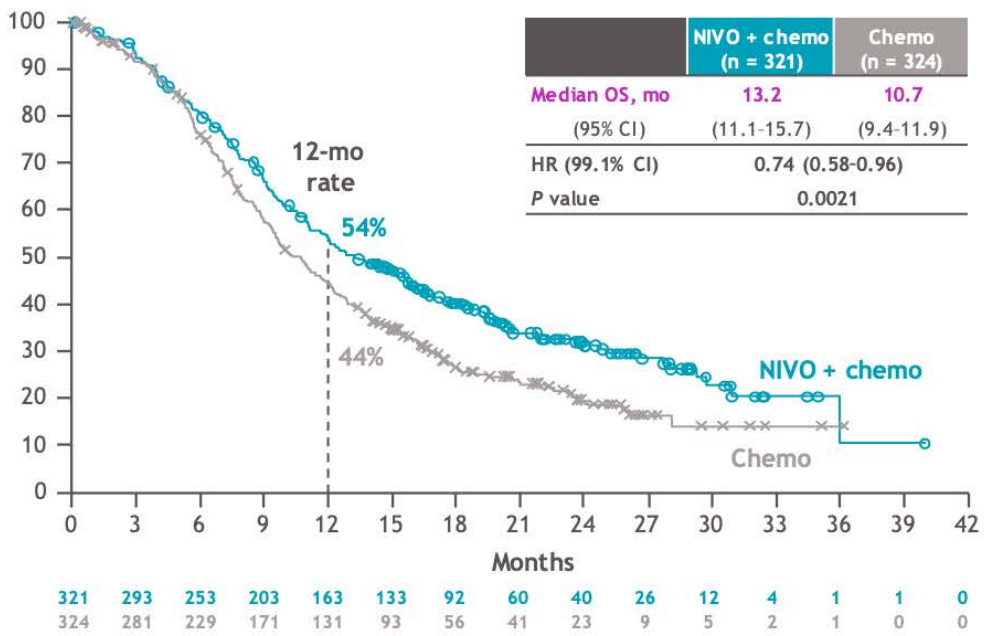
Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



	NIVO + chemo (n = 158)	Chemo (n = 157)
Median OS, mo	15.4	9.1
(95% CI)	(11.9-19.5)	(7.7-10.0)
HR (99.5% CI)	0.54 (0.37-0.80)	
P value	< 0.0001	

No. at risk														
NIVO + chemo	158	143	129	105	88	70	53	36	22	16	4	2	0	0
Chemo	157	135	105	72	52	36	21	12	8	4	2	1	1	0

All randomized[a]



	NIVO + chemo (n = 321)	Chemo (n = 324)
Median OS, mo	13.2	10.7
(95% CI)	(11.1-15.7)	(9.4-11.9)
HR (99.1% CI)	0.74 (0.58-0.96)	
P value	0.0021	

NIVO + chemo	321	293	253	203	163	133	92	60	40	26	12	4	1	1	0
Chemo	324	281	229	171	131	93	56	41	23	9	5	2	1	0	0

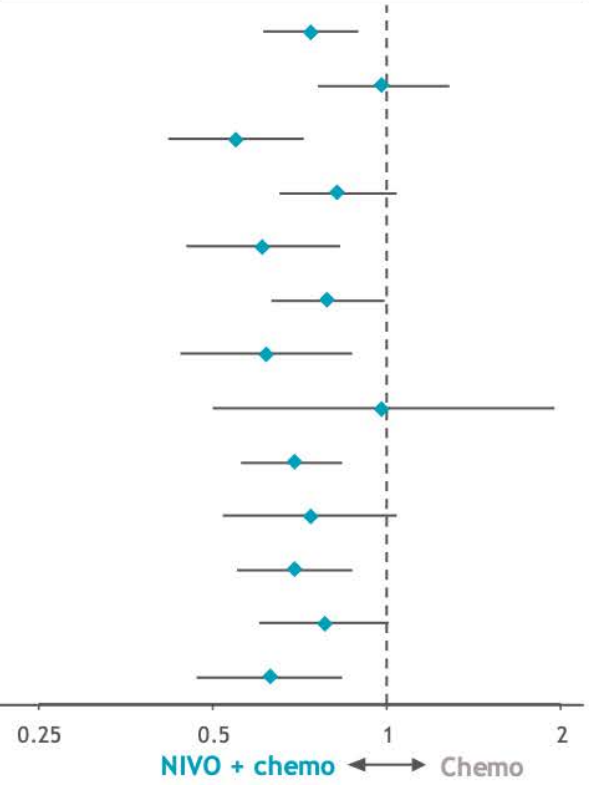
- Superior OS with NIVO + chemo vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 46% reduction in the risk of death and a 6.3-month improvement in median OS
  - All randomized: 26% reduction in the risk of death and a 2.5-month improvement in median OS

Chau, ESMO GI 2022

CheckMate-648: esophageal SCC

Overall survival by baseline PD-L1 status: NIVO + chemo vs chemo

Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 645)		13.2	10.7	0.74	
Tumor cell PD-L1 expression[a]	< 1% (n = 329)	12.0	12.2	0.98	
	≥ 1% (n = 314)	15.4	9.2	0.55	
	< 5% (n = 408)	12.8	11.1	0.82	
	≥ 5% (n = 235)	13.7	9.5	0.61	
	< 10% (n = 444)	12.3	10.8	0.79	
	≥ 10% (n = 199)	14.7	9.5	0.62	
PD-L1 CPS[b,c]	< 1 (n = 51)	9.9	12.1	0.98	
	≥ 1 (n = 558)	13.8	9.8	0.69	
	< 5 (n = 188)	12.0	9.4	0.74	
	≥ 5 (n = 421)	15.2	11.1	0.69	
	< 10 (n = 329)	12.1	9.7	0.78	
	≥ 10 (n = 280)	16.1	11.6	0.63	



Chau, ESMO GI 2022

Summary of Adjuvant/1L Trials in Gastric/GEJ

- Early gastric/esophageal cancer should be treated with a multimodality treatment
  - Esophageal: chemoradiation->surgery->adjuvant nivolumab
  - Gastric: chemo->surgery->chemo

- 1L Therapy Recommendations
  - ESCC CPS $\geq$ 10
    - Chemo + pembro
  - Gastric and GEJ/Esophageal AC CPS $\geq$ 5
    - Chemo + nivo

- NO significant difference in mOS in low PD-L1 CPS groups in CheckMate-649 and KEYNOTE-590

- For borderline PD-L1 CPS (e.g. CPS 4 for gastric or CPS 9 for esophageal SCC), use clinical judgement

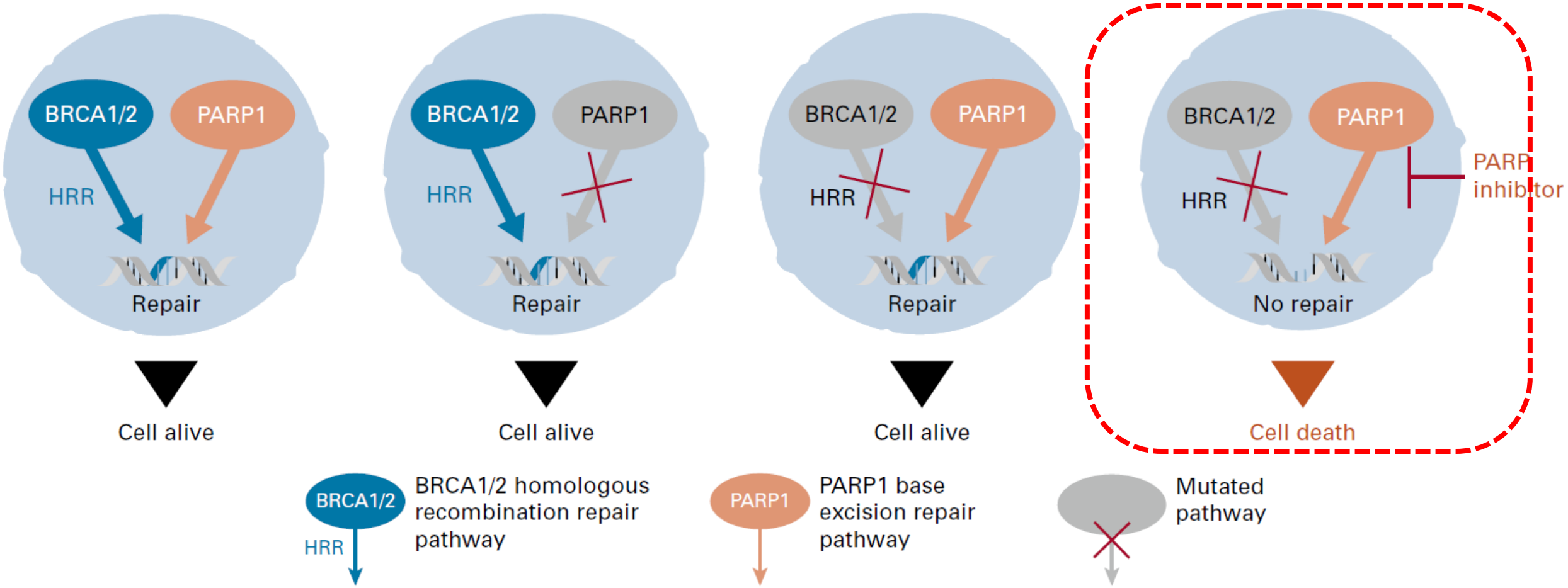
- New biomarker directed trials/results may again change landscape
  - FGFR2, CLDN18.2

PARPi in Pancreatic Cancer

Example Case

- 58-yr-old woman with no family history of cancer presented with pelvic pain
- Workup revealed metastatic pancreatic cancer with diffuse liver metastases; germline testing showed no inherited mutations
- She started first-line FOLFIRINOX and was able to complete 8 cycles of treatment with dose adjustments despite it being poorly tolerated
- Somatic tumor testing revealed a BRCA2 mutation; results returned during cycle 2 of FOLFIRINOX
- Her disease burden improved after 8 cycles of FOLFIRINOX

- What is your recommendation for next steps:
  - Continue FOLFIRINOX
  - Stop FOLFIRINOX and observe
  - PARPi maintenance therapy (note: FDA approved for germline)
  - 5-FU/capecitabine maintenance therapy



PARP poly (ADP-ribose) polymerase

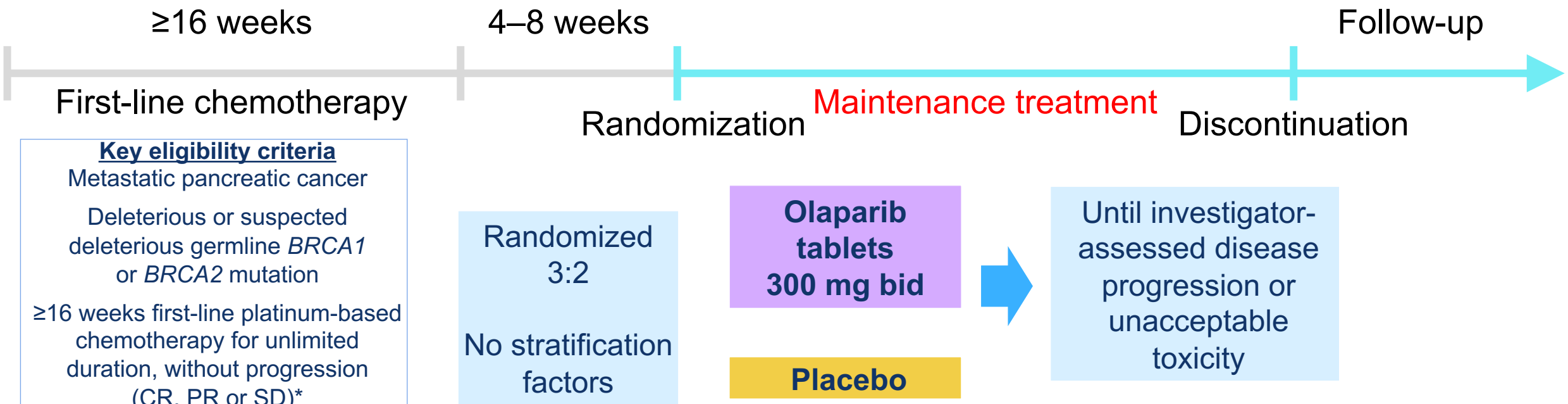
HRR homologous recombination repair

BRCA BReast CAncer gene

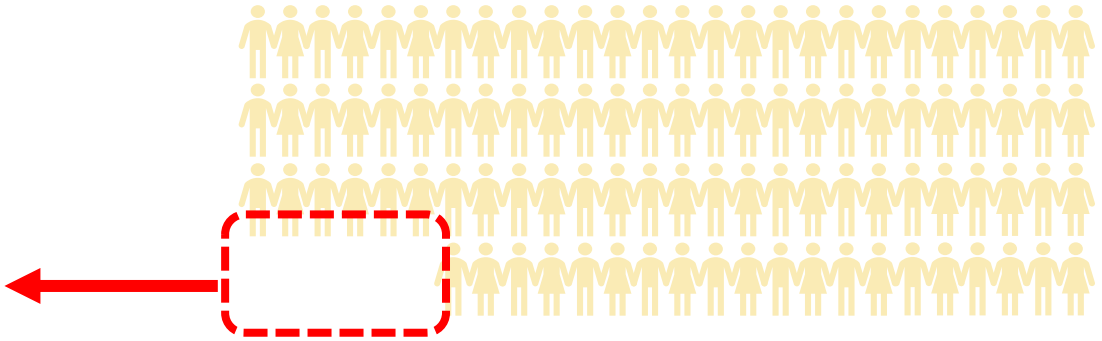
In the setting of deficient BRCA1/2, PARP inhibition causes deficient DNA repair and cell death.

