Immunotherapy in Gastrointestinal Malignancies

Winter Cancer Symposium

Rio Grande, Puerto Rico

Weill Cornell Medicine/ New York-Presbyterian

March 1-3, 2024

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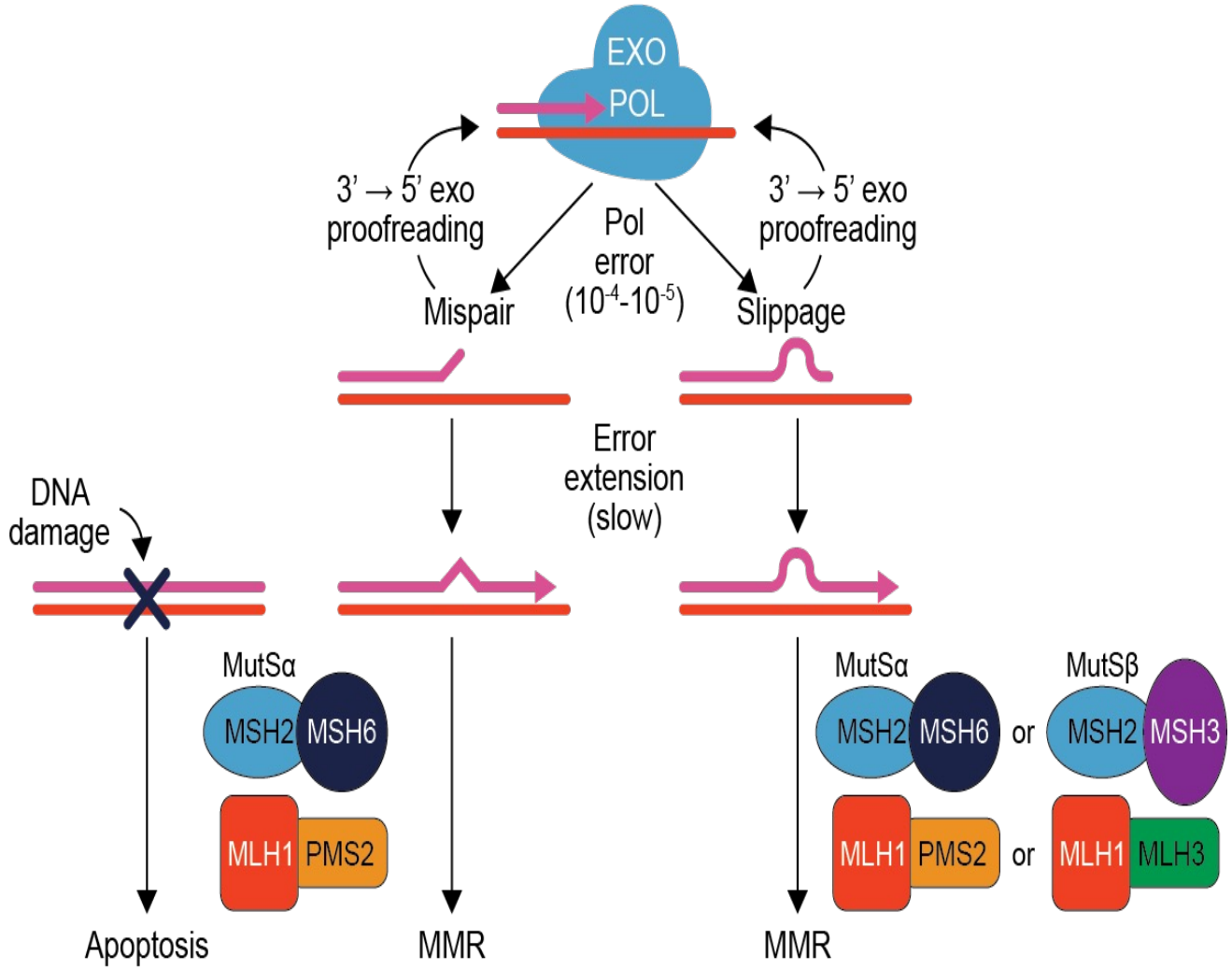
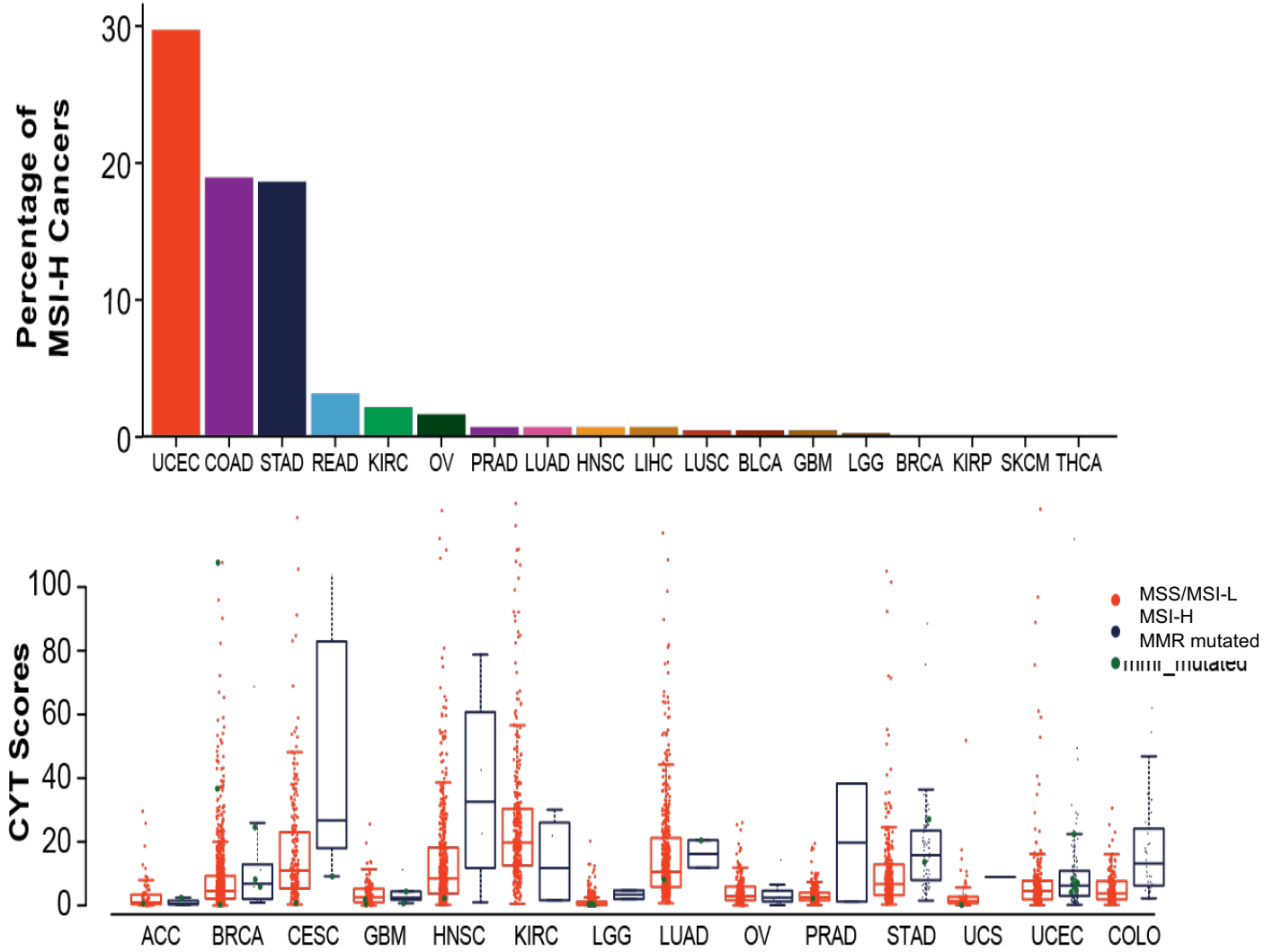
Agenda

- Mismatch Repair
- Rectal cancer
- Localized Colorectal Cancer
- Gastroesophageal Cancer
- Hepatobiliary Cancer
- Immunotherapy toxicity

Mismatch Repair Leads to Very High Mutational Burden



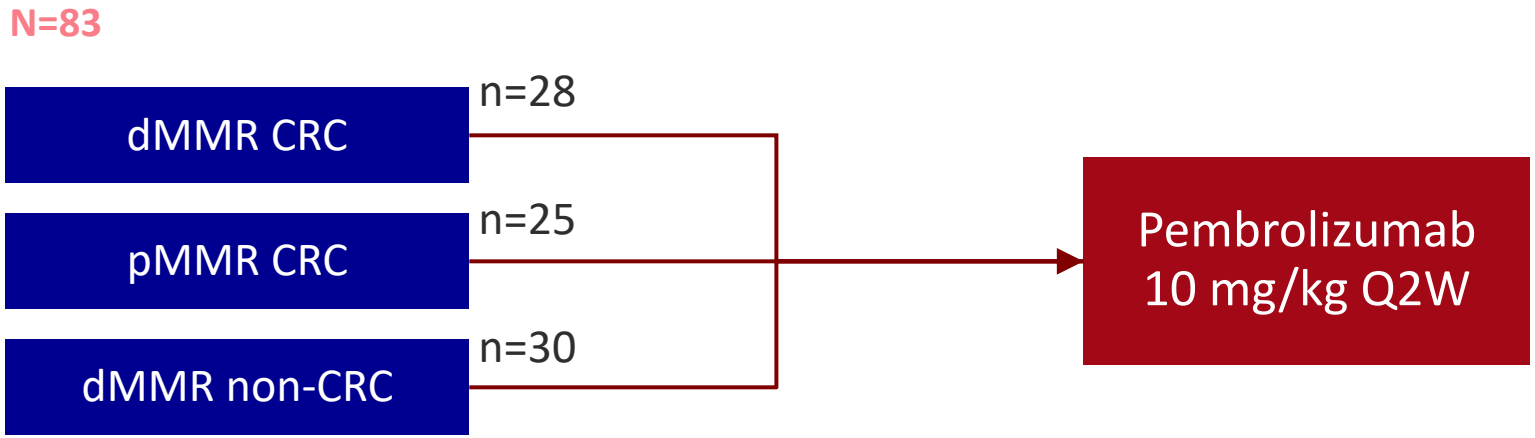
Pan-Cancer Landscape of MMR Deficiency



Hause RJ et al. *Nat Med*. 2016;22:1342-1350.

MIXED-DMMR/MSI-STATUS MCRC[1,2]

Phase II multicenter, open-label trial of pembrolizumab as monotherapy in three different treatment-refractory patient populations