Gourley, *J Clin Oncol* 2019

Study design: Subset of a small subset



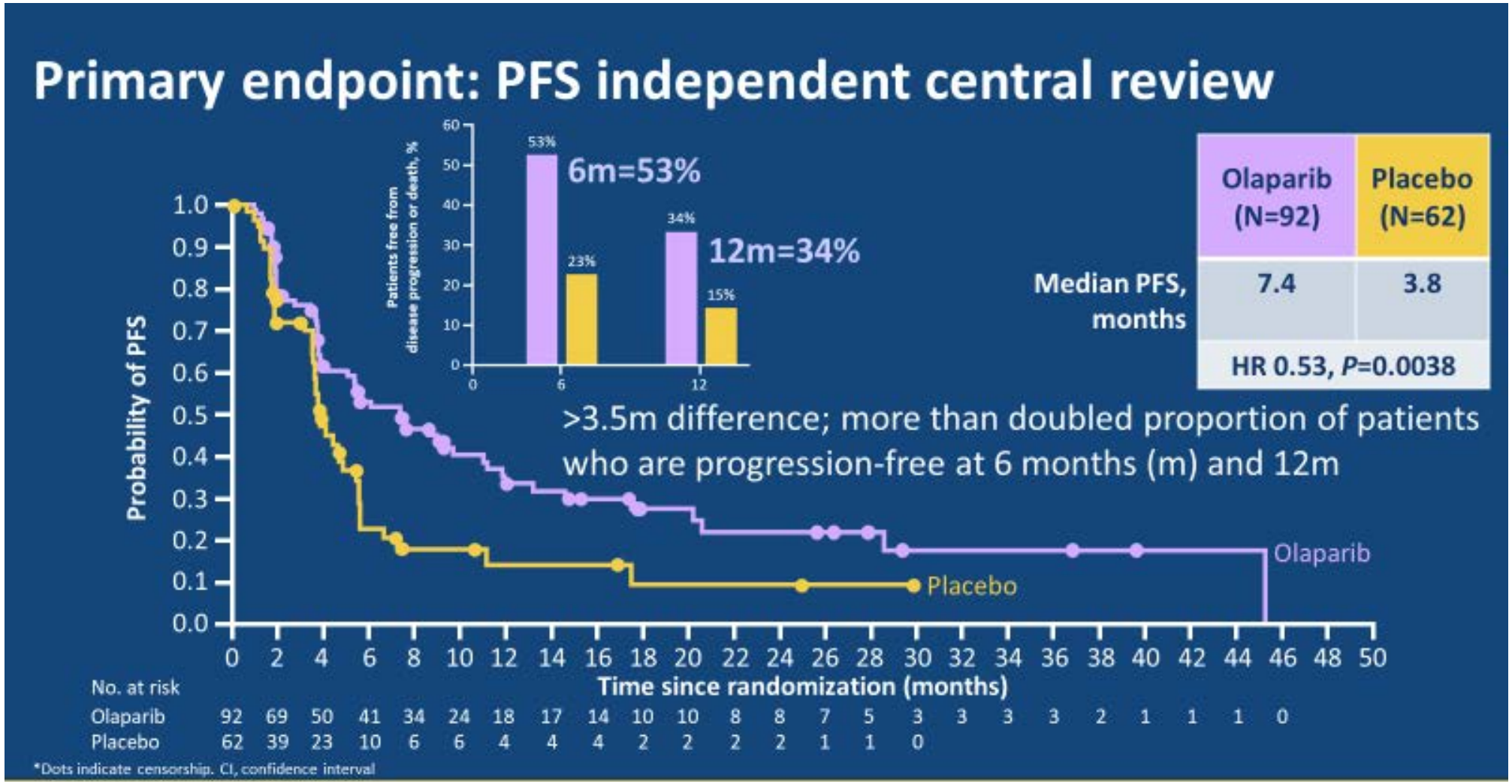
Screened 3315 to find 247 (93 excluded)



38% of gBRCAm patients had disease progression, were ineligible, or declined randomization.

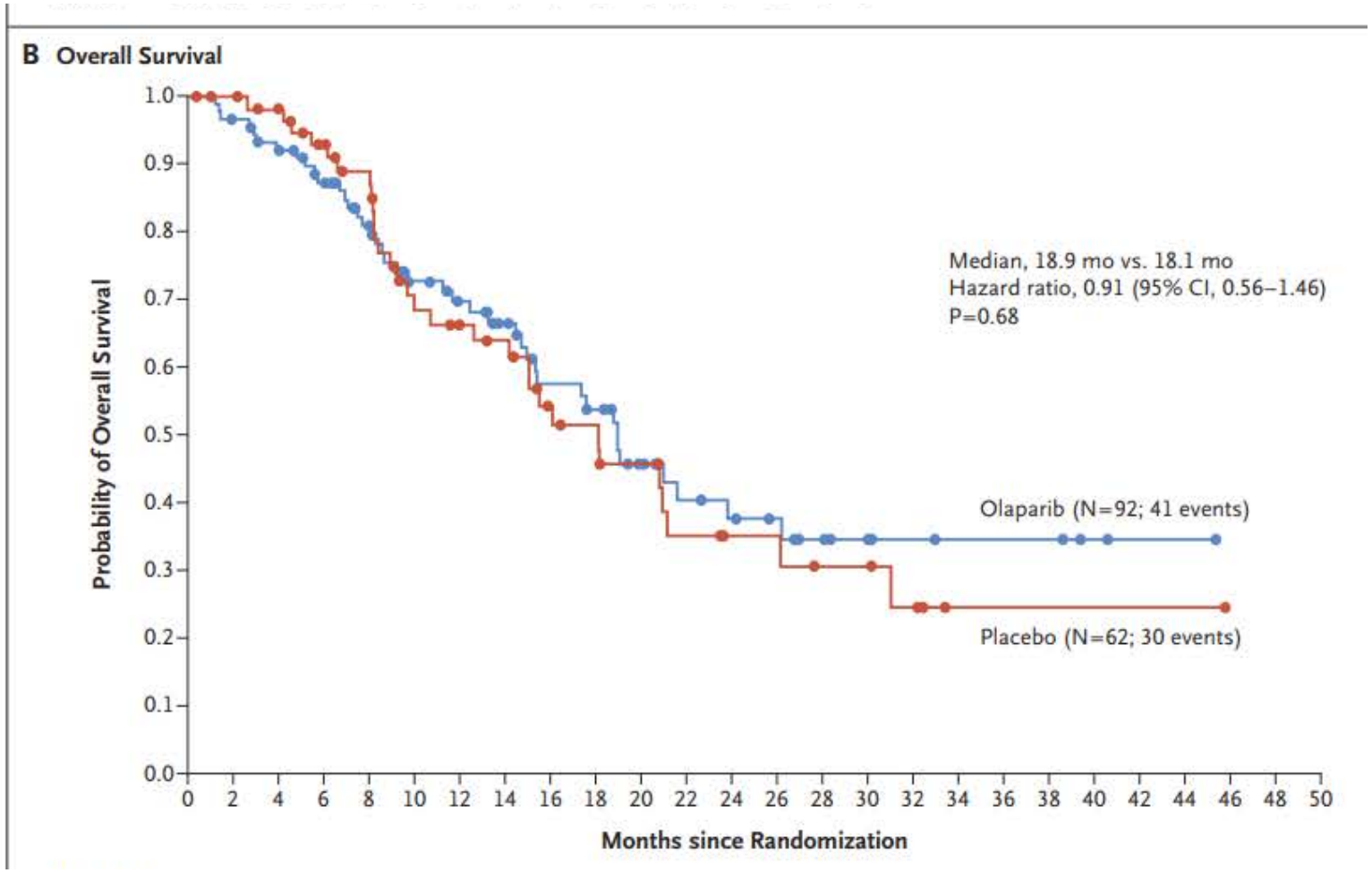
Messersmith, ASCO 2019

POLO: Maintenance Olaparib vs Placebo After First-line Platinum-Based Therapy in Metastatic Pancreatic Cancer



Golan. NEJM. 2019;381:317. Golan. ASCO GI 2021. Abstr 378.

POLO: No Difference in Overall Survival



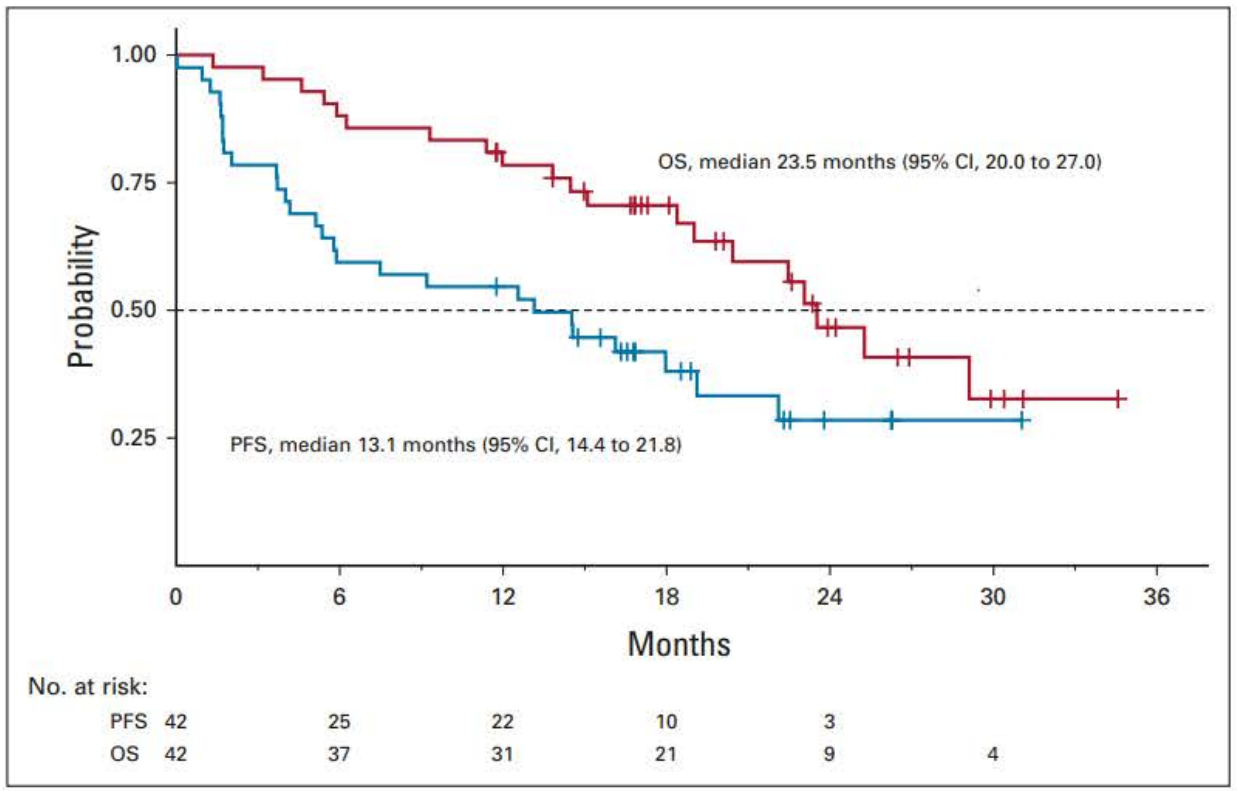
NEJM: only nine patients in the placebo group (15%) who went on to receive a PARP inhibitor after disease progression during the trial intervention.
(low crossover rate)

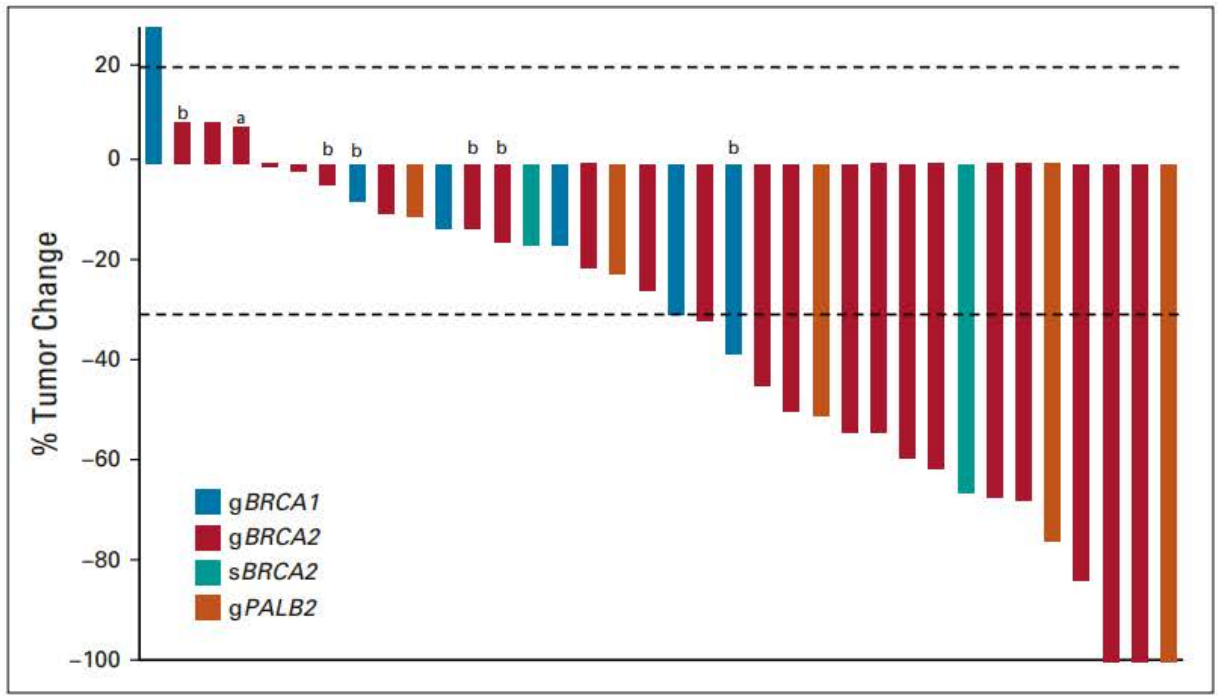
Golan, NEJM 2019

original reports

Phase II Study of Maintenance Rucaparib in Patients With Platinum-Sensitive Advanced Pancreatic Cancer and a Pathogenic Germline or Somatic Variant in *BRCA1*, *BRCA2*, or *PALB2*

Kim A. Reiss, MD[1,2]; Rosemarie Mick, MS[1,3]; Mark H. O'Hara, MD[1,2]; Ursina Teitelbaum, MD[1,2]; Thomas B. Karasic, MD[1,2];

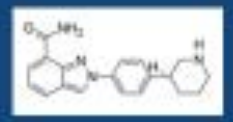


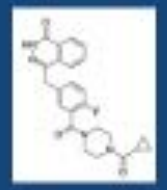


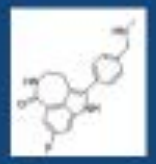
Reiss, JCO 2021

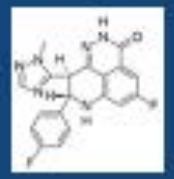
Approximate Costs of PARP inhibitors

AWP pricing for the standard FDA approved doses: one month of therapy

Niraparib 
300 mg (3 x 100 mg) orally daily
AWP for 90 capsules $20,072, $223/capsule

Olaparib 
300 mg (2 x 150 mg) orally twice daily
AWP for 120 tablets $16,830, $140/tablet

Rucaparib 
600 mg (2 x 300 mg) orally twice daily
AWP for 120 tablets $19,106, $159/tablet

Talazoparib 
1 mg (1 x 1 mg) orally once daily
AWP for 30 capsules $17,496, $583/capsule

POLO Study: 7.4 months of (median) progression-free survival would cost ~$124,540

Cindy L. O'Bryant, PharmD; Professor, University of Colorado Skaggs School of Pharmacy Pharmaceutical Sciences
Source: Institute for Clinical and Economic Review, https://icer-review.org

Messersmith, ASCO 2019

Key Points for BRCA mutated pancreatic cancer

Olaparib is FDA-approved as a maintenance therapy in germline mutated BRCA pancreatic cancer patients.

Unclear if simply continuing chemo would also work as well.

PARPi also have activity in patients with somatic BRCA mutations (not FDA approved)

Ongoing combination studies.

Gastrointestinal Cancers Agenda

MODULE 1: Immunotherapy for Gastroesophageal Cancers; PARP Inhibitors in Pancreatic Cancer

MODULE 2: HER2-Positive Gastroesophageal and Colorectal Cancer; Role of Circulating Tumor DNA/Minimal Residual Disease in Colorectal Cancer

MODULE 3: Colorectal Cancer in Younger Patients; Tumor Microbiome

MODULE 4: Neoadjuvant Therapy for Microsatellite Instability-High Gastroesophageal and Colorectal Cancer

MODULE 5: Novel Agents in Pancreatic Cancer

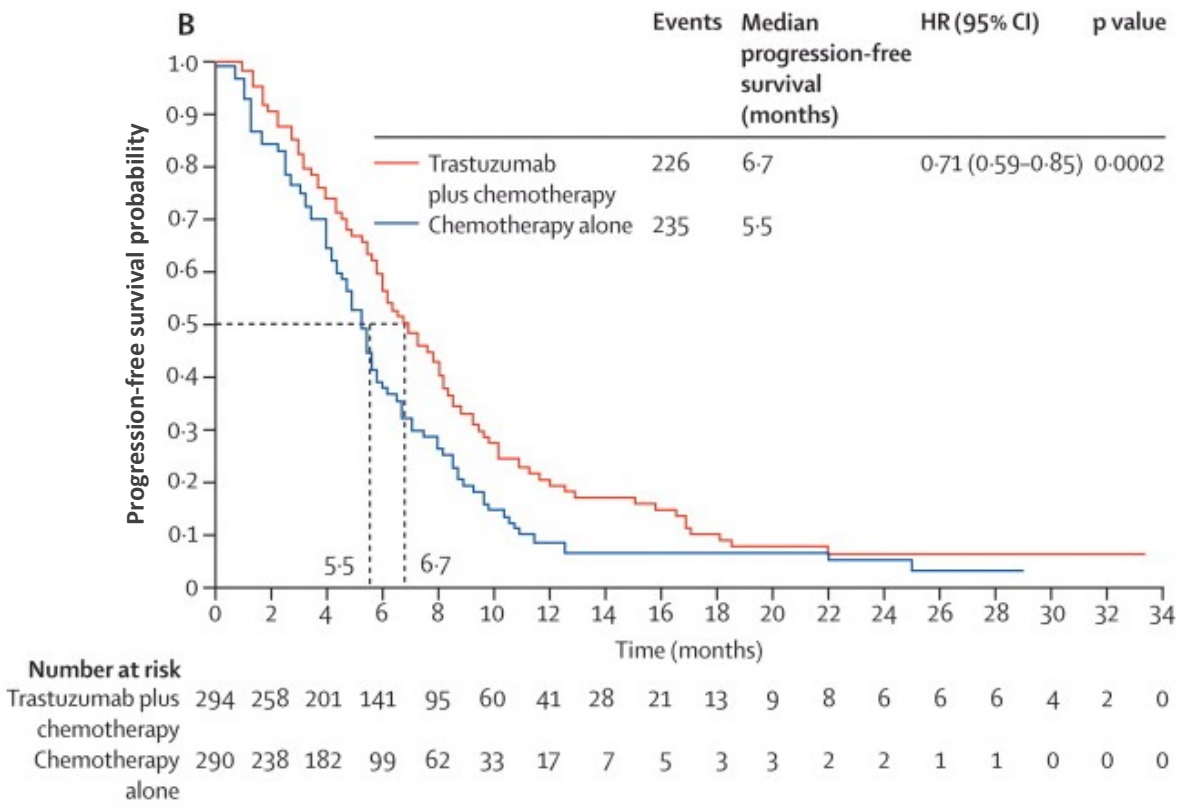
RTP RESEARCH TO PRACTICE

HER2 AS AN ACTIONABLE TARGET IN GI CANCERS

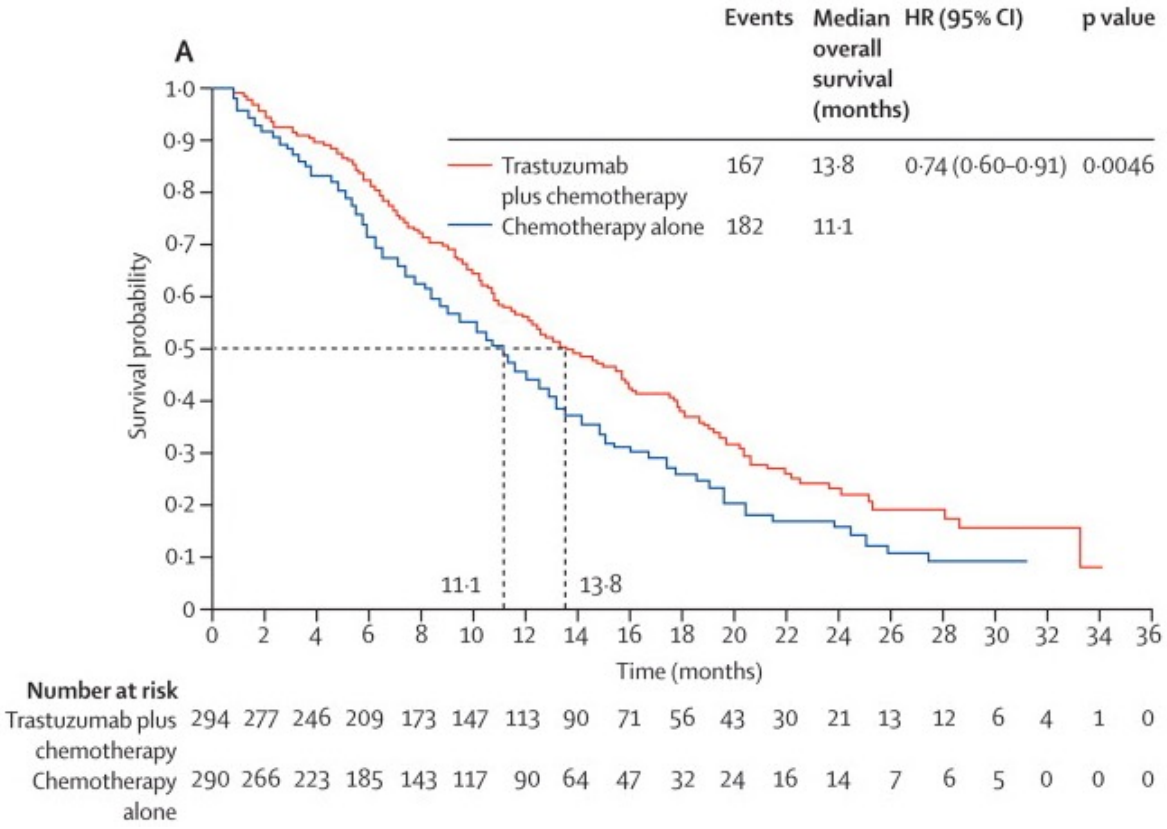
John Strickler, MD
Duke University
October 22, 2022

1L Trastuzumab improves survival for patients with metastatic HER2+ gastric/GEJ adenoca

Progression-free survival



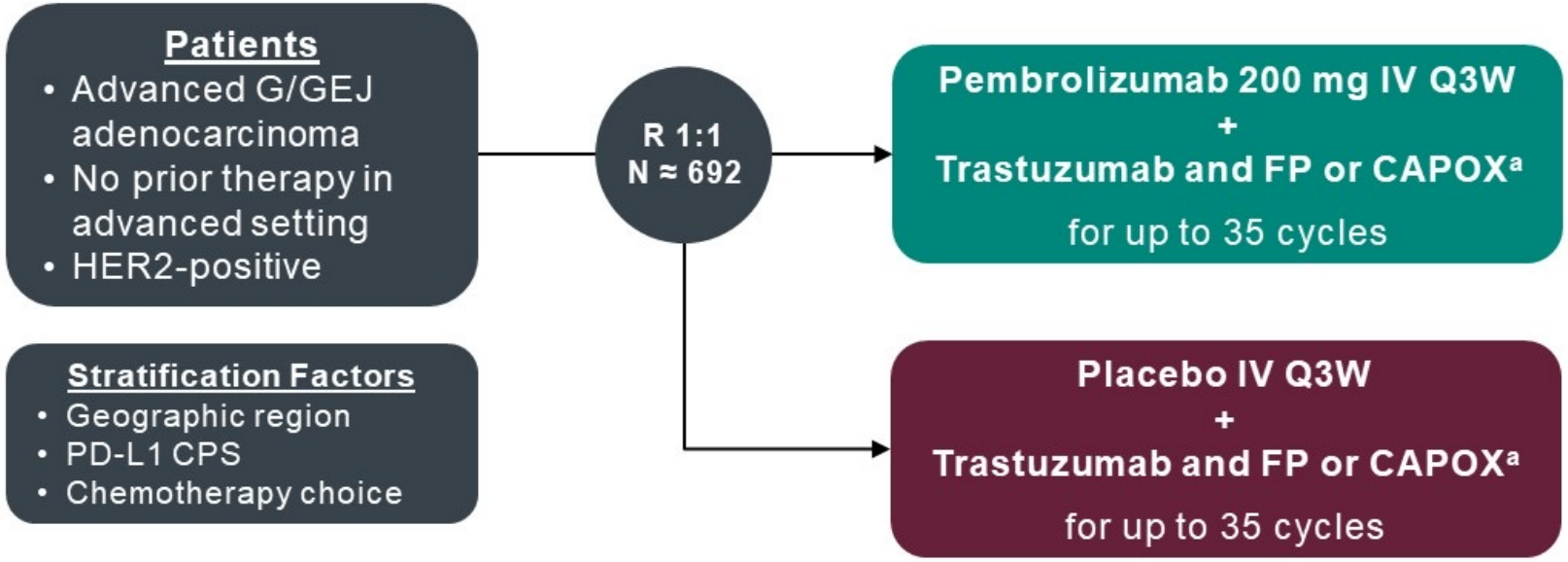
Overall survival



Overall survival for IHC3+ or IHC2+/FISH+: 16.0 vs 11.8 months (HR=0.65; 0.51-0.83)

Bang et al., *Lancet* 2010; 376: 687-97

KEYNOTE-811: Chemo + trastuzumab +/- pembrolizumab



Dual Primary End Points
- OS
- PFS (RECIST v1.1 per BICR)

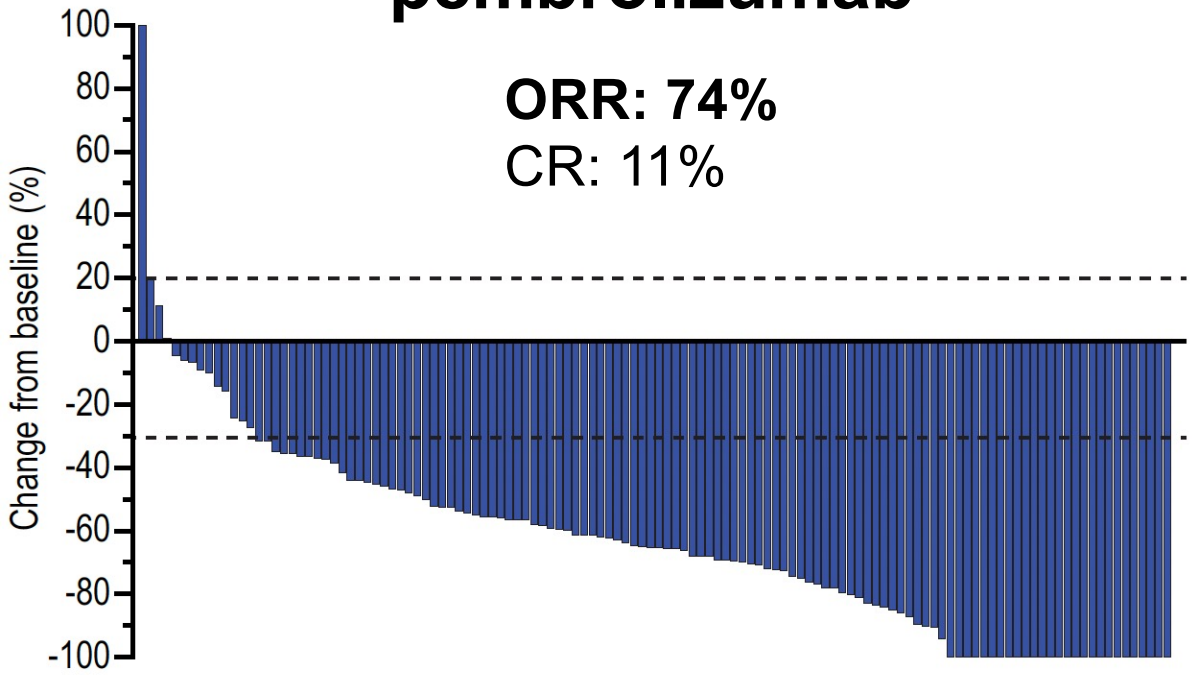
Secondary End Points
- ORR (RECIST v1.1 per BICR)
- DOR (RECIST v1.1 per BICR)
- Safety