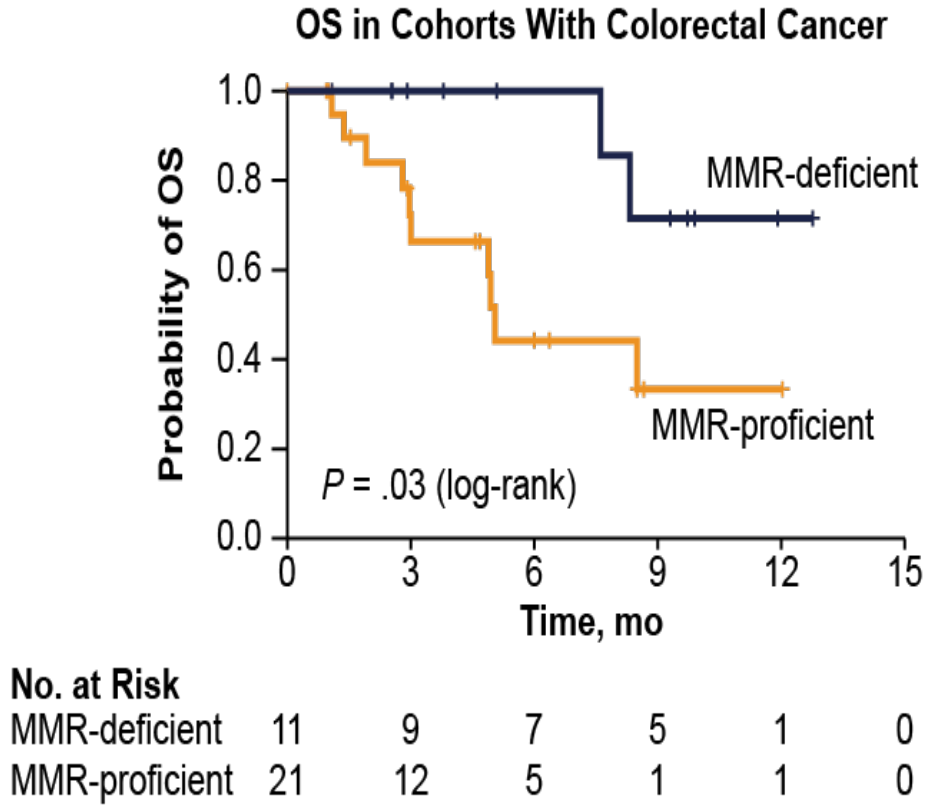


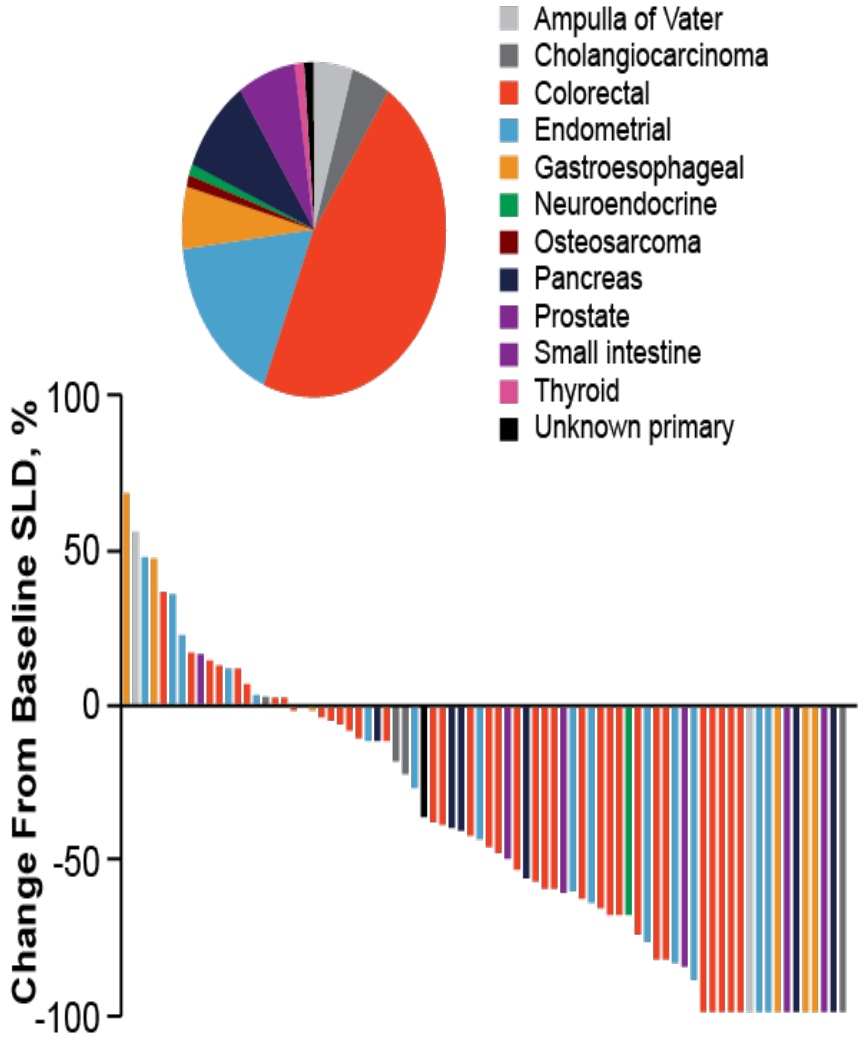
- **Primary Outcome Measures:** irPFS*†, irORR† (using irRC)
- **Secondary Outcome Measures:** OS, irPFS/PFS (using irRC and RECIST 1.1), ORR, IRAEs, MSI and treatment response, markers of MSI status

- dMMR and pMMR CRC groups had received a median of 3 and 4 prior treatment regimens, respectively

1. Clinicaltrials.gov. NCT01876511. 2. Le DT et al. Oral presentation at ASCO 2016. TPS3631.

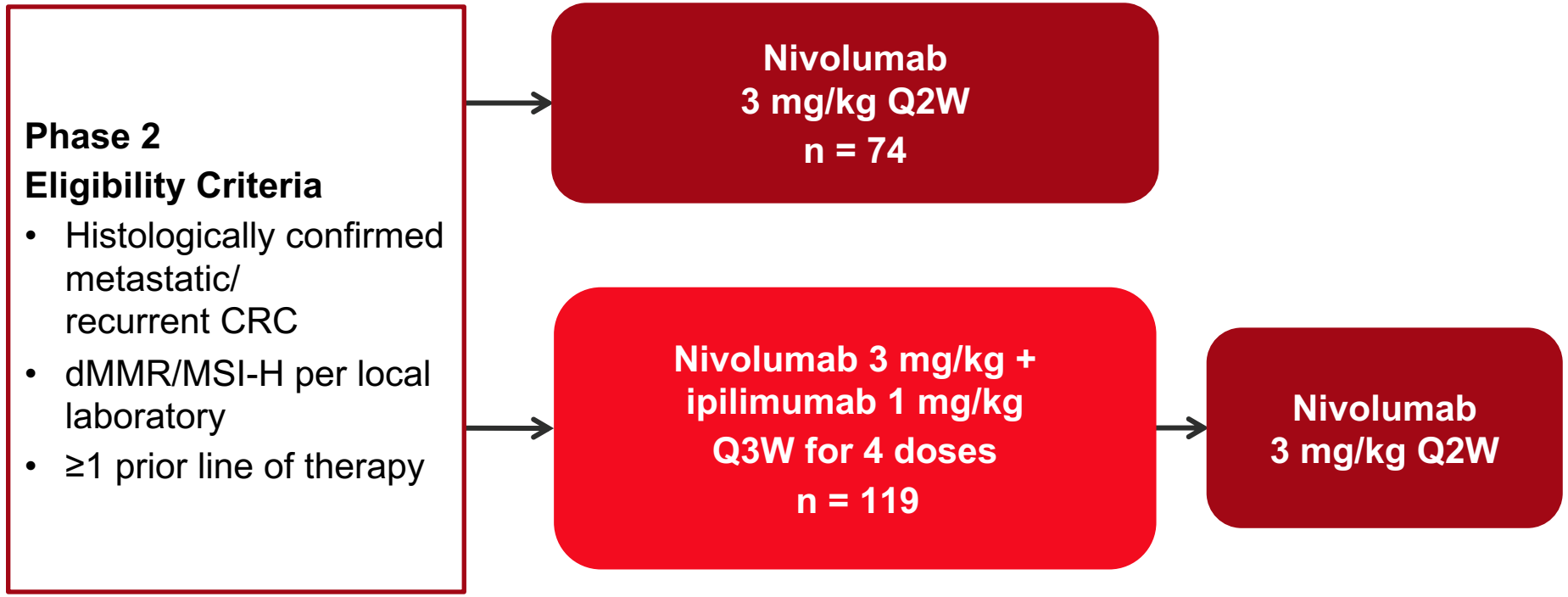
Pan-Cancer Landscape of MMR Deficiency





Le DT et al. *N Engl J Med*. 2015;372:2509-2520.

CheckMate-142: Nivolumab ± Ipilimumab in dMMR/MSI-H CRC



Outcomes

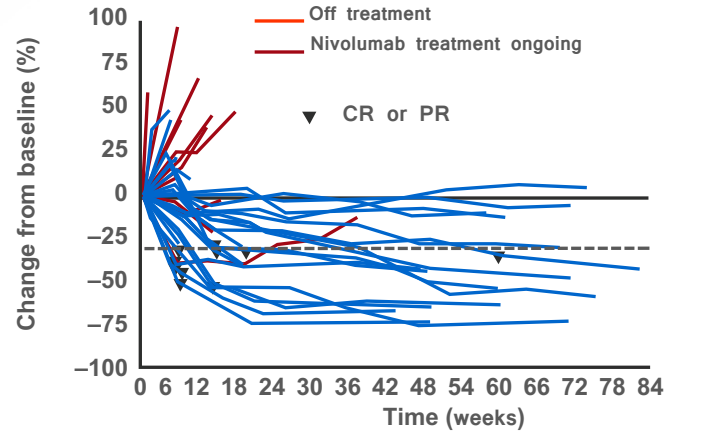
- **Primary**: ORR per investigator assessment
- **Secondary**: ORR per blinded independent central review (BICR), PFS, OS, safety

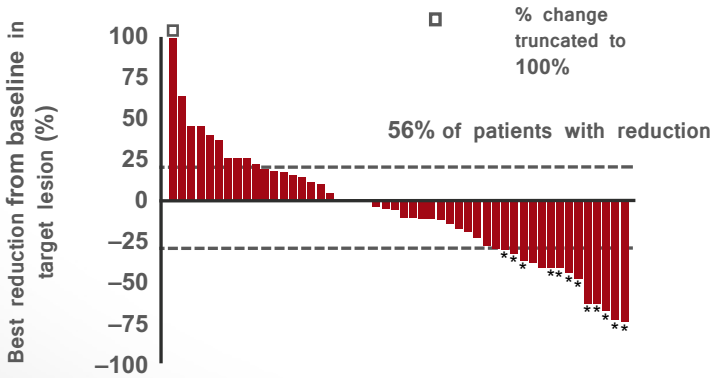
Overman MJ et al. *Lancet Oncol*. 2017;18:1182-1191.
Overman MJ et al. *J Clin Oncol*. 2018;36:773-779.

MSI-high tumours are responsive to PD-1 inhibitors

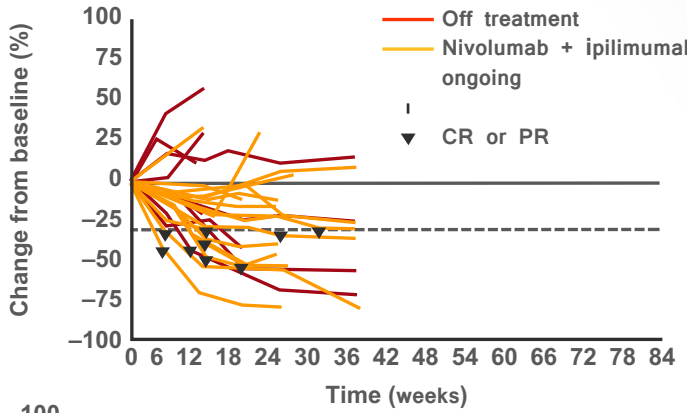
Nivolumab ± ipilimumab (CheckMate-142, phase II)

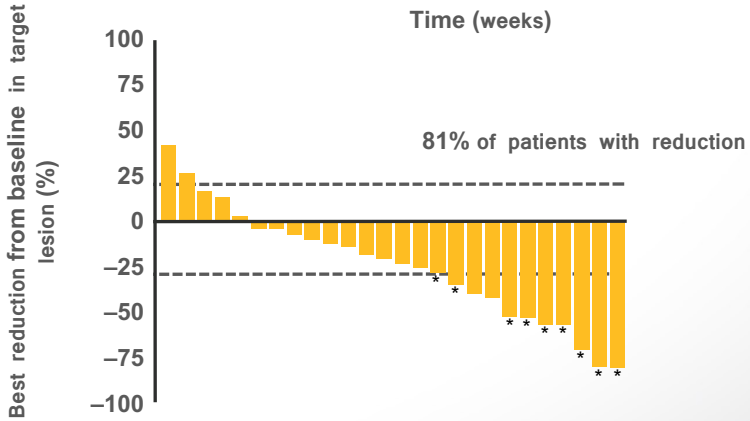
Nivolumab 3mg/kg





Nivolumab 3mg/kg + ipilimumab 1mg/kg



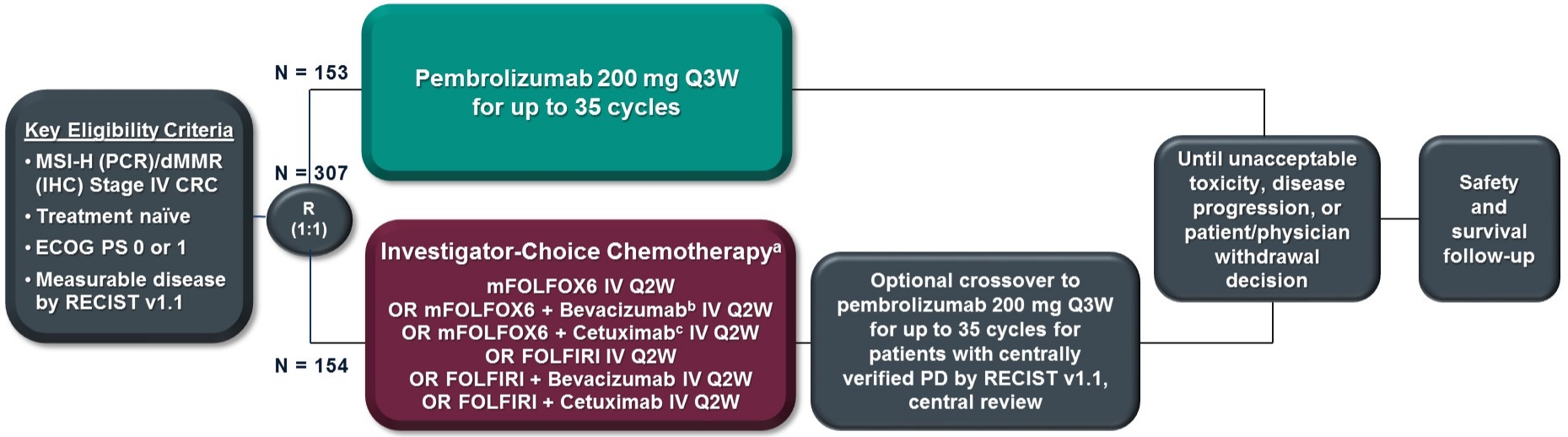


*Lynch Syndrome (yes/no/unknown): MMR-deficient CRC = 54/7/39; MMR-proficient CRC = 0/100/0

Lenz. JCO. 2022;40:161.