Janjigian et al., Presented at 2021 ASCO Annual Meeting

KEYNOTE-811: Overall response rate favors pembrolizumab

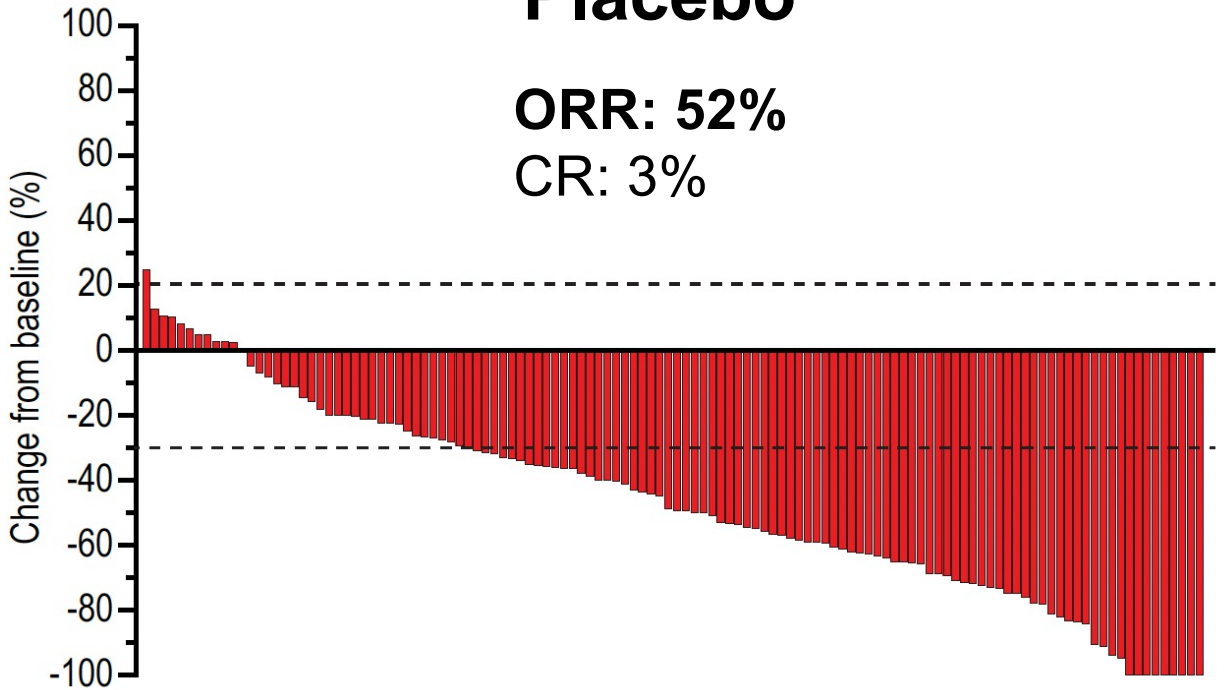
Chemo + trastuzumab + pembrolizumab

ORR: 74%
CR: 11%



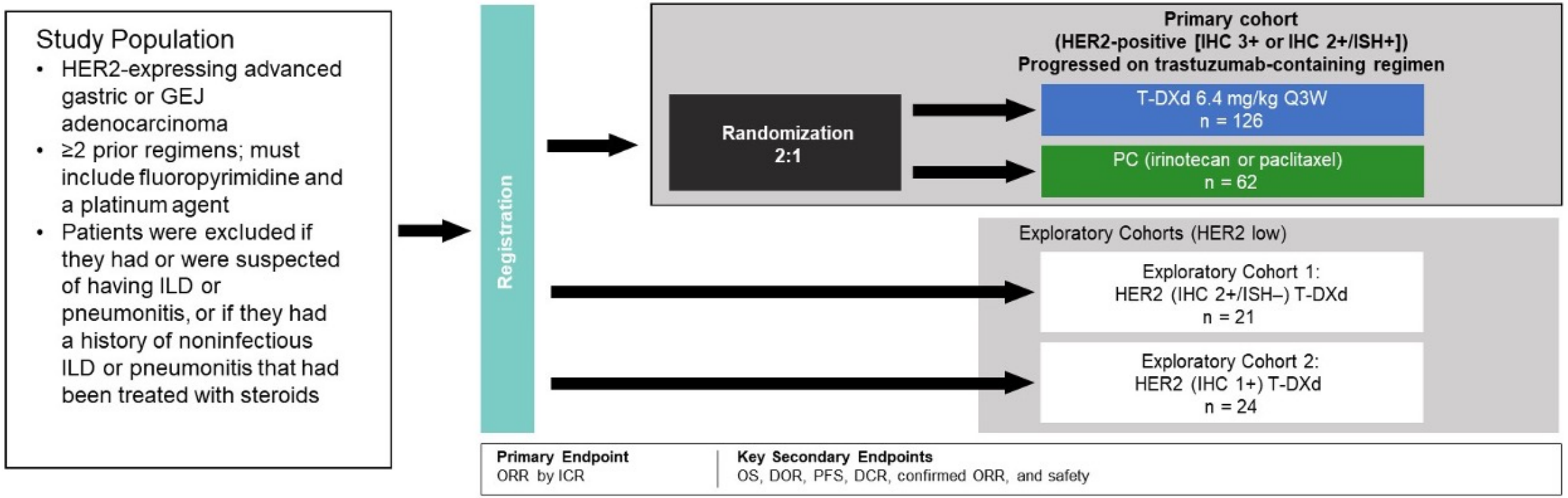
Chemo + trastuzumab + Placebo

ORR: 52%
CR: 3%



Janjigian YY et al. *Nature* 2021;600(7890):727-30.

DESTINY-Gastric01 Randomized, Phase II Study Design

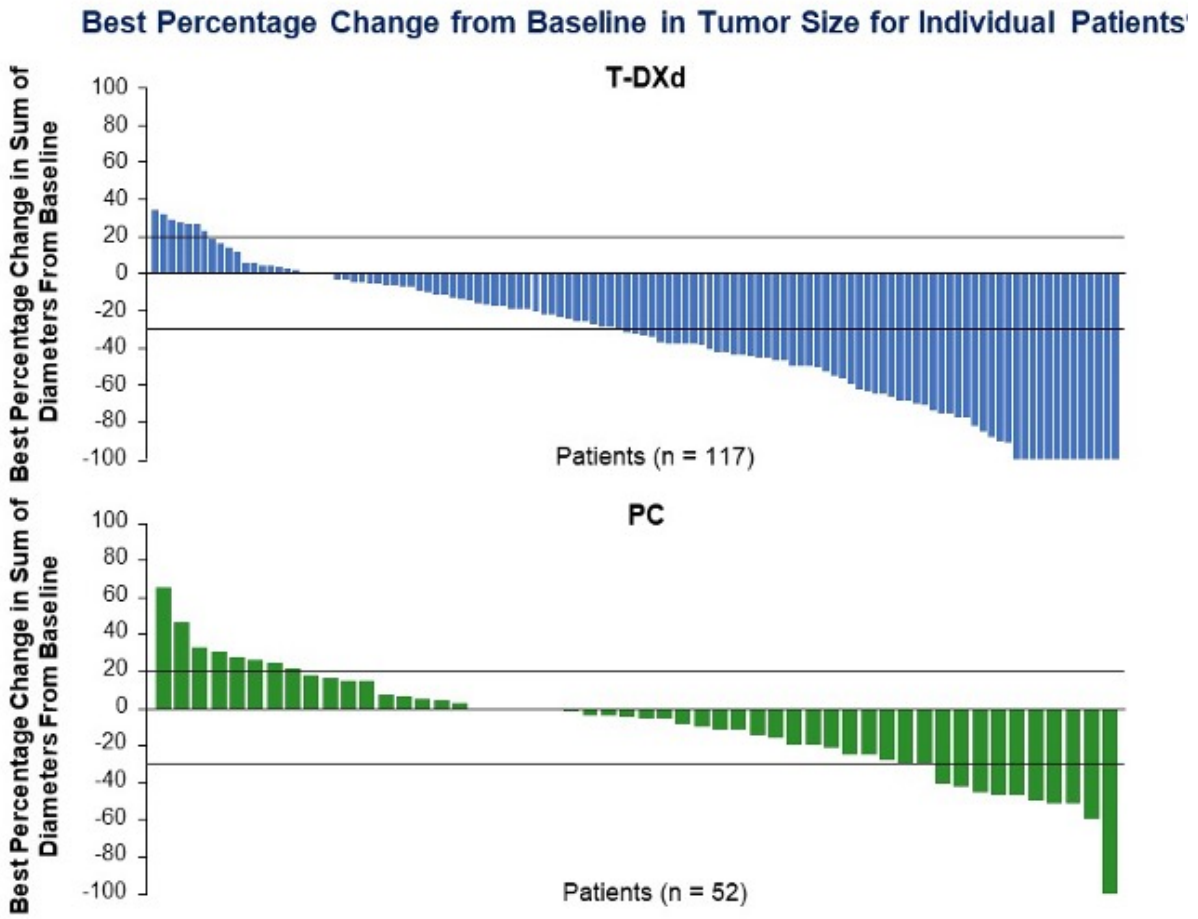


PC = physician's choice

Yamaguchi K et al. Gastrointestinal Cancers Symposium 2022;Abstract 242.

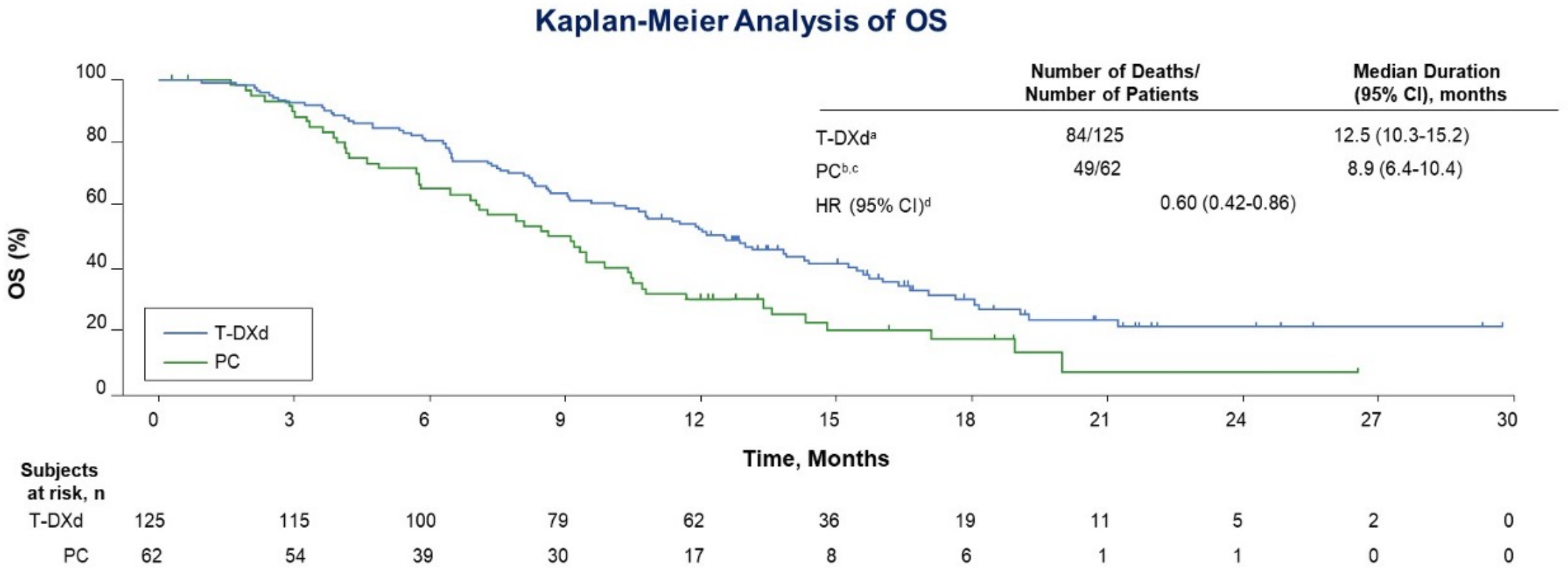
DESTINY-Gastric01: Antitumor Activity

	T-DXd n = 119	PC Overall n = 56
ORR (CR + PR) by ICR, n (%)[a]	**61 (51.3) 95% CI, 41.9-60.5**	**8 (14.3) 95% CI, 6.4-26.2**
	P < 0.0001[b]	
CR	11 (9.2)	0
PR	50 (42.0)	8 (14.3)
SD	42 (35.3)	27 (48.2)
PD	14 (11.8)	17 (30.4)
Not evaluable	2 (1.7)	4 (7.1)
Confirmed ORR (CR + PR) by ICR, n (%)[a]	50 (42.0) 95% CI, 33.0-51.4	7 (12.5) 95% CI, 5.2-24.1
CR	10 (8.4)	0
PR	40[c] (33.6)	7 (12.5)
SD	52 (43.7)	28 (50.0)
PD	14 (11.8)	17 (30.4)
Not evaluable	3 (2.5)	4 (7.1)
Confirmed DCR (CR + PR + SD), n (%)[a]	102 (85.7) 95% CI, 78.1-91.5	35 (62.5) 95% CI, 48.5-75.1
Confirmed DOR, median, months	12.5 95% CI, 5.6-NE	3.9 95% CI, 3.0-4.9
TTR, median, months	1.5 95% CI, 1.4-1.7	1.6 95% CI, 1.3-1.7



Yamaguchi K et al. Gastrointestinal Cancers Symposium 2022;Abstract 242.

DESTINY-Gastric01: Final Overall Survival (OS)



Yamaguchi K et al. Gastrointestinal Cancers Symposium 2022;Abstract 242.

PARIS 2022 ESMO congress

Updated Analysis of DESTINY-Gastric02: a Phase 2 Single-Arm Trial of Trastuzumab Deruxtecan (T-DXd) in Western Patients with HER2-Positive Unresectable/Metastatic Gastric/Gastroesophageal Junction (GEJ) Cancer Who Progressed on or After Trastuzumab-Containing Regimen

Presentation 1205MO

Geoffrey Ku,[a] Maria di Bartolomeo, Elizabeth Smyth, Ian Chau, Haeseong Park, Salvatore Siena, Sara Lonardi, Zev A. Wainberg, Jaffer Ajani, Joseph Chao, Ferdous Barlaskar, Yoshinori Kawaguchi, Amy Qin, Jasmeet Singh, Aashima Puri, Gerold Meinhardt, Eric Van Cutsem

On behalf of the DESTINY-Gastric02 investigators

[a]Memorial Sloan Kettering Cancer Center, New York, NY, USA

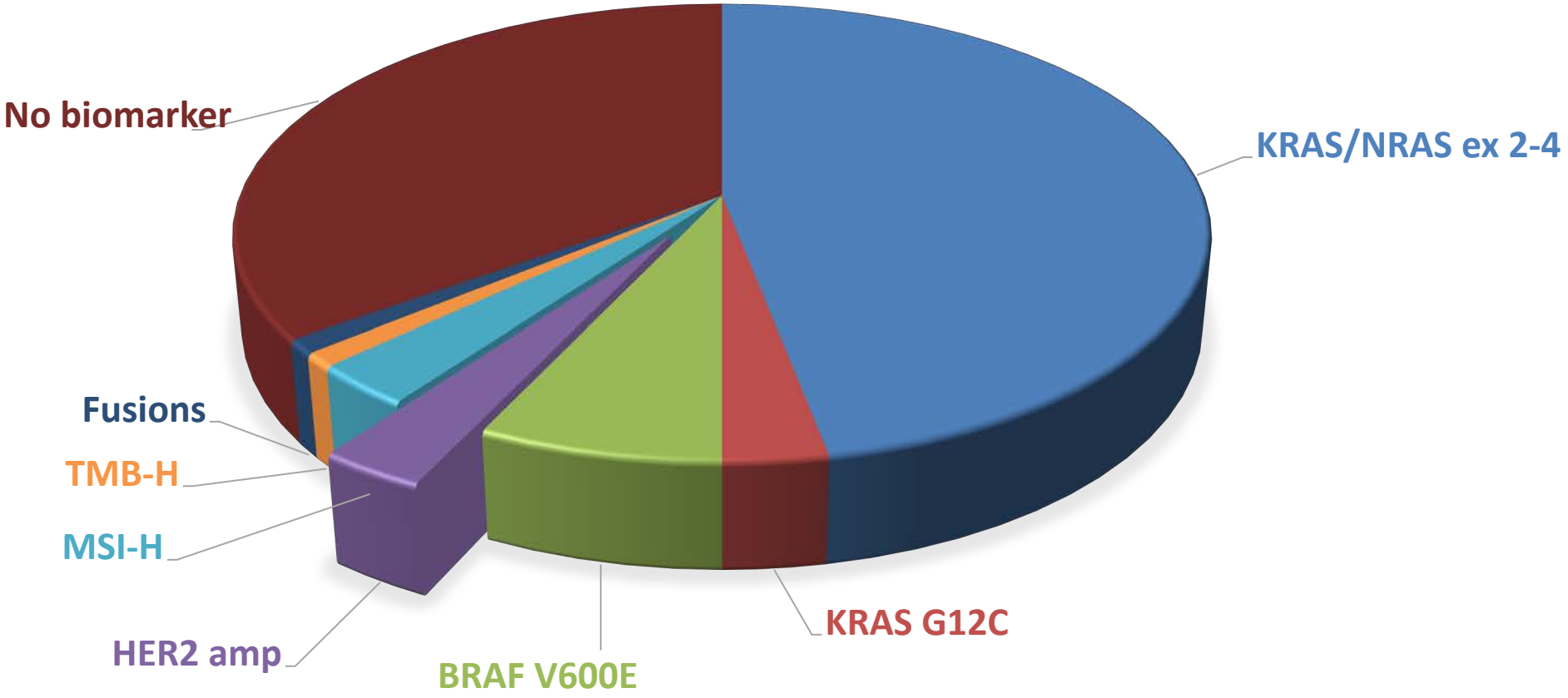
Paris, France, September 9-13, 2022

DESTINY-Gastric02 Primary Endpoint: Objective Response Rate (ORR)

Response Assessment by ICR	April 9, 2021 Data Cutoff[a] Patients (N = 79)	November 8, 2021 Data Cutoff[b] Patients (N = 79)
Confirmed ORR,[c] % (n)	**38.0** (30) (95% CI, 27.3-49.6)	**41.8** (33) (95% CI, 30.8-53.4)
Confirmed best overall response, % (n)		
CR	**3.8** (3)	**5.1** (4)
PR	**34.2** (27)	**36.7** (29)
SD	**43.0** (34)	**39.2** (31)
PD	**16.5** (13)	**16.5** (13)
Not evaluable	**2.5** (2)	**2.5** (2)
Confirmed DCR,[d] % (n)	**81.0** (64) (95% CI, 70.6-89.0)	**81.0** (64) (95% CI, 70.6-89.0)
Median DoR, months	8.1 (95% CI, 4.1-NE)	8.1 (95% CI, 5.9-NE)[e]
Median TTR, months	1.4 (95% CI, 1.4-2.6)	1.4 (95% CI, 1.4-2.7)

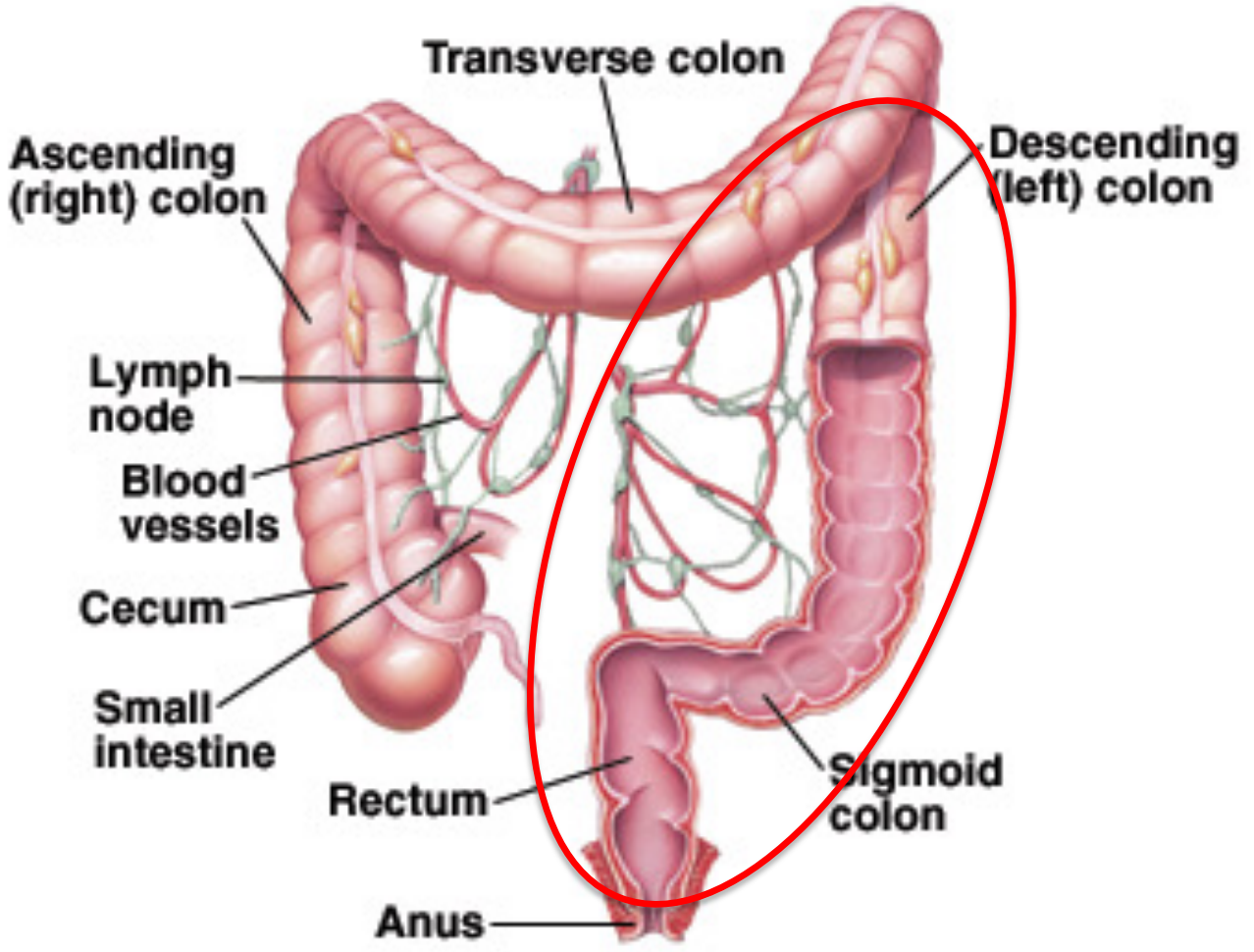
Median OS at November 8, 2021 data cutoff = 12.1 mo; median PFS = 5.6 mo

Actionable colorectal cancer targets in 2022



HER2 in Metastatic CRC

- Usually left sided
- Distinctive pattern of metastatic disease
- Not mutually exclusive with *RAS* or *BRAF* mutations
- Not associated with worse prognosis
- Associated with EGFR resistance



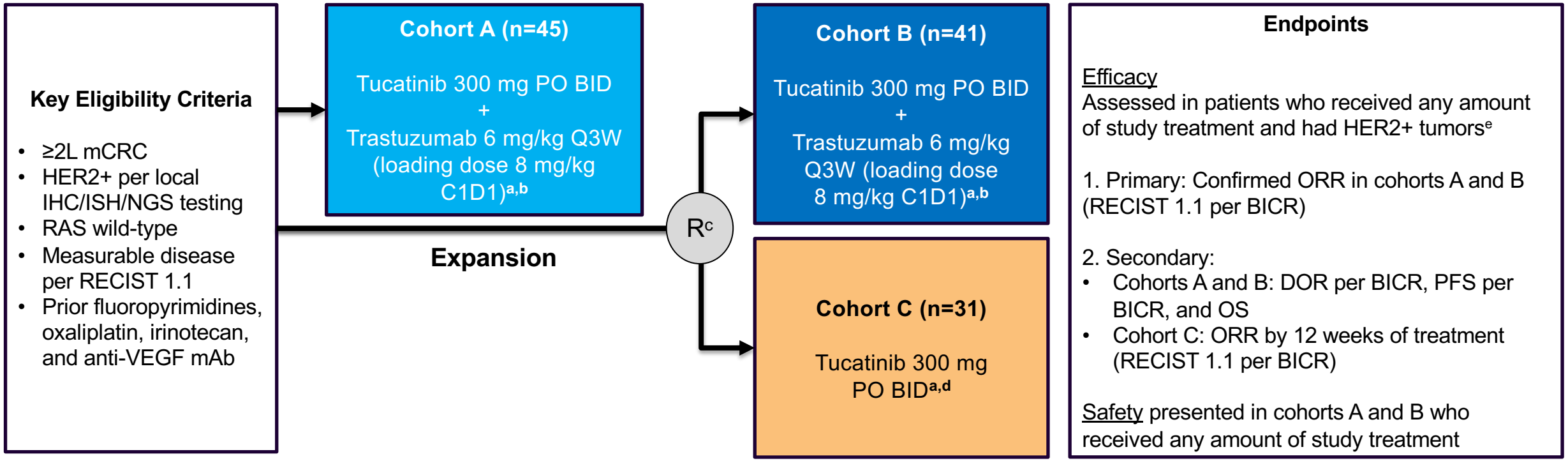
Results of dual anti-HER2 clinical trials in patients with treatment refractory HER2+ metastatic CRC

Clinical trial	Therapies	Patients (N)	Response Rate	PFS (median)
HERACLES	Lapatinib + Trastuzumab	27	28% (Inv)	4.7 months
MyPathway	Pertuzumab + Trastuzumab	68 (RAS WT)	31% (Inv)	5.3 months*
MOUNTAINEER	Tucatinib + Trastuzumab	84	38% (ICR)	8.2 months

* Based on first 43 patients treated, not updated

Sartore-Bianchi et al., *Lancet Oncology* 2016 17, 738-746.
Meric-Bernstam et al., *Lancet Oncol* Vol20, Issue 4, April 2019, 518-530.
Meric-Bernstam et al., J Clin Oncol 39, 2021 (suppl 15; abstr 3004)
Strickler et al., ESMO World GI 2022 - presentation

MOUNTAINEER: Global, Open-Label Phase II Trial



MOUNTAINEER began as a US investigator-sponsored trial and initially consisted of a single cohort (cohort A) and was expanded globally to include patients randomly assigned to receive tucatinib + trastuzumab (cohort B) or tucatinib monotherapy (cohort C)

Data cut-off for current analysis, March 28, 2022

a. Each treatment cycle is 21 days; b. Patients remained on therapy until evidence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or study closure; c. Stratification: Left sided tumor primary vs other; d. Patients were allowed to cross over and receive tucatinib and trastuzumab if they experienced radiographic progression at any time point or if they had not achieved a PR or CR by week 12; e. Patients had HER2+ tumors as defined by one or more protocol required local tests: IHC 3+ (n=46), amplification by ISH (n=36), or amplification by NGS (n=69)

2L+, second line and later; BICR, blinded independent central review; BID, twice a day; C1D1, cycle 1 day 1; CR, complete response; DOR, duration of response; HER2, human epidermal growth receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; PR, partial response; R, randomisation; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; US, United States; VEGF, vascular endothelial growth factor.

https://clinicaltrials.gov/ct2/show/NCT03043313

Strickler JH et al. ESMO GI 2022;Abstract LBA2.