Keynote-177:
Pembrolizumab vs Chemotherapy in 1L Treatment

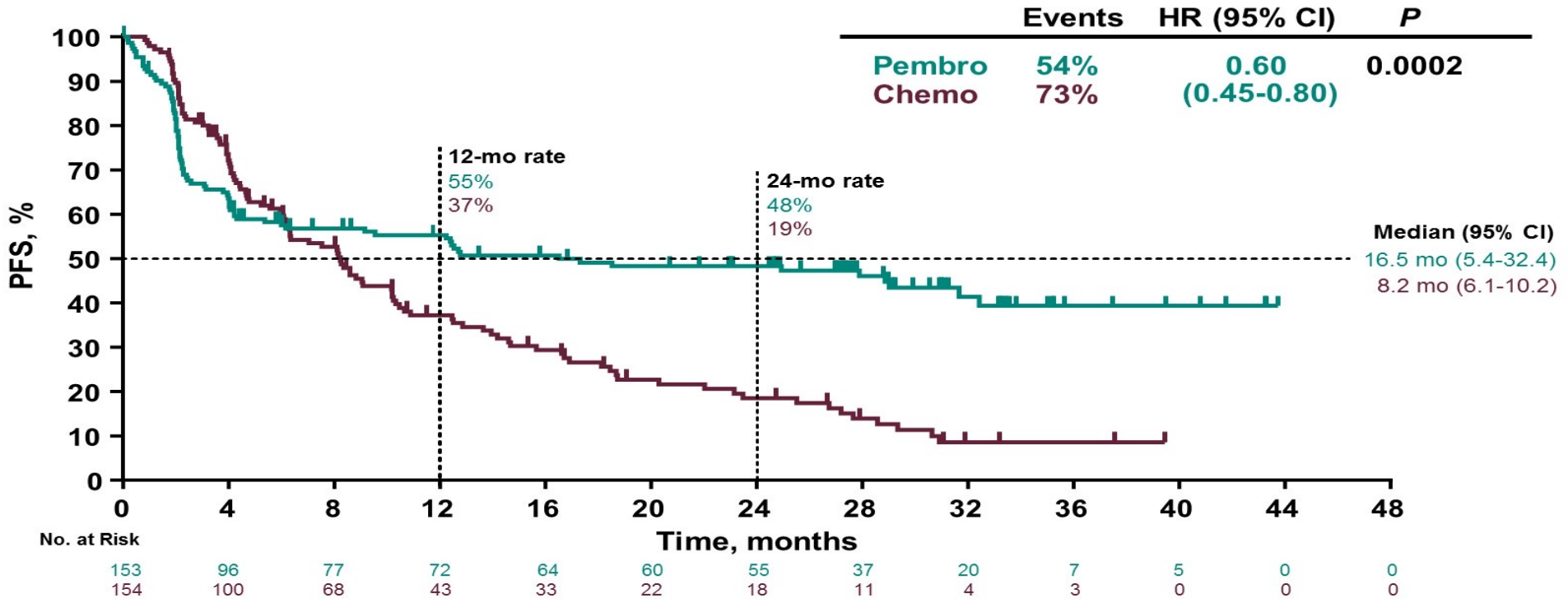
KEYNOTE-177 Study Design (NCT02563002)



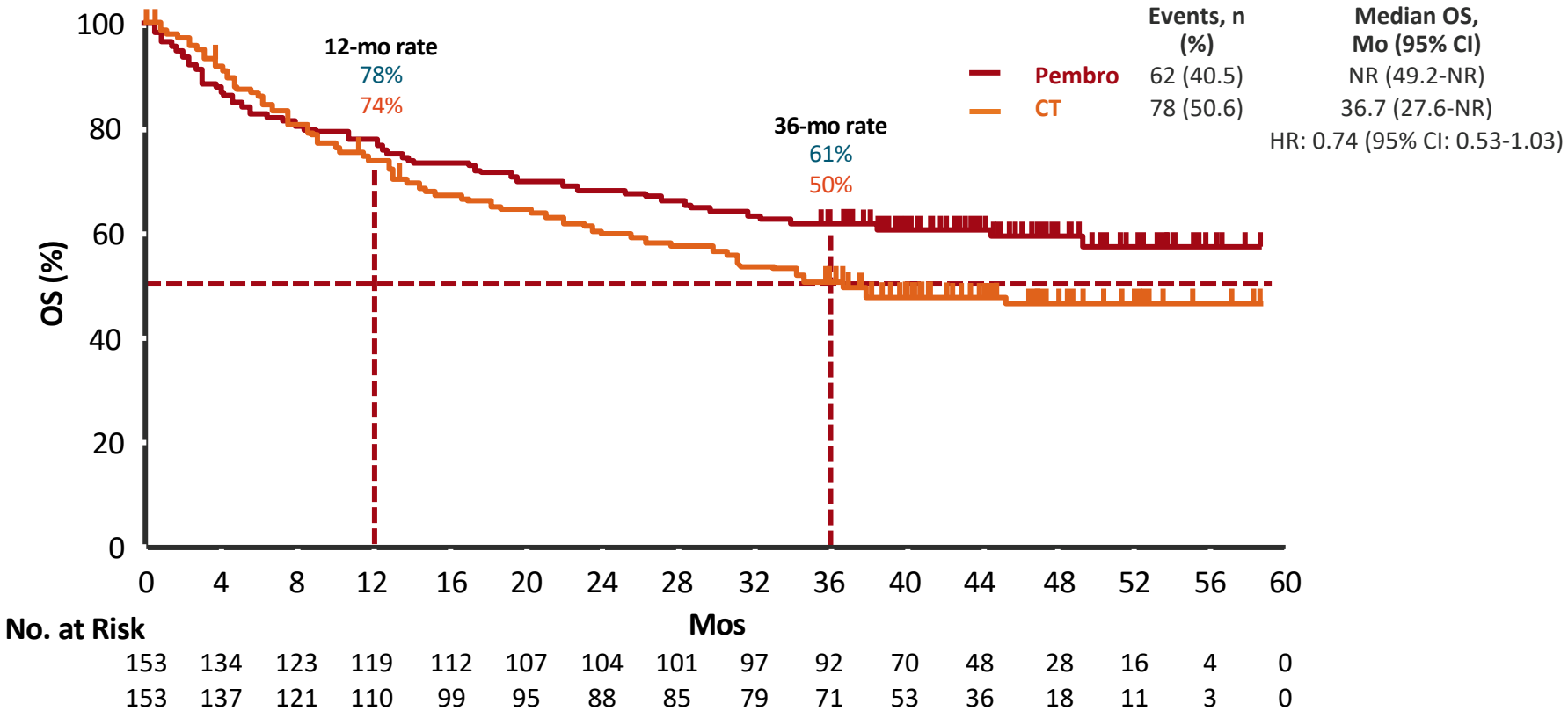
- Dual-Primary endpoints: PFS per RECIST v1.1 per blinded independent central review (BICR) and OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

KEYNOTE-177: PEMBROLIZUMAB VS CHEMOTHERAPY IN 1L TREATMENT

Progression-Free Survival

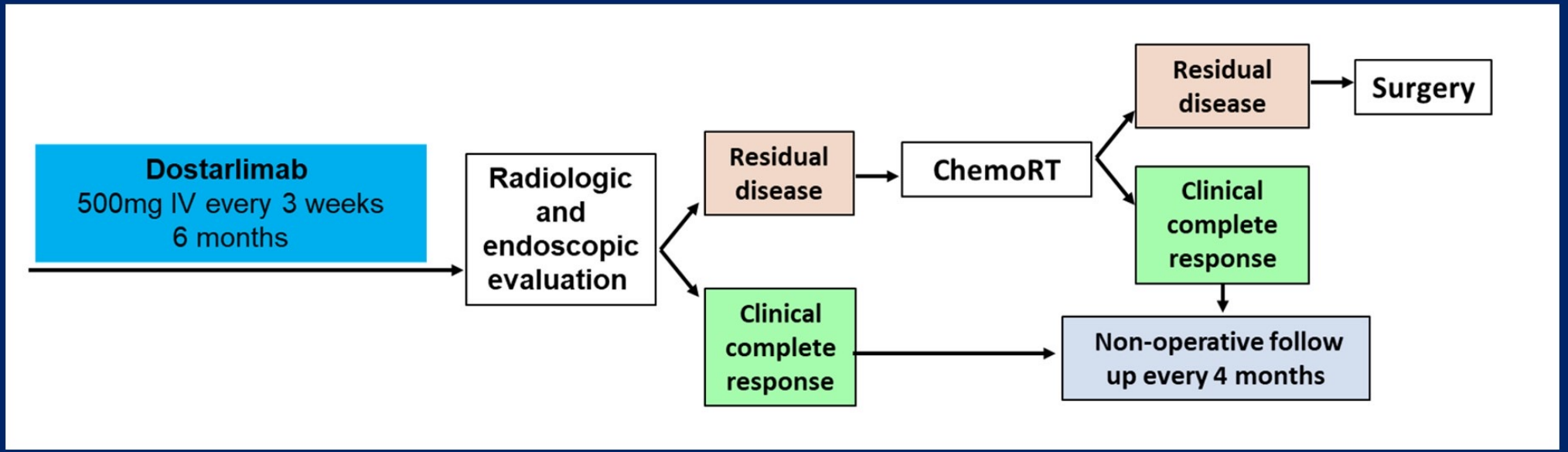


KEYNOTE-177 Final Analysis: OS



André. ASCO 2021. Abstr 3500..

Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer



Patient population: Stage II and III mismatch repair deficient rectal cancer

Target Enrollment: 30 subjects

Study Design: Simon's two stage minimax design

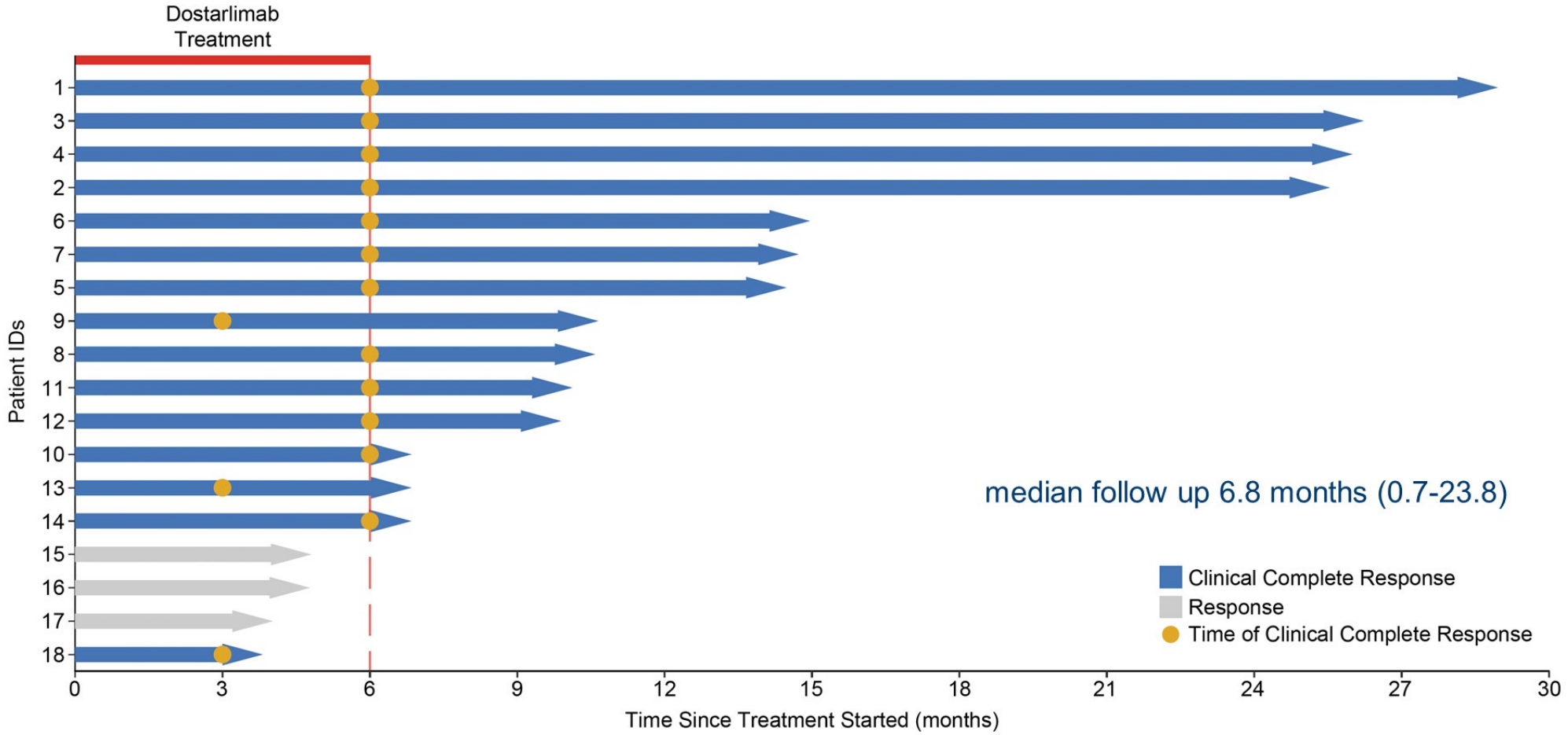
NCT04165772

Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

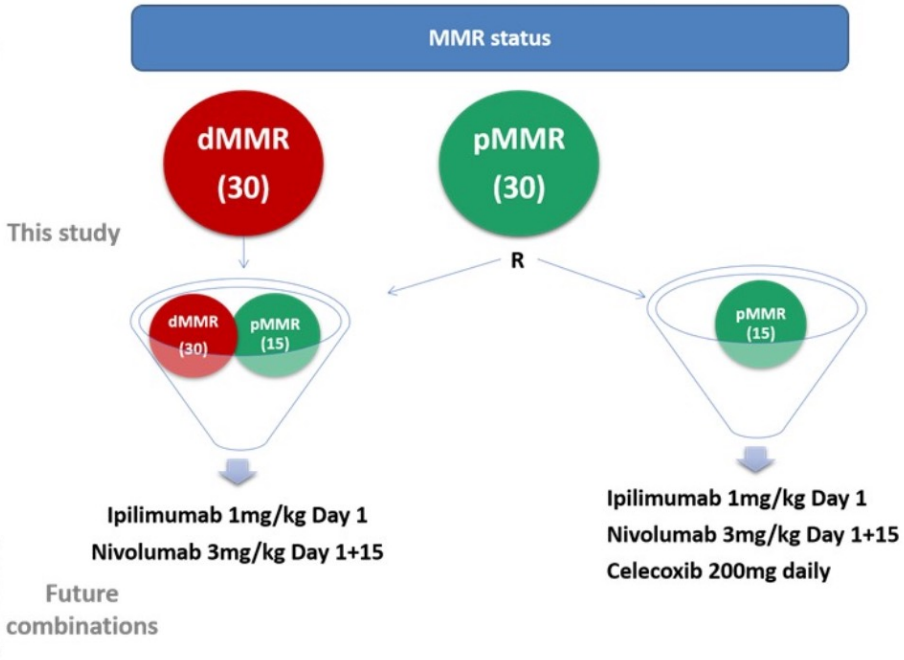
ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response 100%
1	38	T4	N+	23.8	CR	CR	CR	**cCR**
2	30	T3	N+	20.5	CR	CR	CR	**cCR**
3	61	T1/2	N+	20.6	CR	CR	CR	**cCR**
4	28	T4	N+	20.5	CR	CR	CR	**cCR**
5	53	T1/2	N+	9.1	CR	CR	CR	**cCR**
6	77	T1/2	N+	11.0	CR	CR	CR	**cCR**
7	77	T1/2	N+	8.7	CR	CR	CR	**cCR**
8	55	T3	N+	5.0	CR	CR	CR	**cCR**
9	68	T3	N+	4.9	CR	CR	CR	**cCR**
10	78	T3	N-	1.7	CR	CR	CR	**cCR**
11	55	T3	N+	4.7	CR	CR	CR	**cCR**
12	27	T3	N+	4.4	CR	CR	CR	**cCR**
13	26	T3	N+	0.8	CR	CR	CR	**cCR**
14	43	T3	N+	0.7	CR	CR	CR	**cCR**

Duration of response



NICHE study design

- Open-label, exploratory study with an adaptive design
- **Study population:** non-metastatic, resectable and previously untreated adenocarcinoma of the colon
- **Original cohorts:** 30 patients with dMMR and 30 with pMMR tumors
- **Treatment** in all patients: nivolumab 3 mg/kg on D1+15 *plus* ipilimumab 1 mg/kg on D1
  - **pMMR cohort:** randomized to additionally receive celecoxib
  - **Surgery within 6 weeks** of registration
- Tumor and normal tissue at baseline and resection, plasma + PBMCs baseline during treatment and follow-up



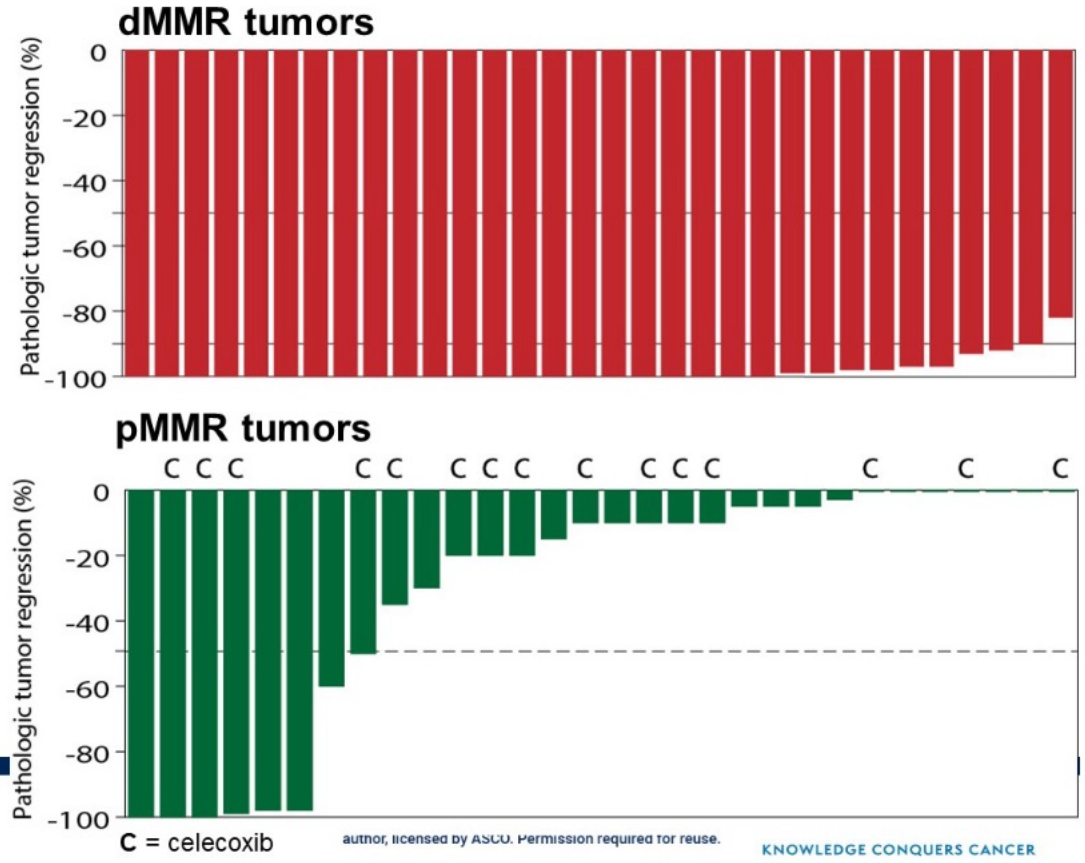
Responses in 29% of pMMR and 100% of dMMR tumors

Pathologic response	dMMR *n*= 32	pMMR *n*= 31
Major (≤10% VTR)	31 (97%)	7 (23%) *
Complete	22 (69%)	4 (13%) *
Partial (≤50% VTR)	1 (3%)	2 (6%)
Nonresponse (>50% VTR)	0 (0%)	22 (71%)

- **dMMR: 32/32 (100%) responders**
  - Lynch: 13/13 MPR, 12 pCR
  - Non-Lynch: 18/19 MPR, 10 pCR; 1 PR
- **pMMR: 9/31 (29%) responders**

*1 patient has not undergone surgery, now 1 year after treatment completion and no longer evidence of intraluminal or radiological disease, incl neg biopsies

VTR= viable tumor rest; MPR = major pathologic response; pCR = pathologic complete response; PR= partial response



ASCO Gastrointestinal Cancers Symposium

Neoadjuvant botensilimab plus balstilimab (BOT/BAL) in resectable mismatch repair proficient and deficient colorectal cancer: NEST-1 clinical trial

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#authors share senior authorship

ASCO Gastrointestinal Cancers Symposium #GI24

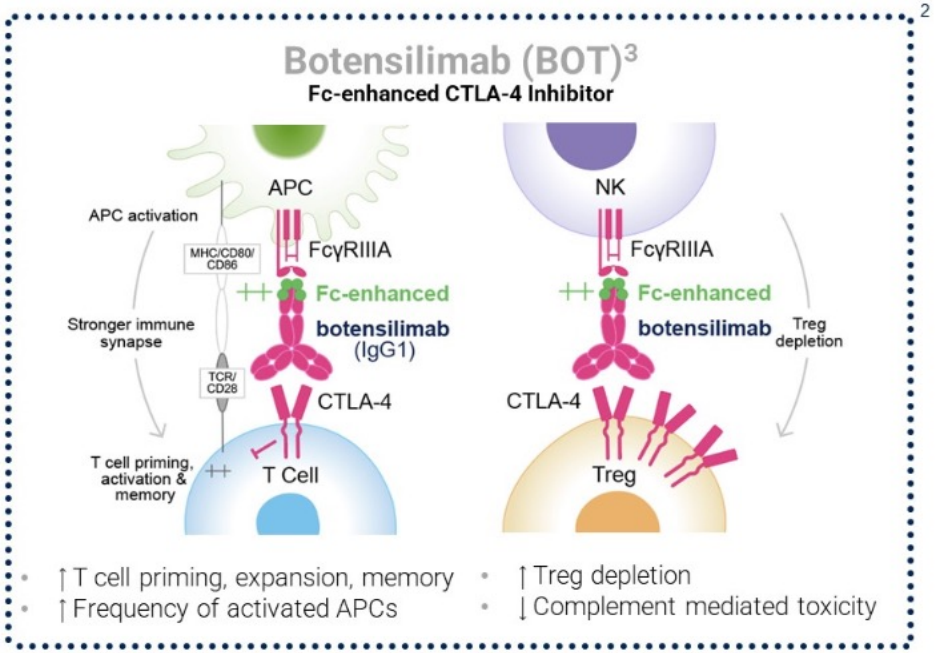
PRESENTED BY: Pashtoon Kasi, MD, MS

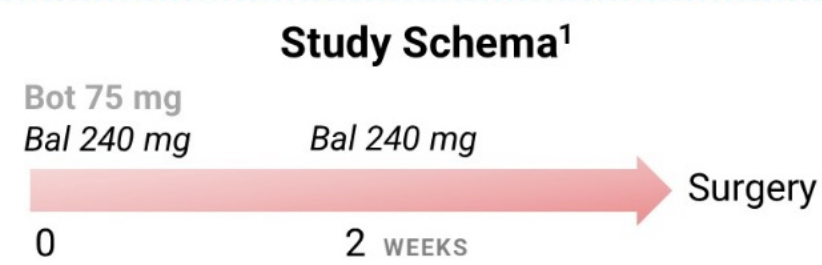
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

THE NEST-1 CLINICAL TRIAL

Background/Methods

- Effective therapies for colorectal cancer (CRC), particularly in those ~85-95% with **proficient mismatch repair/ microsatellite stable (pMMR/MSS)** cancer, are a critical unmet need.[1]
- **Botensilimab (BOT),** a multifunctional next-generation **anti-CTLA-4 antibody**, with balstilimab (BAL), an anti-PD-1 antibody, has a response rate of >20% in patients with heavily pretreated pMMR/MSS metastatic CRC.[2]
- NEST-1 (NCT05571293) is the first study to evaluate **neoadjuvant** BOT and BAL in CRC patients eligible for surgery.
- **Investigator-initiated trial supported by Agenus Inc.**