Tucatinib + Trastuzumab: Efficacy Outcomes

Responses	Tucatinib + Trastuzumab Cohorts A+B n=84
Best overall response per BICR[a], n (%)	
CR	3 (3.6)
PR	29 (34.5)
SD[b]	28 (33.3)
PD	22 (26.2)
Not available[c]	2 (2.4)
cORR per BICR, % (95% CI)[d]	**38.1 (27.7, 49.3)**
cORR per Investigator, % (95% CI)[d]	42.9 (32.1, 54.1)
Median time to objective response per BICR[e], months (range)	2.1 (1.2, 9.8)
DCR[f] per BICR, n (%)	60 (71.4)
Median DOR per BICR, months (95% CI)	**12.4 (8.5, 20.5)**

a. Confirmed best overall response assessed per RECIST 1.1; b. Includes SD and non-CR/non-PD; c. Includes patients with no post-baseline response assessment and patients whose disease assessments are not evaluable; d. Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934); e. Time from the start of study treatment (Cohort A) or date of randomisation (Cohort B) to the first documentation of objective response (CR or PR that is subsequently confirmed); f. Defined as sum of CR, PR, and SD

BICR, blinded independent central review; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

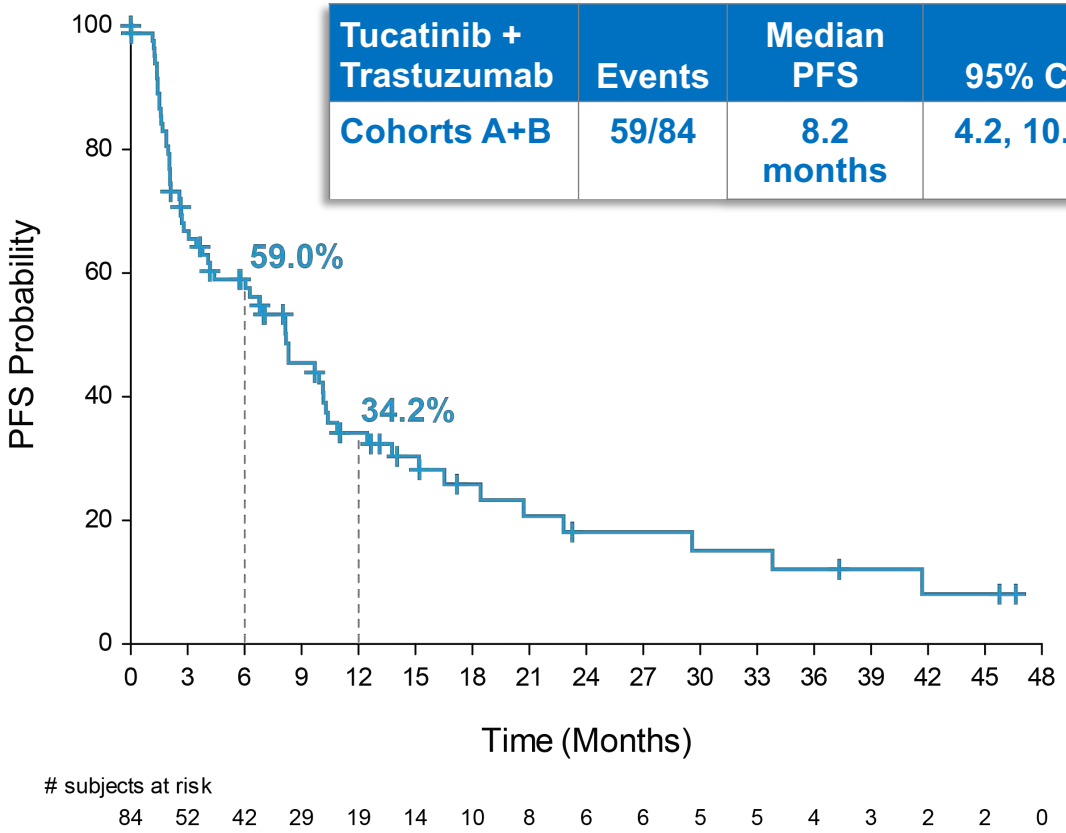
Data cutoff: 28 Mar 2022

Strickler JH et al. ESMO GI 2022;Abstract LBA2.

Tucatinib + Trastuzumab: PFS and OS

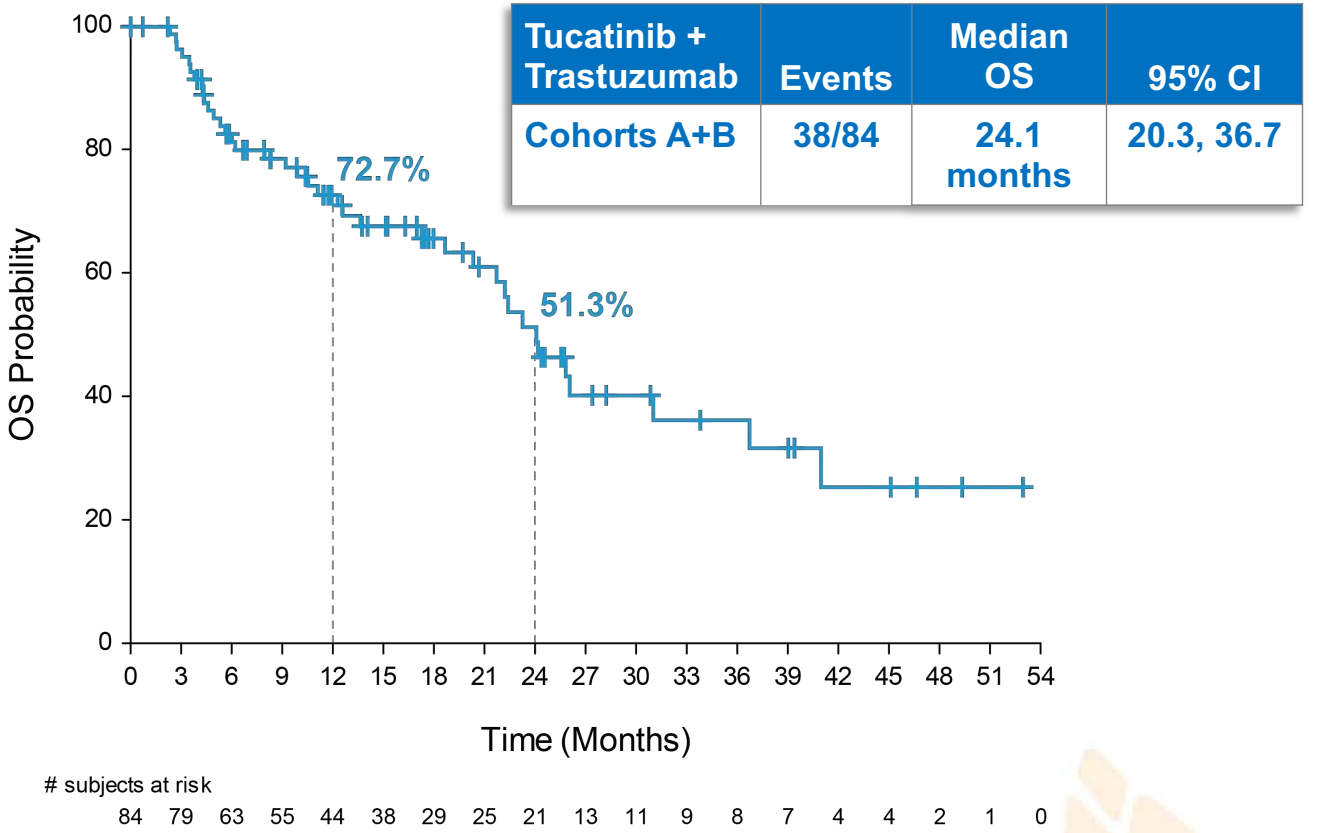
Progression-Free Survival per BICR

Tucatinib + Trastuzumab	Events	Median PFS	95% CI
Cohorts A+B	59/84	8.2 months	4.2, 10.3



Overall Survival

Tucatinib + Trastuzumab	Events	Median OS	95% CI
Cohorts A+B	38/84	24.1 months	20.3, 36.7



Median follow-up for Cohorts A+B was 20.7 months (IQR, 11.7, 39.0)

BICR, blinded independent central review; IQR, interquartile range; OS, overall survival; PFS, progressive-free survival.

Data cutoff: 28 Mar 2022

Strickler JH et al. ESMO GI 2022;Abstract LBA2.

Adverse Events of Special Interest with Tucatinib + Trastuzumab

- Diarrhea
  - Most common TEAE: Grade 1, 50.0%; Grade 2, 10.5%; Grade 3, 3.5%
    - No treatment discontinuations due to diarrhea
    - Tucatinib dose modifications for diarrhea: dose reduction, 2.3%; dose hold, 3.5%
  - Antidiarrheal prophylaxis was not mandated

- Hepatotoxicity
  - Grade ≥3: increased ALT (3.5%), increased AST (2.3%), and hypertransaminasemia (1.2%)
  - Hepatotoxicity leading to tucatinib modification or discontinuation occurred in 5.8%
  - No Hy's law cases identified

- Cardiotoxicity
  - Asymptomatic LVEF decrease leading to dose modification or discontinuation occurred in 3.5%

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LVEF, left ventricular ejection fraction; TEAE, treatment-emergent adverse event.
Data cutoff: 28 Mar 2022

Strickler JH et al. ESMO GI 2022;Abstract LBA2.

DESTINY-CRC-01: Trastuzumab deruxtecan (T-DXd; ds8201a) for HER2+ mCRC - Phase 2 study design

Key Eligibility Criteria (n=86)[2]

≥2L+ mCRC

HER2+ per **central confirmation**

RAS/BRAF wild type Prior anti-HER2 allowed

All patients received trastuzumab deruxtecan 6.4mg/kg IV Q3 weeks

NCT03384940

Cohort A
HER2 Positive – IHC3+ or IHC2+/ISH+ (n=53)

ORR= 45%
PFS= 6.9 m

Cohort B
HER2 IHC2+/ISH- (n=15)[2]

ORR= 0% [2]
PFS= 2.1m

Cohort C
HER2 IHC 1+ (n=18)

ORR= 0% [2]
PFS= 1.4m

At data cutoff (Dec 28, 2020)

Primary Endpoint:

- Confirmed ORR (RECIST v1.1 by BICR)

Secondary Endpoints:

- DOR
- DCR
- PFS
- OS
- ORR in cohorts B and C (RECIST 1.1 by BICR)

- T-DXd is an antibody drug conjugate with a humanized anti-HER2 IgG1 mAb similar to trastuzumab[1]
- Topoisomerase I inhibitor payload[1]
- High payload-to-antibody ratio (8:1)[3]

BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; HER2+, HER2 gene amplification; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

1. Siena et al., Lancet Oncol 2021; 2. Yoshino T et al., JCO.2021; 3. Nakada T et al., Chem Pharm Bull (Tokyo). 2019

DESTINY-CRC-01: Trastuzumab deruxtecan for HER2+ mCRC - Most common TEAEs (≥10%)

(All cohorts, N=78)

	Grade 1-2	Grade 3	Grade 4	Grade 5
Nausea	42 (54%)	5 (6%)	0	0
Decreased appetite	26 (33%)	0	0	0
Fatigue	25 (32%)	1 (1%)	0	0
Vomiting	22 (28%)	1 (1%)	0	0
Diarrhoea	21 (27%)	1 (1%)	0	0
Anaemia	18 (23%)	10 (13%)	1 (1%)	0
Platelet count decreased	16 (21%)	5 (6%)	2 (3%)	0
Alopecia	15 (19%)	0	0	0
Constipation	11 (14%)	0	0	0
Asthenia	10 (13%)	0	0	0
Neutrophil count decreased	9 (12%)	12 (15%)	5 (6%)	0
Cough	9 (12%)	0	0	0
Oedema peripheral	9 /12%)	0	0	0
Pyrexia	9 (12%)	0	0	0
Hypokalaemia	8 (10%)	4 (5%)	1 (1%)	0

- Five (6%) of 78 patients had interstitial lung disease or pneumonitis
  - Grade 2 = 2 patients
  - Grade 3 = 1 patient
  - Grade 5 = 2 patients
- Median time to onset date of interstitial lung disease or pneumonitis was 77 days
- 2 recovered, 1 did not recover and died of disease progression, and 2 died due to the AE

AE, adverse event; HER2+, HER2 gene amplification; mCRC, metastatic colorectal cancer; TEAE, treatment-emergent adverse event.

Siena et al., Lancet Oncol 2021.

HER2 in GI cancers: Final thoughts

- For HER2+ metastatic gastric/ GEJ adenoca
  - 1L SOC: FOLFOX+trastuzumab+pembro
  - 2nd/3rd line: Trastuzumab deruxtecan (consider repeat biopsy to confirm HER2+)

- For RAS wild-type HER2+ metastatic CRC
  - *HER2* amp associated with resistance to anti-EGFR therapies
  - Lapatinib + trastuzumab, pertuzumab + trastuzumab, and trastuzumab deruxtecan in NCCN guidelines after 1L chemotherapy
  - Tucatinib + trastuzumab has high ORR and DoR with favorable tolerability – may become a new SOC option
  - Trastuzumab deruxtecan retains activity after progression on prior anti-HER2 therapies

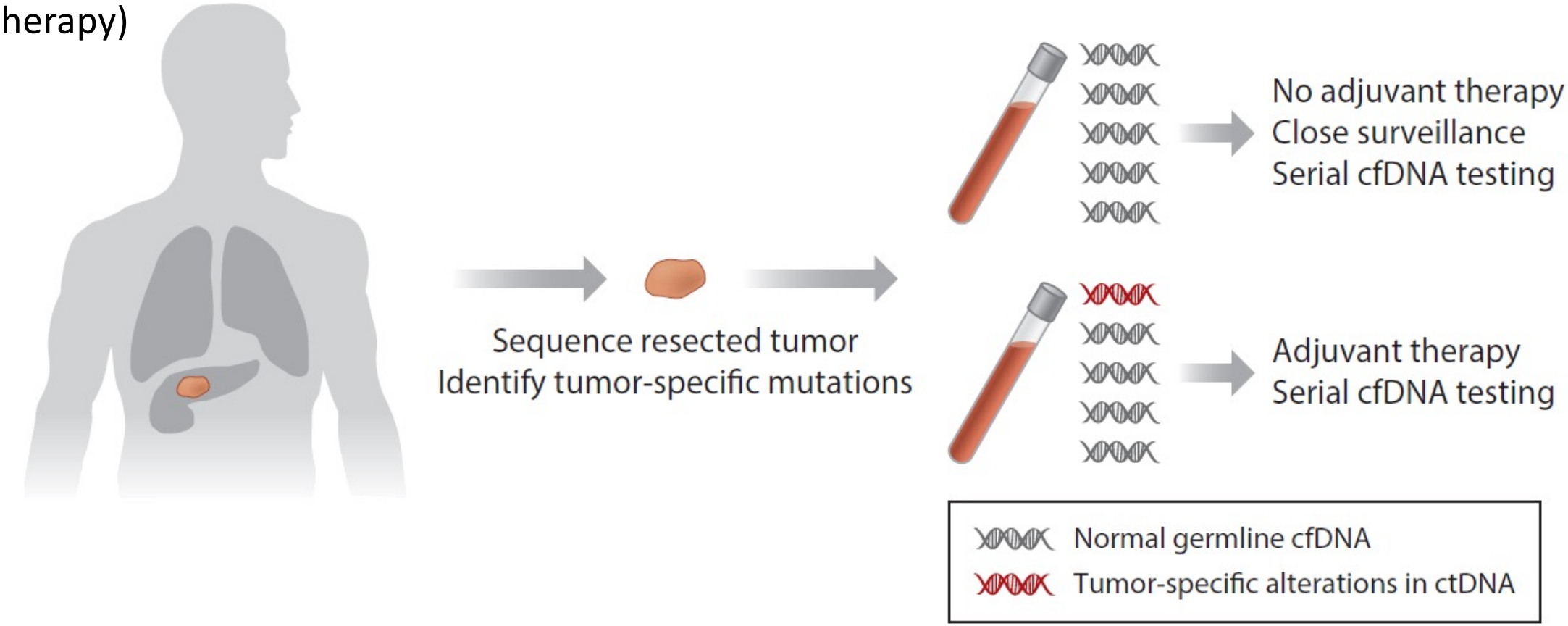
MRD TESTING FOR COLORECTAL CANCER

John Strickler, MD
Duke University
October 22, 2022

Can we integrate MRD into clinical care?

Potential applications:

- Selecting high risk patients for aggressive therapy when post-operative observation is SOC
- Spare patients chemotherapy/treatment if no residual disease (when SOC calls for additional therapy)



Morris and Strickler, Annu Rev Med. 2021. 72:399–413.

Stage I-III colon ca: Recurrence risk impacted by ctDNA status (tumor informed assay)

Relapse free survival

218 pts with stage I-III colon ca, monitored with Signatera assay

	Post-op ctDNA status	After end of adjuvant chemotherapy	Longitudinal monitoring (Q3 months for 3 yrs)
ctDNA positive	20%	17%	11%
ctDNA negative	87%	88%	97%

Henriksen et al., J Clin Oncol 39, 2021 (suppl 3; abstr 11)

GALAXY : Observational cohort from the CIRCULATE-Japan study

- CIRCULATE-Japan enrolled patients with resectable CRC (all stages) to evaluate the clinical utility of ctDNA MRD analysis
- CIRCULATE-Japan consists of 3 studies:
  - Observational cohort: GALAXY study
  - 2 randomized phase III trials (VEGA and ALTAIR trials)
- Blood samples are collected before surgery and 4, 12, 24, 36, 48, 72, and 96 weeks after surgery
- 1,564 patients enrolled in CIRCULATE-Japan
- 1,040 patients included in the GALAXY study
  - Median follow up time: 11.4 months
  - Data cutoff: 11/9/2021

Kotaka et. al., *Journal of Clinical Oncology* 40, no. 4_suppl (February 01, 2022) 9-9.

ctDNA detection at a single post-operative timepoint (4 weeks post op) is associated with poor prognosis

Disease free survival: Post-op-4w ctDNA status

712 pts with stage II-III colon ca, monitored with Signatera assay

ctDNA	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
Negative	22/597	97.8% (96.3-98.7)	95.2% (92.6–96.9)
Positive	46/115	73.0% (63.9-80.2)	55.5% (44.8-65.0)

HR = 13.3
95% CI, 8.0 to 22.2, P<0.001

Sensitivity for recurrence= 68%

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

Kotaka et. al., *Journal of Clinical Oncology* 40, no. 4_suppl (February 01, 2022) 9-9.

Adjuvant chemotherapy is not associated with improved DFS for patients with negative post-op ctDNA

Disease free survival: Negative post-op-4w ctDNA status

531 pts with high risk stage II/ stage III colon ca receiving adjuvant chemotherapy, monitored with Signatera assay

ctDNA	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	7/214	98.6% (95.7-99.5)	96.2% (92.1–98.2)
W/O ACT	12/317	97.5% (95.0-98.7)	94.7% (90.5–97.1)

Adjusted HR = 1.3
95% CI, 0.5 to 3.6, P=0.63

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

Kotaka et. al., *Journal of Clinical Oncology* 40, no. 4_suppl (February 01, 2022) 9-9.

DYNAMIC Study Design

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

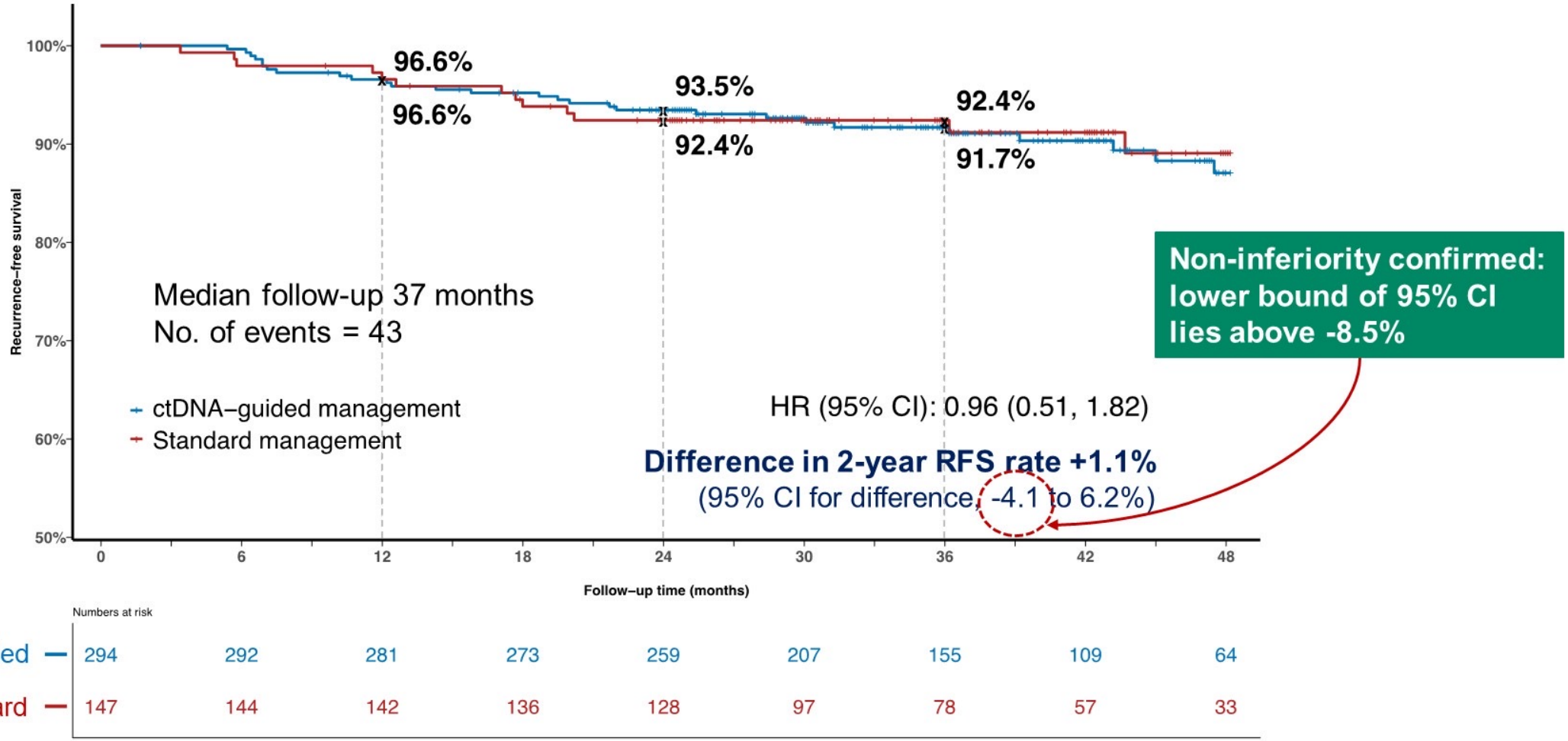
Tie et al., Presented at 2022 ASCO Annual Meeting

DYNAMIC: Adjuvant chemotherapy given less in the ctDNA-guided management group

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

Tie et al., Presented at 2022 ASCO Annual Meeting

DYNAMIC: RFS identical despite lower use of adjuvant chemotherapy for ctDNA guided management



Tie et al., Presented at 2022 ASCO Annual Meeting

MRD testing to guide patient management- Final thoughts

- MRD testing is a validated prognostic tool
  - Particularly valuable for patients with stage II disease
  - May have utility in patients with stage III disease
  - Other use cases (stage IV s/p resection, elevated CEA, etc)

- Rapid uptake in the clinic (ahead of the evidence) indicates that clinicians see an unmet need in CRC survivorship

- Prospective trials are ongoing to explore clinical utility of MRD testing… this is an area of rapid change

Gastrointestinal Cancers Agenda

MODULE 1: Immunotherapy for Gastroesophageal Cancers; PARP Inhibitors in Pancreatic Cancer

MODULE 2: HER2-Positive Gastroesophageal and Colorectal Cancer; Role of Circulating Tumor DNA/Minimal Residual Disease in Colorectal Cancer

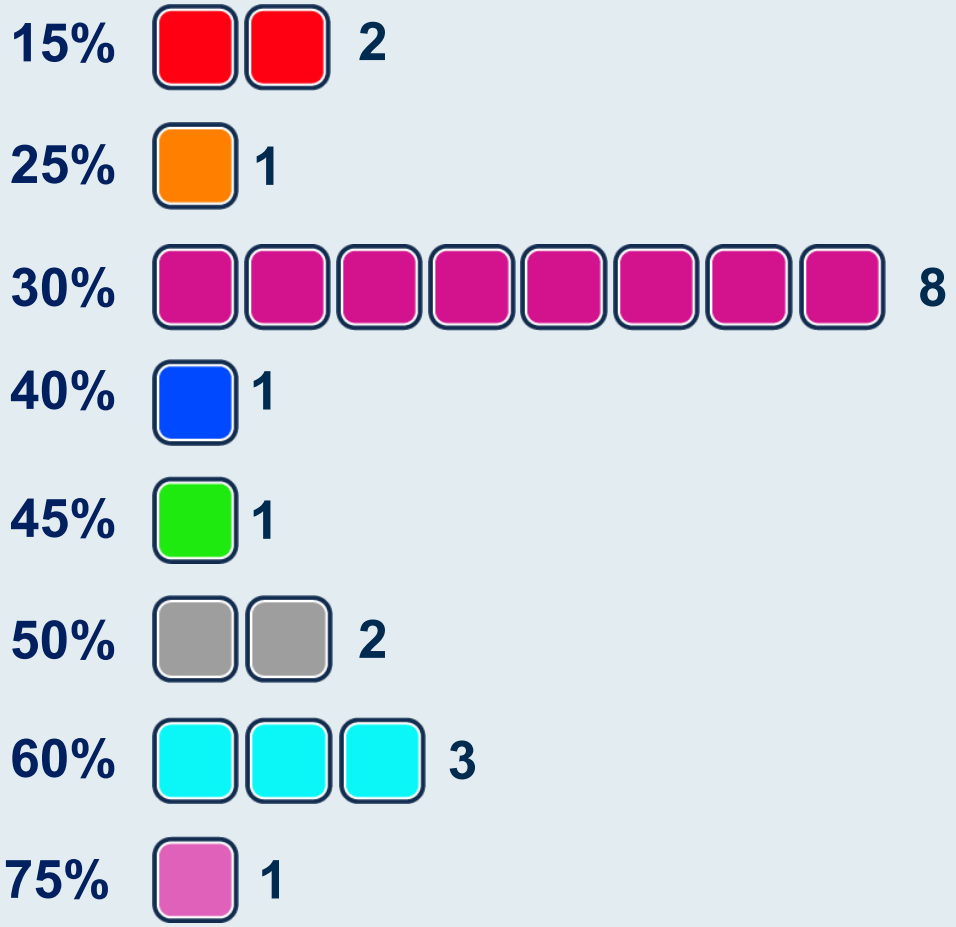
MODULE 3: Colorectal Cancer in Younger Patients; Tumor Microbiome

MODULE 4: Neoadjuvant Therapy for Microsatellite Instability-High Gastroesophageal and Colorectal Cancer

MODULE 5: Novel Agents in Pancreatic Cancer

RTP RESEARCH TO PRACTICE

In your practice, approximately what proportion of new patients whom you evaluate with colorectal cancer (CRC) are under the age of 50?