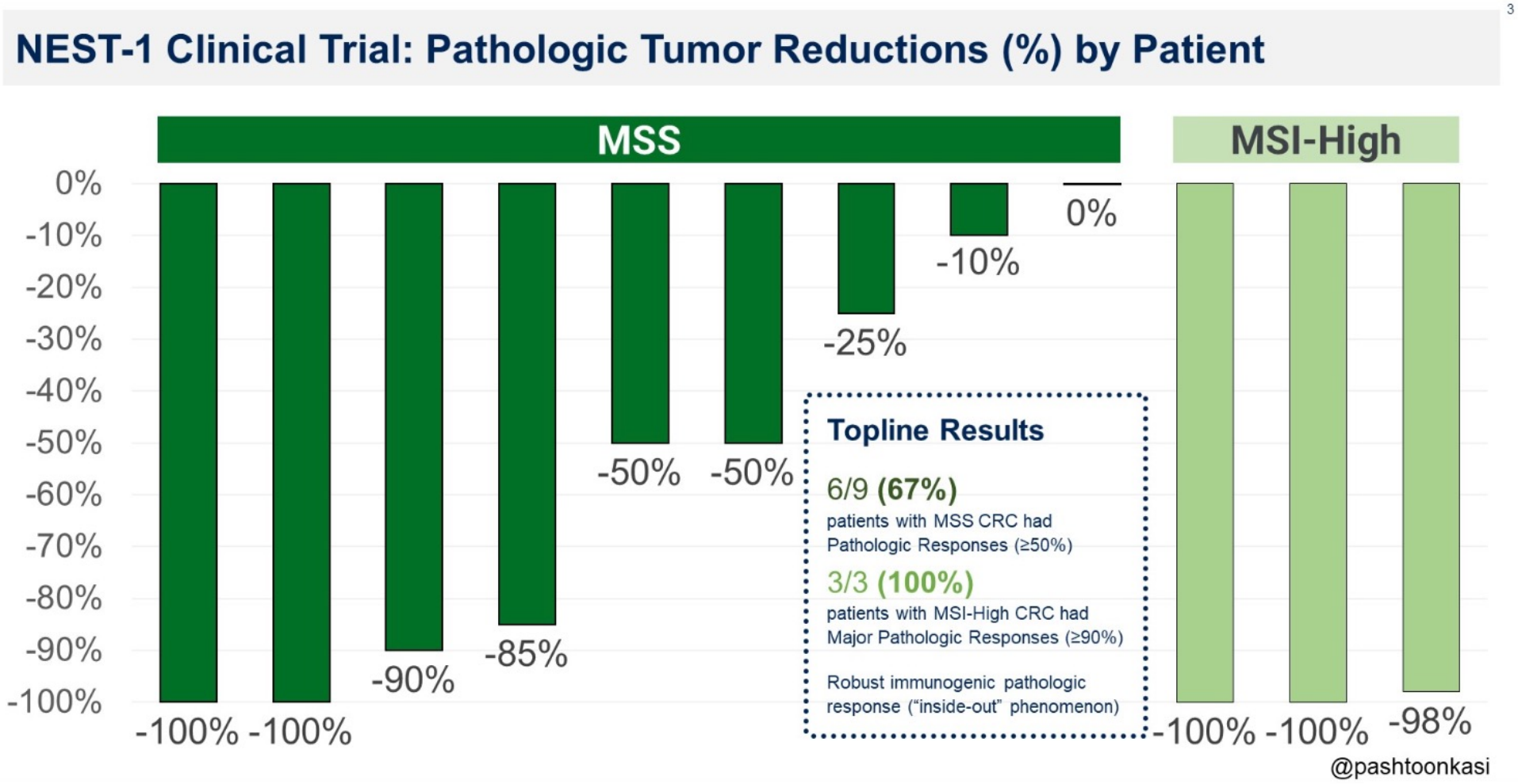




@pashtoonkasi

1. Kasi PM et al. Oncogene. 2023 Oct; 42 (44): 3252-3259.
2. El-Khoueiry AB. Journal of Clinical Oncology 2023 41:4_suppl, LBA8
3. Adapted from Wilky B, et al. Oral Presentation at CTOS 2023. Dublin, Ireland. Paper 31

THE NEST-1 CLINICAL TRIAL



SUMMARY

- Immunotherapy is effective in mismatch repair deficient colon cancer, and standard first line therapy for metastatic disease
  - **KeyNote 177**

- In non-metastatic colorectal cancer, immunotherapy is associated with high rates of pathologic response
  - **In both – MMR deficient and MMR proficient CRC**

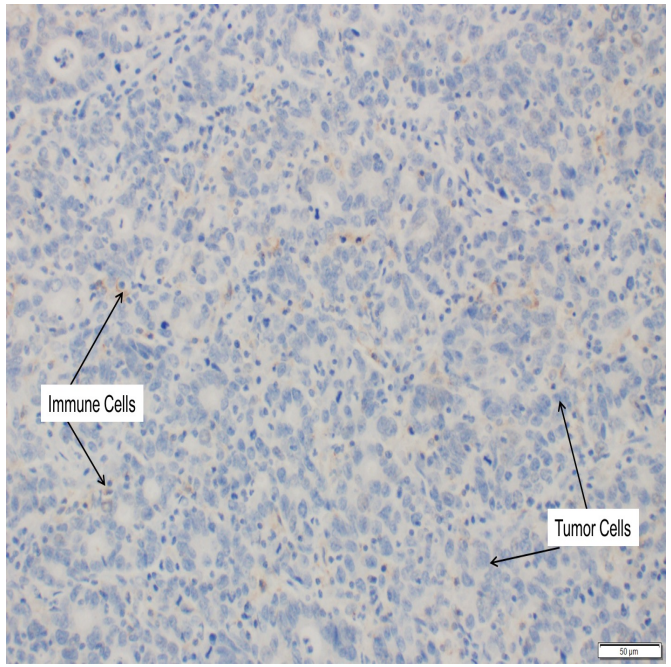
PD-L1 Expression IHC[A]

- PD-L1 expression in gastric cancer is determined by Combined Positive Score (CPS)

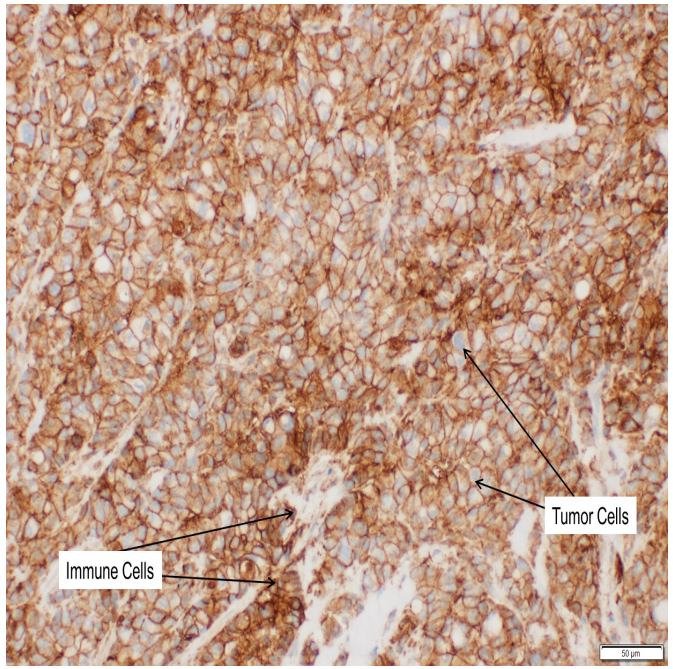
$$\text{CPS} = \frac{\text{No. of PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total No. viable tumor cells}} \times 100$$

- A specimen is considered to have positive PD-L1 expression if CPS ≥1

PD-L1–negative



PD-L1–positive

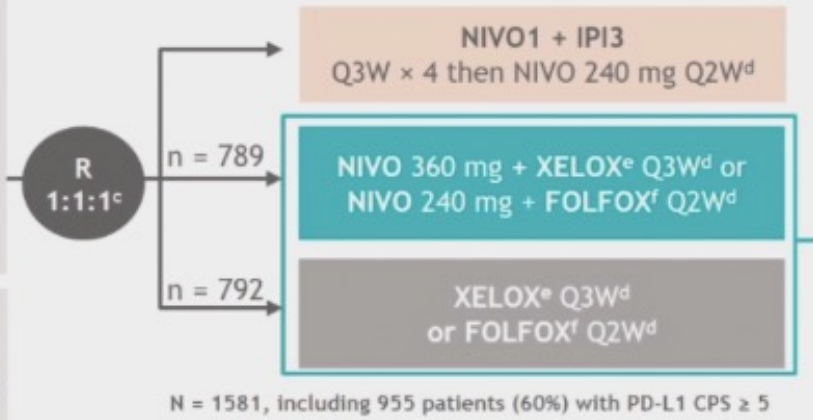


CheckMate 649 study design

- 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)



N = 1581, including 955 patients (60%) with PD-L1 CPS ≥ 5

Dual primary endpoints:
- OS and PFS[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:
- OS (PD-L1 CPS ≥ 1 or all randomized)
- OS (PD-L1 CPS ≥ 10)
- PFS[g] (PD-L1 CPS ≥ 10, 1, or all randomized)
- ORR[g]

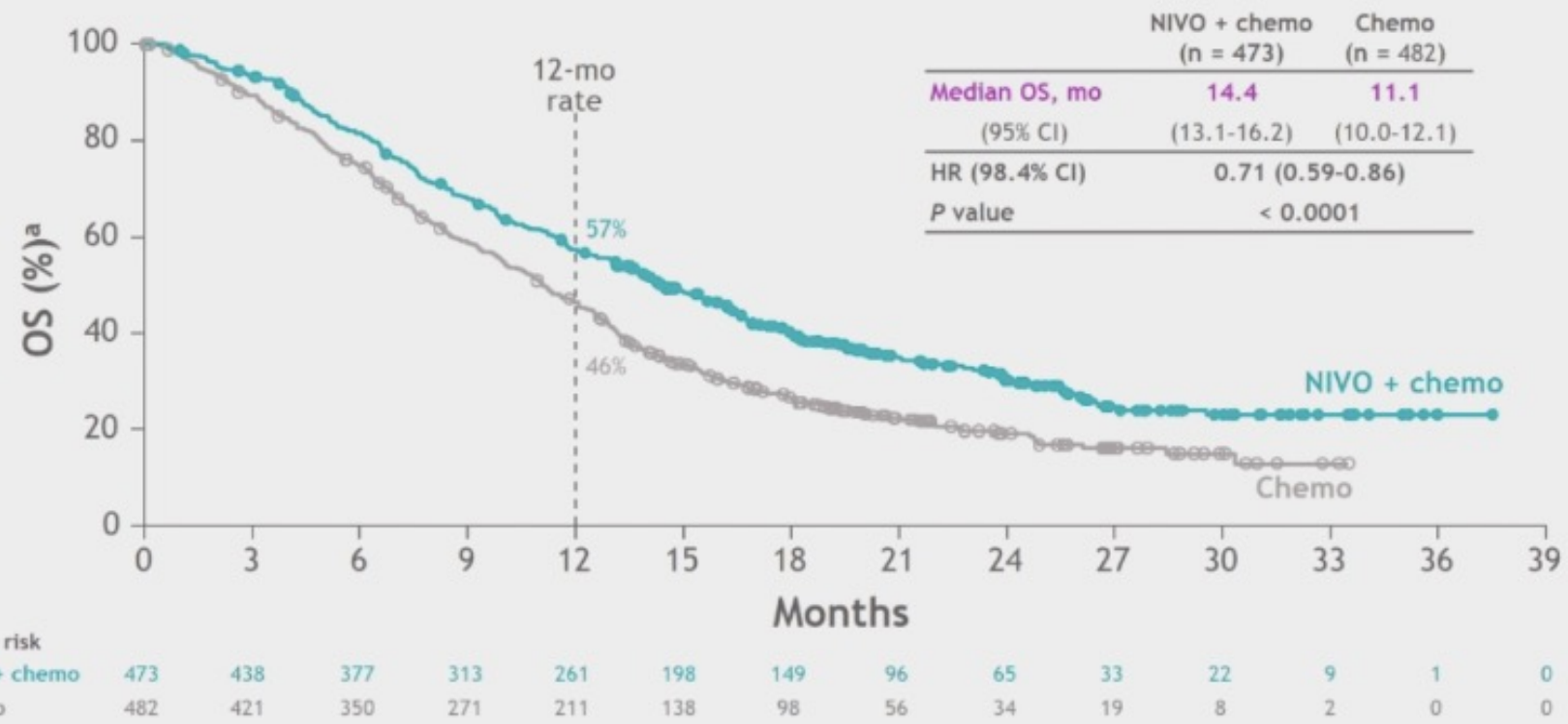
- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]

[a]ClinicalTrials.gov number, NCT02872116; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]After NIVO + chemo arm was added and before new patient enrollment in the NIVO1+IPI3 group was closed; [d]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1-14); [f]Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1-2); [g]BICR assessed; [h]Time from concurrent randomization of the last patient to NIVO + chemo vs chemo to data cutoff.

4

Overall survival

Primary endpoint (PD-L1 CPS ≥ 5)



	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (98.4% CI)	0.71 (0.59-0.86)	
P value	< 0.0001	

No. at risk														
NIVO + chemo	473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemo	482	421	350	271	211	138	98	56	34	19	8	2	0	0

- 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

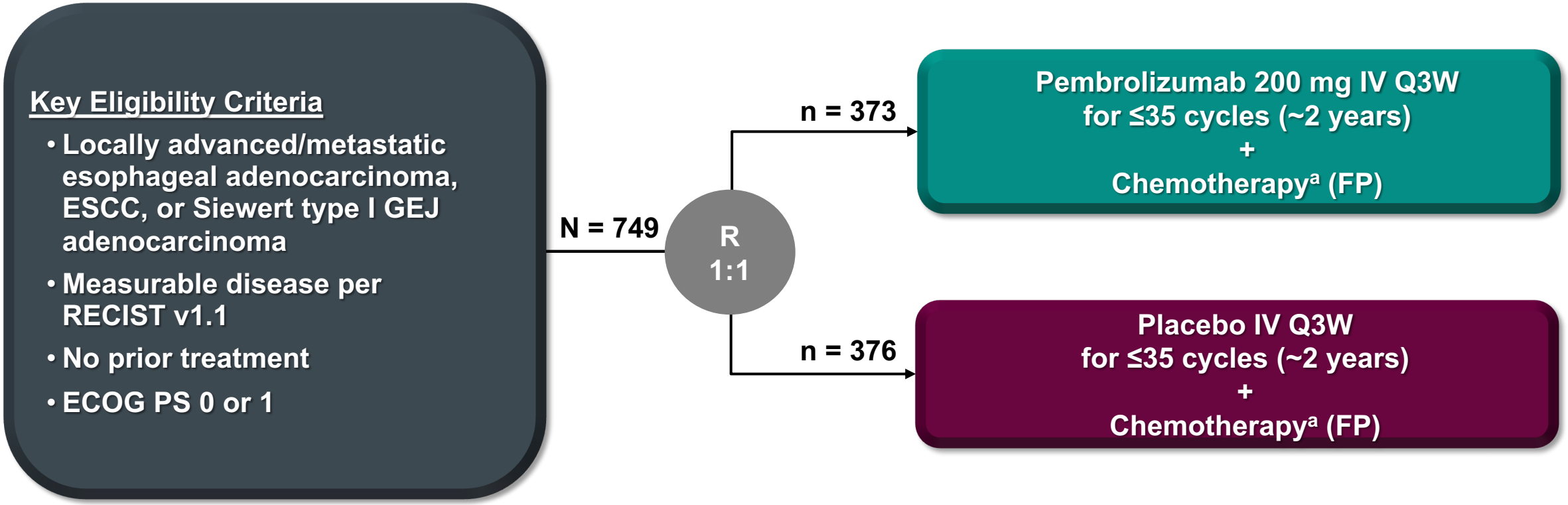
[a]Minimum follow-up 12.1 months.

First-Line Pembrolizumab Plus Chemotherapy for Advanced Esophageal Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-590 Study

Manish A. Shah[1]; Jong-Mu Sun[2]; Lin Shen[3]; Ken Kato[4]; Peter C. Enzinger[5]; Antoine Adenis[6]; Toshihiko Doi[7]; Takashi Kojima[7]; Zhigang Li[8]; Sung-Bae Kim[9]; Byoung Chul Cho[10]; Wasat Mansoor[11]; Shau-Hsuan Li[12]; Patrapim Sunpaweravong[13]; Maria Alsina Maqueda[14]; Gary L. Buchschacher Jr[15]; Jimin Wu[16]; Sukrut Shah[16]; Pooja Bhagia[16]; Jean-Philippe Metges[17]

[1]Weill Cornell Medical College, New York, NY, USA; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [3]Peking University Cancer Hospital and Institute, Beijing, China; [4]National Cancer Center Hospital, Tokyo, Japan; [5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]IRCM, Université Montpellier, ICM, Montpellier, France; [7]National Cancer Center Hospital East, Kashiwa, Japan; [8]Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [10]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; [11]The Christie NHS Foundation Trust, Manchester, United Kingdom; [12]Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan; [13]Prince of Songkla University Hospital, Songkhla, Thailand; [14]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [15]Kaiser Permanente Southern California, Los Angeles Medical Center, Los Angeles, CA, USA; [16]Merck & Co., Inc., Rahway, NJ, USA; [17]CHU Brest–Institut de Cancerologie et d'Hematologie ARPEGO Network, Brest, France

Study Design of KEYNOTE-590 (NCT03189719)



Stratification Factors

- Geographic region (Asia vs rest of world)
- Histology (adenocarcinoma vs squamous cell carcinoma)
- ECOG PS (0 vs 1)

End Points

- Primary: OS,[b] PFS[c,d]
- Secondary: ORR[d], DOR[d], safety, PROs[e]

[a]FP: 5-fluorouracil 800 mg/m^2/d continuous IV Q3W on days 1-5 (≤35 cycles) + cisplatin 80 mg/m^2 IV Q3W on day 1 (≤6 cycles). [b]Assessed in patients with ESCC and PD-L1 CPS ≥10, patients with ESCC regardless of PD-L1 expression, all randomly assigned patients with CPS ≥10, and all randomly assigned patients regardless of PD-L1 expression. [c]Assessed in patients with ESCC regardless of PD-L1 expression, all randomly assigned patients with CPS ≥10, and all randomly assigned patients regardless of PD-L1 expression. [d]Assessed per RECIST v1.1 by investigator. [e]PROs (change from baseline to week 18 in EORTC QLQ-C30 and EORTC QLQ-OES18 scores) were analyzed in the FAS, defined as all randomly assigned patients who received ≥1 dose of study treatment and who had completed ≥1 PRO assessment during the follow-up period.

Phase 3 KEYNOTE-590 Study (NCT03189719)

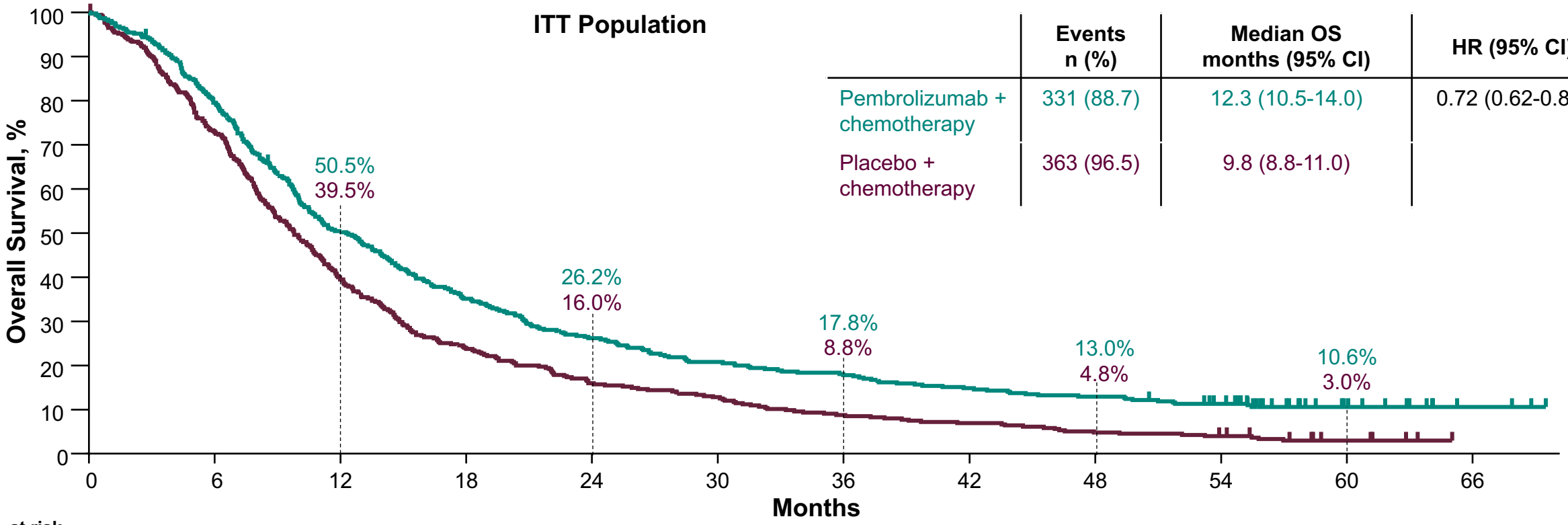
- It was determined at the first interim analysis, with a median follow-up of 22.6 months, pembrolizumab + chemotherapy significantly improved survival compared with placebo + chemotherapy in patients with advanced esophageal cancer[1]

	ITT N = 749	ESCC n = 548	CPS ≥10 n = 383	ESCC and CPS ≥10 n = 286
OS, HR (95% CI)	0.73 (0.62-0.86)	0.72 (0.60-0.88)	0.62 (0.49-0.78)	0.57 (0.43-0.75)
2-year OS rate,[a,b] %	28 vs 16	29 vs 17	31 vs 15	31 vs 15
PFS, HR (95% CI)	0.65 (0.55-0.76)	0.65 (0.54-0.78)	0.51 (0.41-0.65)	—

- Current analysis: 5-year efficacy and safety outcomes update
  - Median time from randomization to data cutoff (July 10, 2023)
    - 58.8 months (range, 49.2-70.6 months)

[a]Kaplan-Meier estimate.
[b]Data are for pembrolizumab + chemotherapy versus placebo + chemotherapy.
[c]Per RECIST v1.1 by investigator review.
1. Sun J-M et al. *Lancet.* 2021;398:759-771.

Overall Survival



	Events n (%)	Median OS months (95% CI)	HR (95% CI)
Pembrolizumab + chemotherapy	331 (88.7)	12.3 (10.5-14.0)	0.72 (0.62-0.84)
Placebo + chemotherapy	363 (96.5)	9.8 (8.8-11.0)	

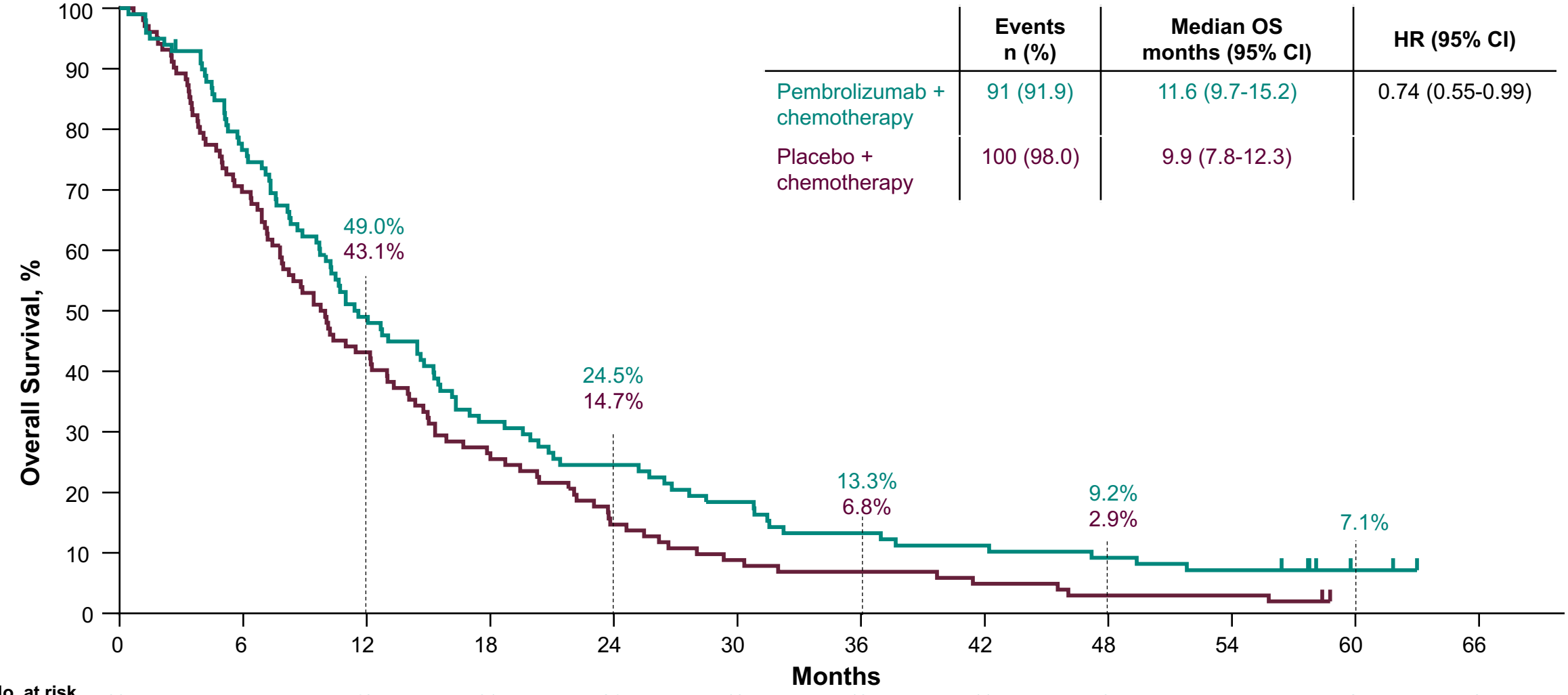
No. at risk											
	373	296	187	130	97	77	66	55	48	38	12	3
	376	274	148	90	60	48	33	26	18	14	5	0

	CPS ≥10		ESCC		ESCC and CPS ≥10	
	Pembro + chemo n = 186	Placebo + chemo n = 197	Pembro + chemo n = 274	Placebo + chemo n = 274	Pembro + chemo n = 143	Placebo + chemo n = 143
OS, HR (95% CI)	0.64 (0.52-0.80)		0.71 (0.60-0.85)		0.60 (0.46-0.76)	
5-y OS rate,[a] %	12.8	3.8	11.8	3.4	13.8	3.7

[a]Kaplan-Meier estimate. Data cutoff: July 10, 2023.