Median: 30%
Range: 15%-75%

Survey of US-based clinical investigators

What is your primary hypothesis for the increased incidence of CRC in younger patients in recent years?

- Western lifestyle
- Multifocal etiology
- Lifestyle primarily and potential effect on microbiome
- Increasing obesity, change in diet/lifestyle exposures
- Combination of genetic and environmental/lifestyle factors
- Microbiome
- Diet
- Environmental exposure to carcinogens. Patients require screening at a younger age
- Environmental and lifestyle (obesity/diet) microbiome
- Better screening and recognition. True increased incidence secondary to dietary risk factors
- Microbiome changes

Gastrointestinal Cancers Agenda

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RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 23, 2022 VOL. 386 NO. 25

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A
K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J.
M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz,

2022 ASCO ANNUAL MEETING

Abstract LBA5.

Late breaking abstract

PD-1 blockade as curative-intent therapy in mismatch repair deficient locally advanced rectal cancer

Andrea Cercek, MD
Head, Colorectal Cancer Section
Co-Director Center for Young Onset Colorectal and Gastrointestinal Cancers
Memorial Sloan Kettering Cancer Center

ASCO Gastrointestinal Cancers Symposium

GERCOR

Neo-adjuvant nivolumab plus ipilimumab and adjuvant nivolumab in patients (pts) with localized MSI/dMMR gastric or oeso-gastric junction (G-OGJ) adenocarcinoma NEONIPIGA phase II GERCOR study

T André,[1] D Tougeron, G Piessen, C de la Fouchardière, C Louvet, A Adenis, M Jary, C Tournigand, T Aparicio, J Desrame, A Lièvre, ML Garcia-Larnicol, T Pudlarz, J Henriques, R Cohen, J Lefèvre, M Svrcek

[1]Sorbonne University, Saint-Antoine Hospital, Department of Medical Oncology, Paris, France

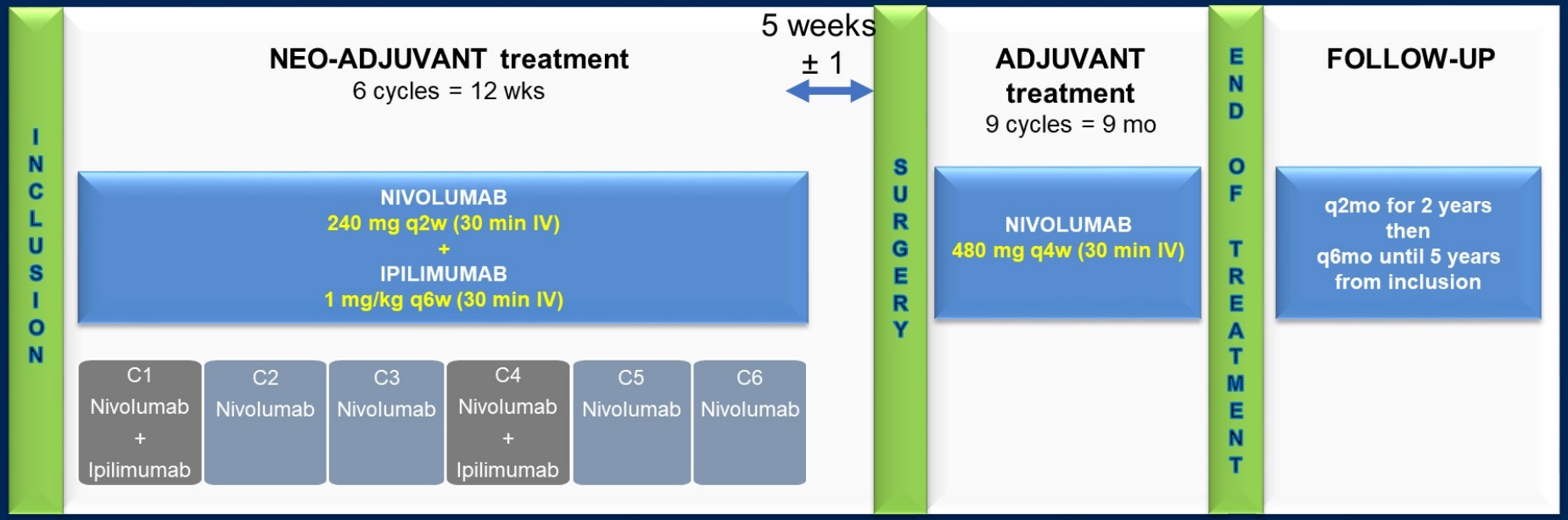
Gastrointestinal Cancers Symposium 2022;Abstract 244.

RTP RESEARCH TO PRACTICE

NEONIPIGA Design

NEONIPIGA: Study design/methods

- Phase II study evaluating efficacy of neo-adjuvant nivolumab and ipilimumab followed by adjuvant nivolumab in pts with resectable OGA MSI/dMMR, T2-T4 NxM0
- The primary objective was pathological complete response rate (pCRR).



ClinicalTrials.gov: NCT04006262

OGA = oeso-gastric adenocarcinoma

Andre T et al. Gastrointestinal Cancers Symposium 2022;Abstract 244.

NEONIPIGA Conclusions

Conclusions

- The primary objective with **59% pathological complete Response Rate was met (17/29 pts evaluable for** pCRR**)**
- Neo-adjuvant nivolumab & ipilimumab is feasible in pts with MSI/dMMR resectable OGJ/gastric adenocarcinoma
- No new safety concerns: with 25% of grade 3-4 TRAE (max/pts)
- Surgical complications are as expected with this type of surgeries
- 94% of pts included are free of events with 12 months follow-up
- Neonipiga raises the question whether the surgery can be delayed or avoided for some pts with localized MSI/dMMR G-OGJ adenocarcinoma if immune-check point inhibitors are effective.

Andre T et al. Gastrointestinal Cancers Symposium 2022;Abstract 244.

Gastrointestinal Cancers Agenda

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RTP RESEARCH TO PRACTICE

N Engl J Med 2022;386:2112-9

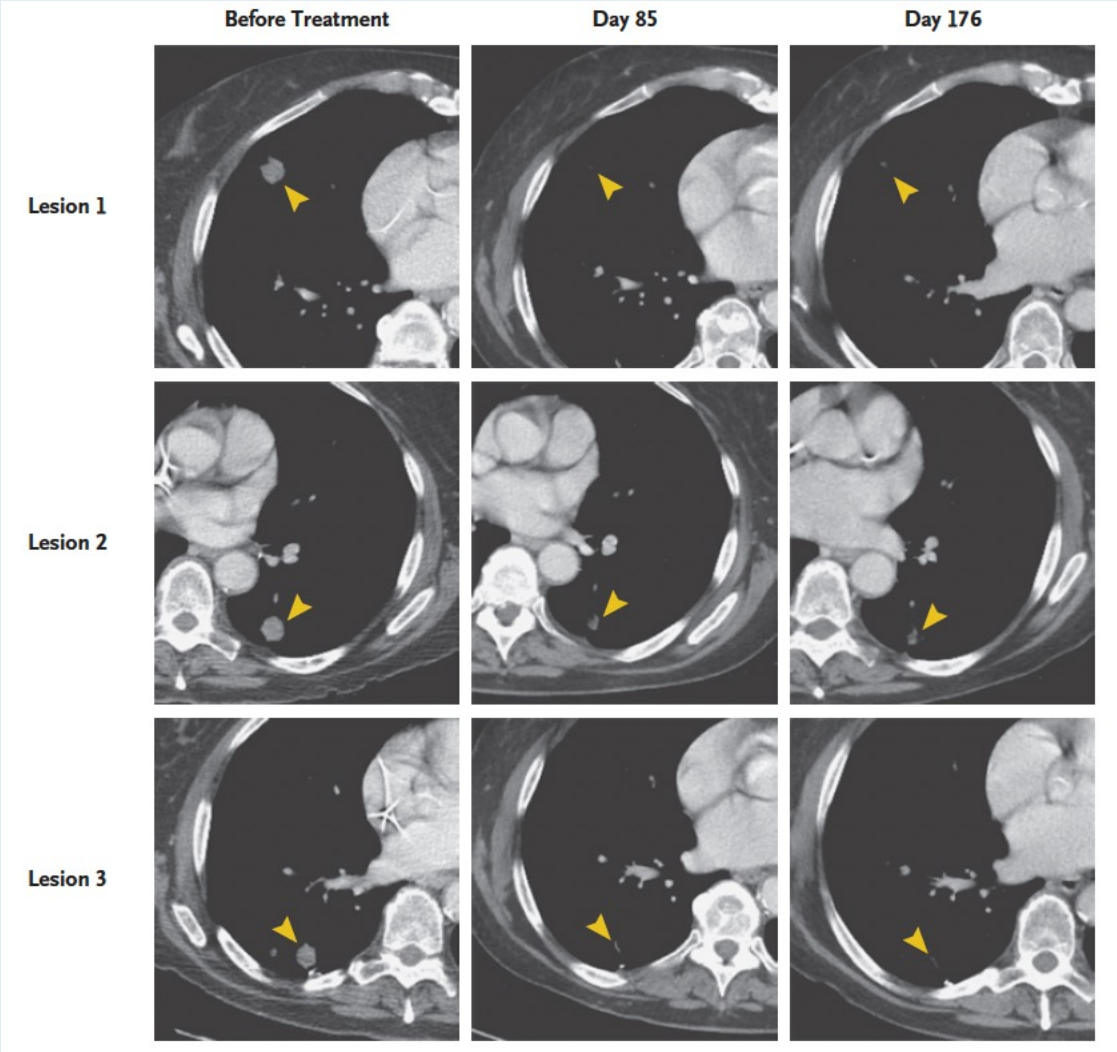
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Neoantigen T-Cell Receptor Gene Therapy in Pancreatic Cancer

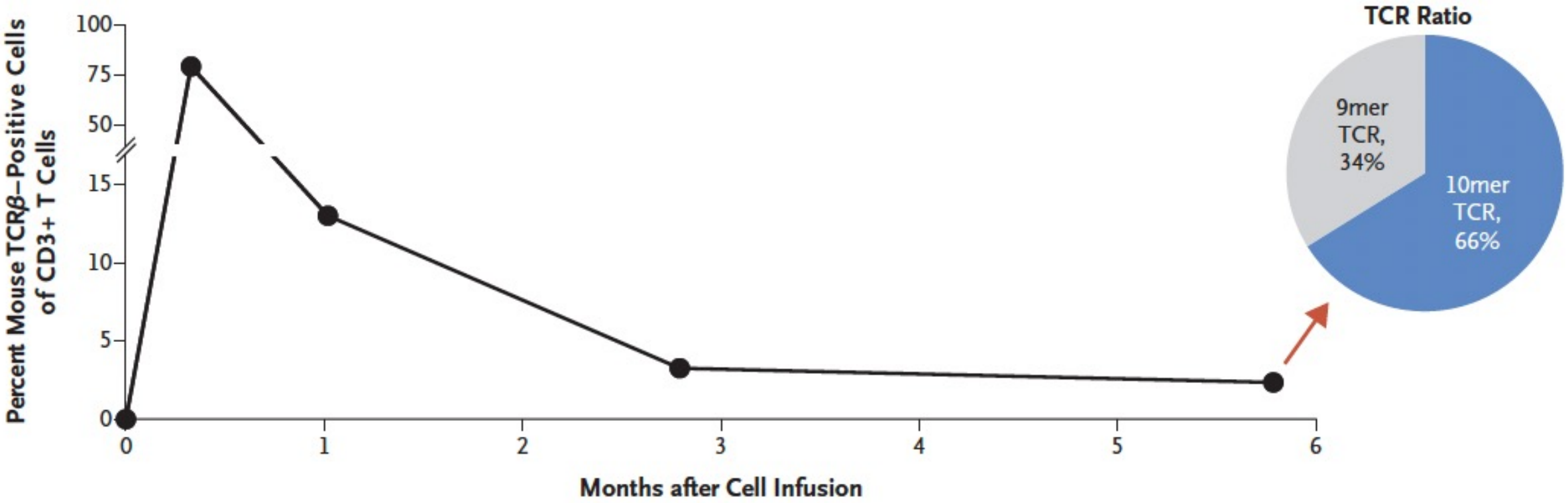
Rom Leidner, M.D., Nelson Sanjuan Silva, B.S., Huayu Huang, M.S., David Sprott, B.S., Chunhong Zheng, Ph.D., Yi-Ping Shih, Ph.D., Amy Leung, B.S., Roxanne Payne, M.N., Kim Sutcliffe, B.S.N., Julie Cramer, M.A., Steven A. Rosenberg, M.D., Ph.D., Bernard A. Fox, Ph.D., Walter J. Urba, M.D., Ph.D., and Eric Tran, Ph.D.

CT Scans of the Patient's Chest Before Infusion and at 85 and 176 Days After the Infusion of 16.2×10^9 T Cells



Leidner R et al. *N Engl J Med* 2022;386:2112-9.

In Vivo Persistence of the Transferred TCR-Engineered T Cells in the Peripheral Blood as Determine by Flow Cytometric Analysis of Mouse TCR-Beta



Leidner R et al. *N Engl J Med* 2022;386:2112-9.

Thank you for joining us!

CME/MOC and NCPD credit information will be emailed to each participant within 5 business days.