Overall Survival: Adenocarcinoma

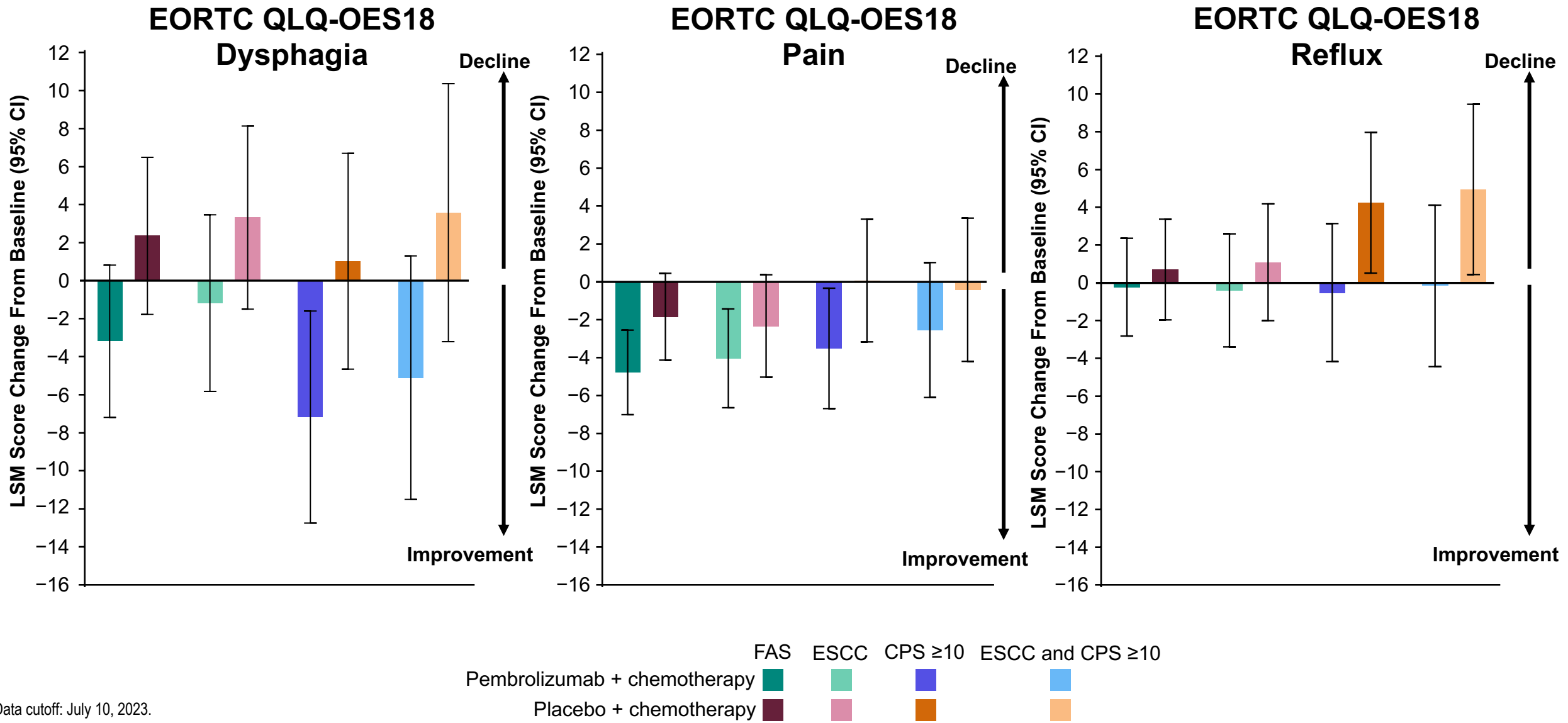
	Events n (%)	Median OS months (95% CI)	HR (95% CI)
Pembrolizumab + chemotherapy	91 (91.9)	11.6 (9.7-15.2)	0.74 (0.55-0.99)
Placebo + chemotherapy	100 (98.0)	9.9 (7.8-12.3)	



No. at risk											
	99	75	48	31	24	18	13	11	9	7	2	0
	102	71	44	27	15	9	7	5	3	3	0	0

[a]Kaplan-Meier estimate. Data cutoff: July 10, 2023.

Least Squares Mean Change From Baseline to Week 18 in Patient-Reported Outcomes



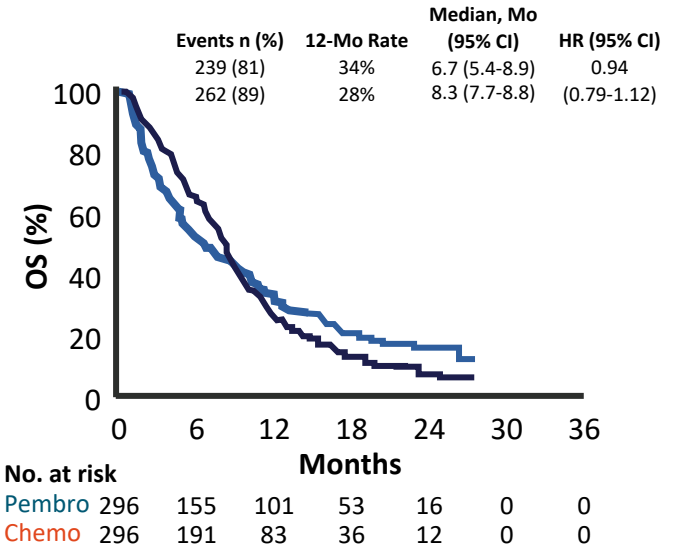
Data cutoff: July 10, 2023.

Conclusions

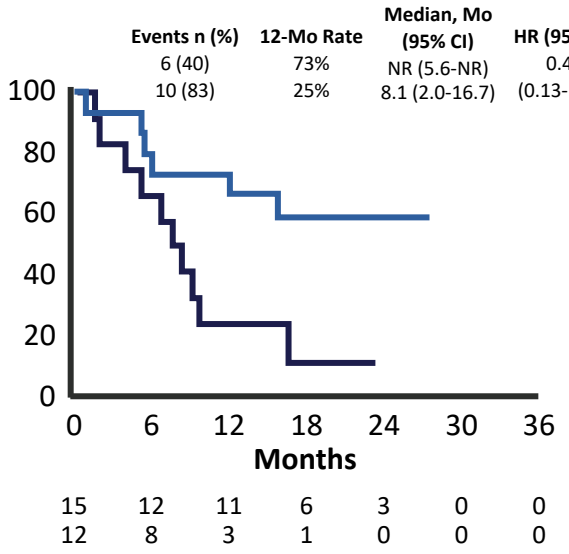
- After 5 years of follow-up, the addition of pembrolizumab to chemotherapy shows continued, durable efficacy compared with placebo + chemotherapy in advanced esophageal cancer
  - 5-year OS rates were higher with pembrolizumab + chemotherapy (10.6%) than with placebo + chemotherapy (3.0%) for the ITT population
- The addition of pembrolizumab to chemotherapy did not have a detrimental effect on health-related quality of life during treatment
- No new safety signals were observed
- These data continue to support the use of pembrolizumab + chemotherapy for advanced esophageal cancer as first-line therapy

PD-1 Inhibitors in MSI-H/dMMR Gastric Cancer

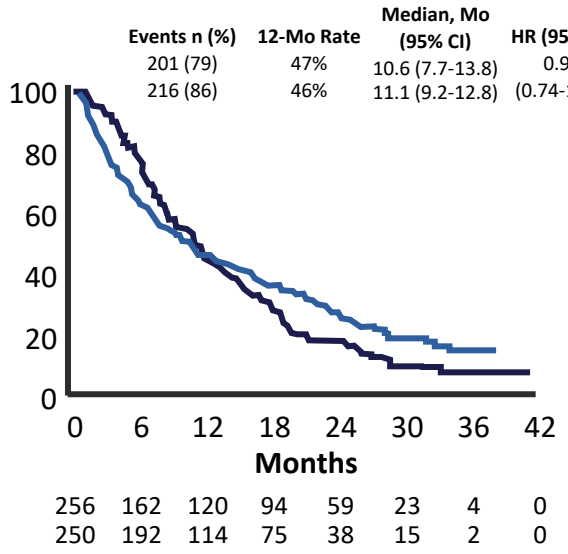
KEYNOTE-061: 2L Pembrolizumab vs Chemo



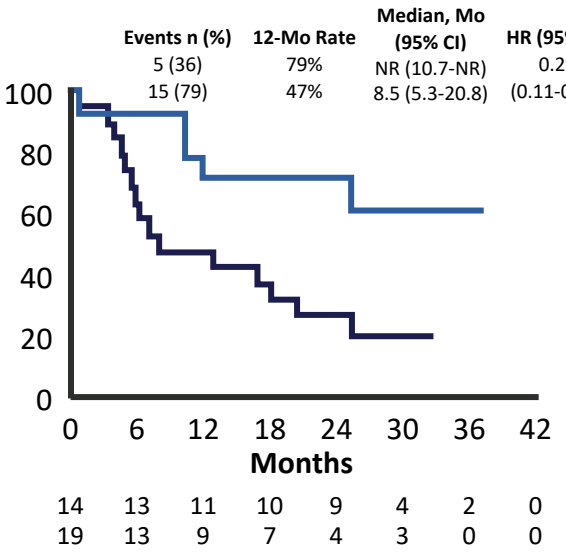
KEYNOTE-061: Pembrolizumab vs Chemo in MSI-H



KEYNOTE-062: 1L Pembrolizumab vs Chemo



KEYNOTE-062: Pembrolizumab vs Chemo in MSI-H



Response	Keynote-059 (3L+)	KEYNOTE-061 (2L)		KEYNOTE-062 (1L)	
	Pembro (n = 7)	Pembro (n = 15)	Chemo (n = 12)	Pembro (n = 14)	Chemo (n = 19)
ORR, n (%)	4 (57)	7 (47)	2 (17)	8 (57)	7 (37)
Median DOR, mo (range)	Not reached (20.0+ to 26.8+)	Not reached (5.5 to 26.0+)	Not reached (2.2+ to 12.2+)	21.2 (1.4+ to 33.6+)	7.0 (2.0 to 30.4+)

MSI-H or dMMR is strongly associated with improved outcomes with immune checkpoint inhibitor therapy. Activity is independent of the line of therapy.

Chao J. *JAMA Oncol.* 2021;7(6):895-902.

IMbrave150: Atezolizumab + Bevacizumab vs Sorafenib for First-line Treatment of Hepatocellular Cancer

- Multicenter, randomized, open-label phase III trial[1]
  - GO30140: randomized phase Ib study showed potential benefit of atezolizumab + bevacizumab for patients with advanced HCC (ORR 36%)[2]

Patients with locally advanced or metastatic and/or unresectable HCC with no previous systemic therapy, Child-Pugh A, and ECOG PS ≤ 1*
(N = 501)

Atezolizumab 1200 mg Q3W + **Bevacizumab** 15 mg/kg Q3W
(n = 336)

Sorafenib 400 mg BD
(n = 165)

Treatment until Progressive disease (PD) or intolerable toxicity

- Coprimary endpoints: OS and PFS

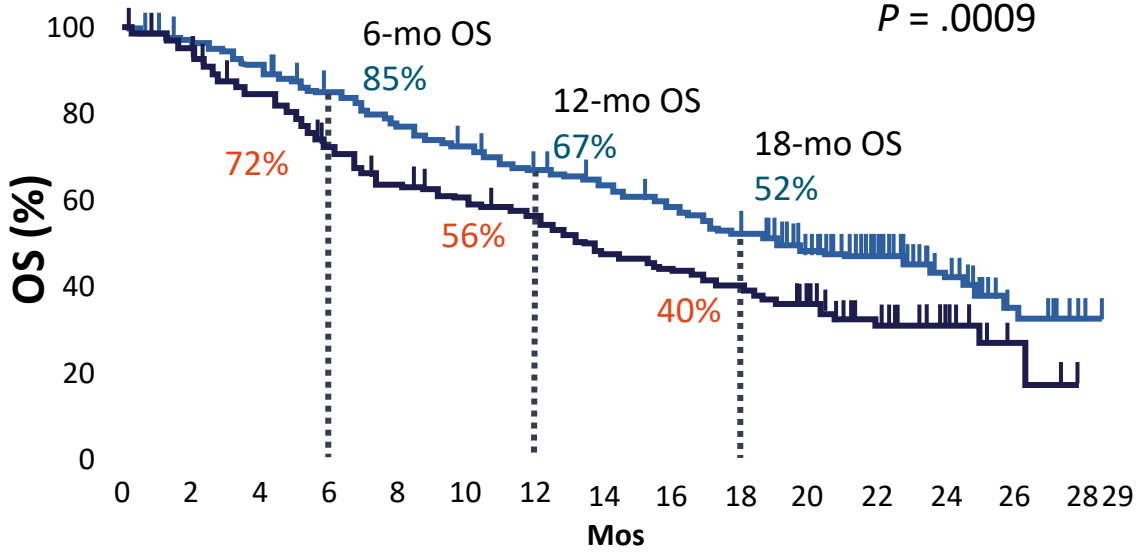
*Trial included subgroups of high-risk patients excluded from other contemporary phase III trials: ~ 40% had macrovascular invasion; specifically included patients with 50% hepatic involvement or main portal vein invasion or invasion of the portal vein branch contralateral to the primarily involved lobe.

1. Finn. NEJM. 2020;382:1894. 2. Lee. Lancet Oncol. 2020;21:808.

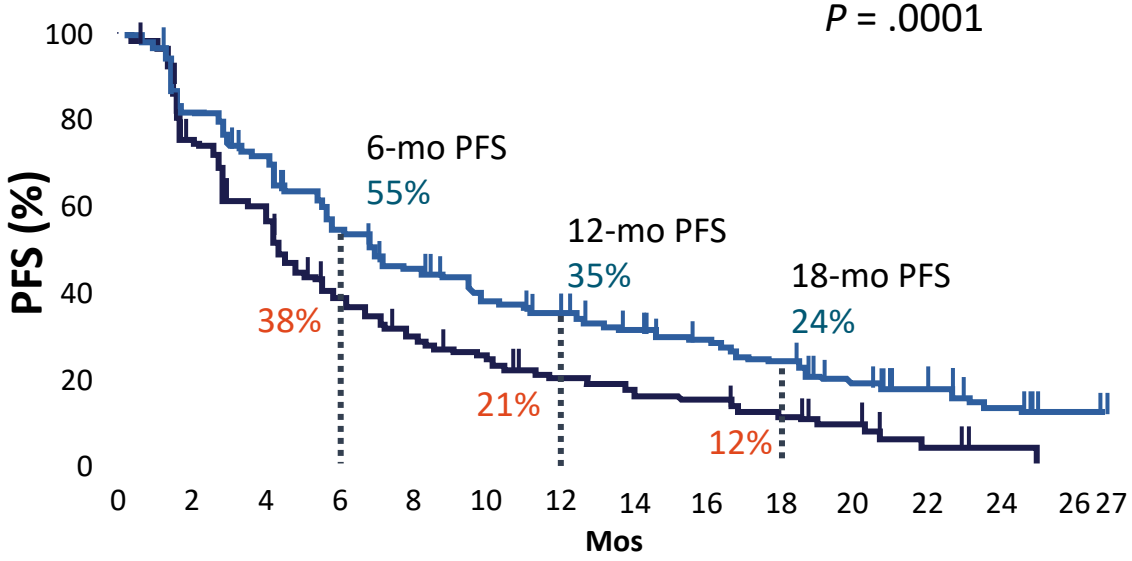
IMbrave150: Updated OS and PFS

- Primary analysis OS/PFS HR: 0.58/0.59 (median f/u 8.6 mos)

	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median OS, mos (95% CI)	**19.2** (17.0-23.7)	**13.4** (11.4-16.9)
Stratified HR (95% CI)	0.66 (0.52-0.85)	
	P = .0009	



	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median PFS, mos (95% CI)	**6.9** (5.7-8.6)	**4.3** (4.0-5.6)
Stratified HR (95% CI)	0.65 (0.53-0.81)	
	P = .0001	



Median follow-up: 15.6 mos.

Finn. NEJM. 2020;382:1894. Finn. ASCO GI 2021. Abstr 267.

Durvalumab ± tremelimumab

HIMALAYA trial is a multicentre phase III trial exploring the safety and efficacy of

Durvalumab (a PD-L1 inhibitor) ±

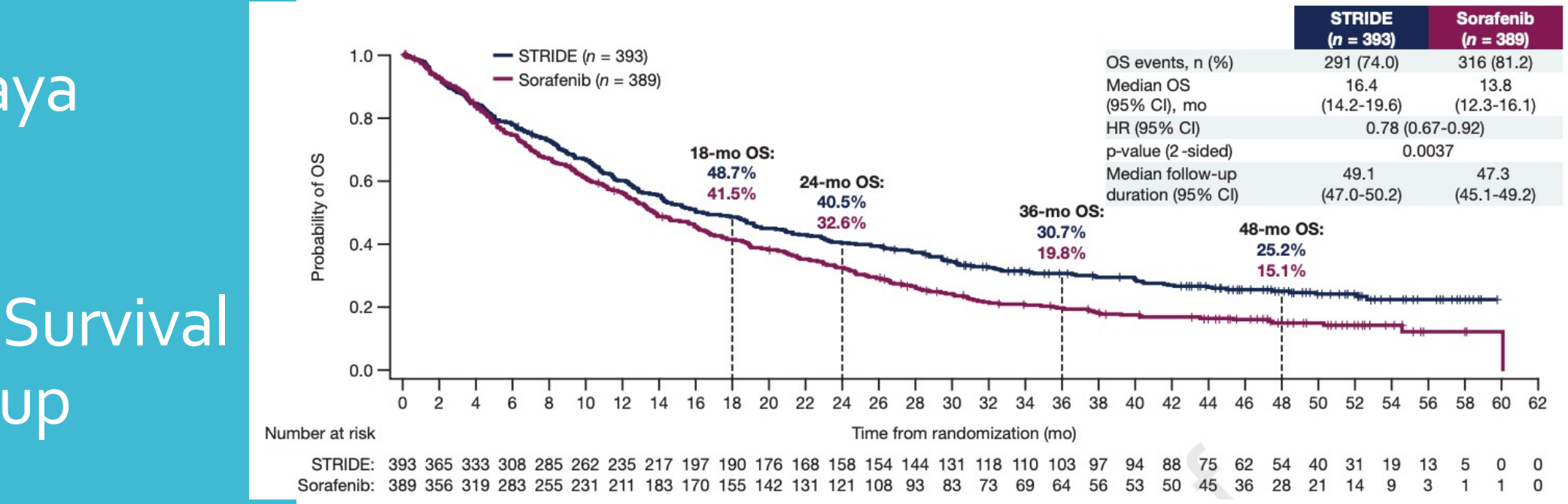
Tremelimumab (a CTLA-4 inhibitor)

VS

Sorafenib in patients with advanced HCC who have not received prior systemic therapy and are also not eligible for locoregional therapy

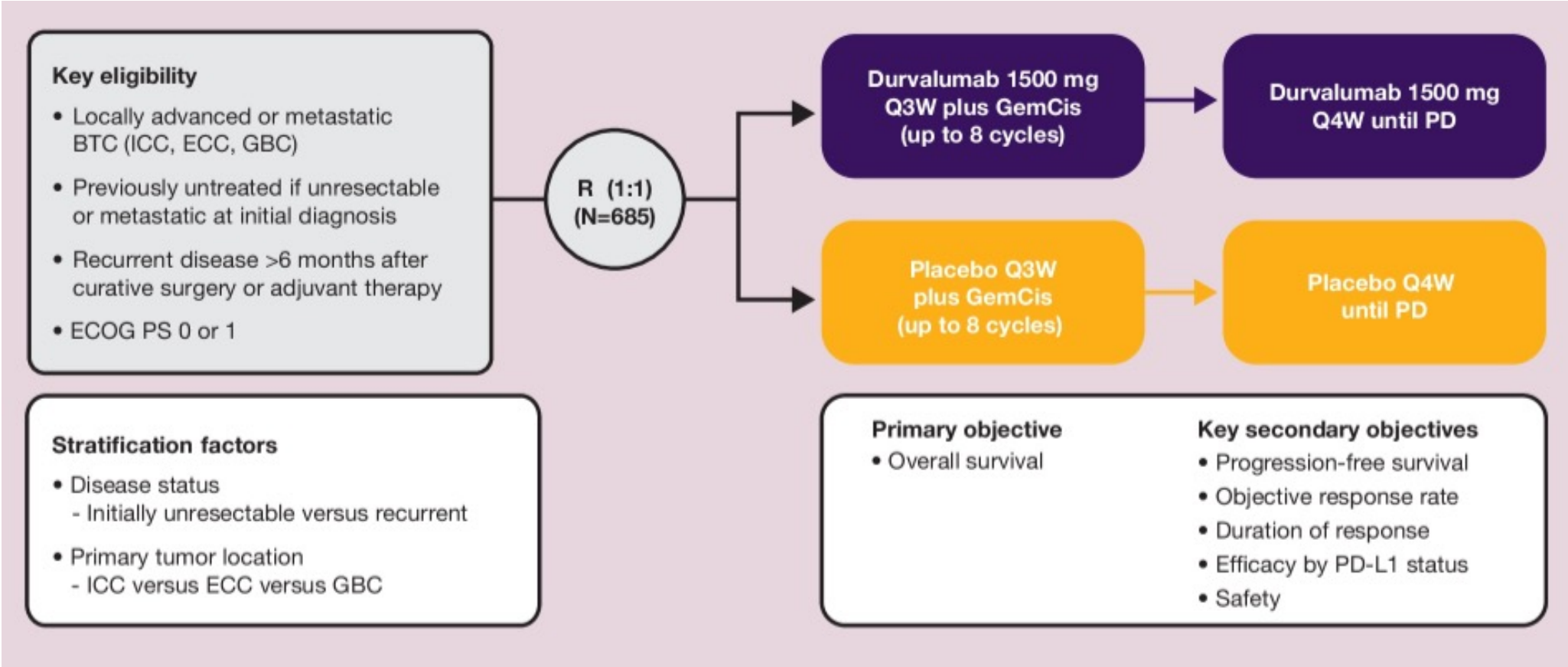
Himalaya Study

4-year Survival follow up



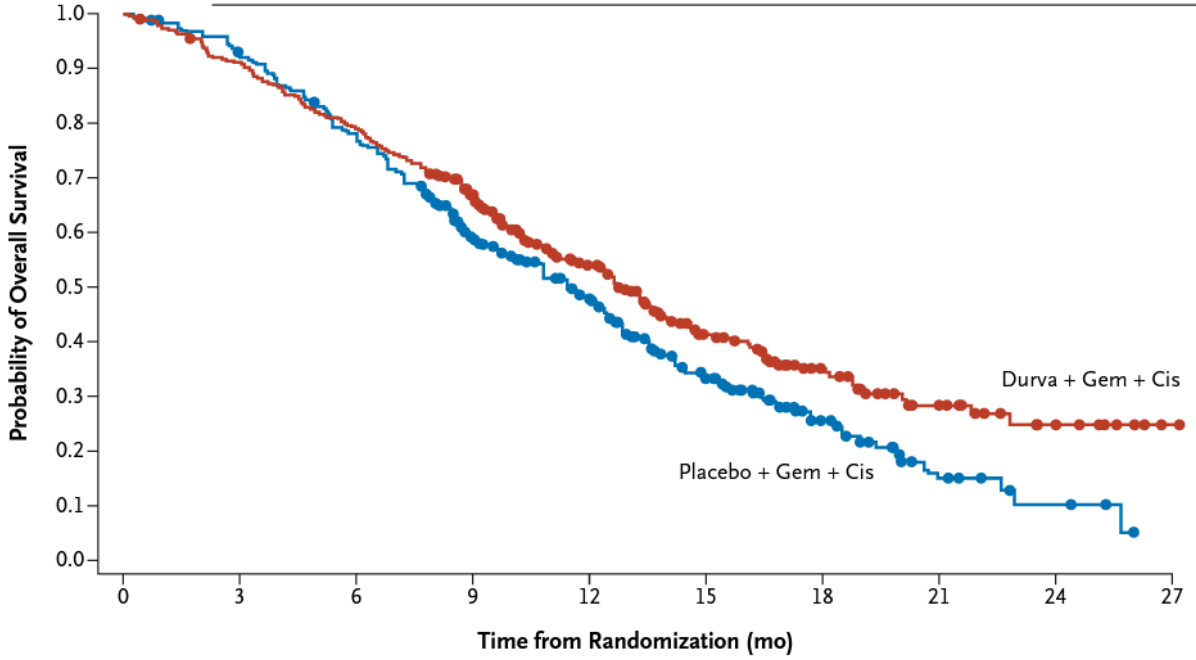
	STRIDE (n = 393)	Sorafenib (n = 389)
OS events, n (%)	291 (74.0)	316 (81.2)
Median OS (95% CI), mo	16.4 (14.2-19.6)	13.8 (12.3-16.1)
HR (95% CI)	0.78 (0.67-0.92)	
p-value (2-sided)	0.0037	
Median follow-up duration (95% CI)	49.1 (47.0-50.2)	47.3 (45.1-49.2)

Topaz-1 Trial – Gem/Cis/ Durvalumab in Biliary Tract Cancer



Gem/Cis /Durva improves Overall Survival

	Median Overall Survival, mo (95% CI)	Hazard Ratio (95% CI)	Stratified Log-rank P Value
Durva + Gem + Cis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + Gem + Cis (n=344)	11.5 (10.1–12.5)		



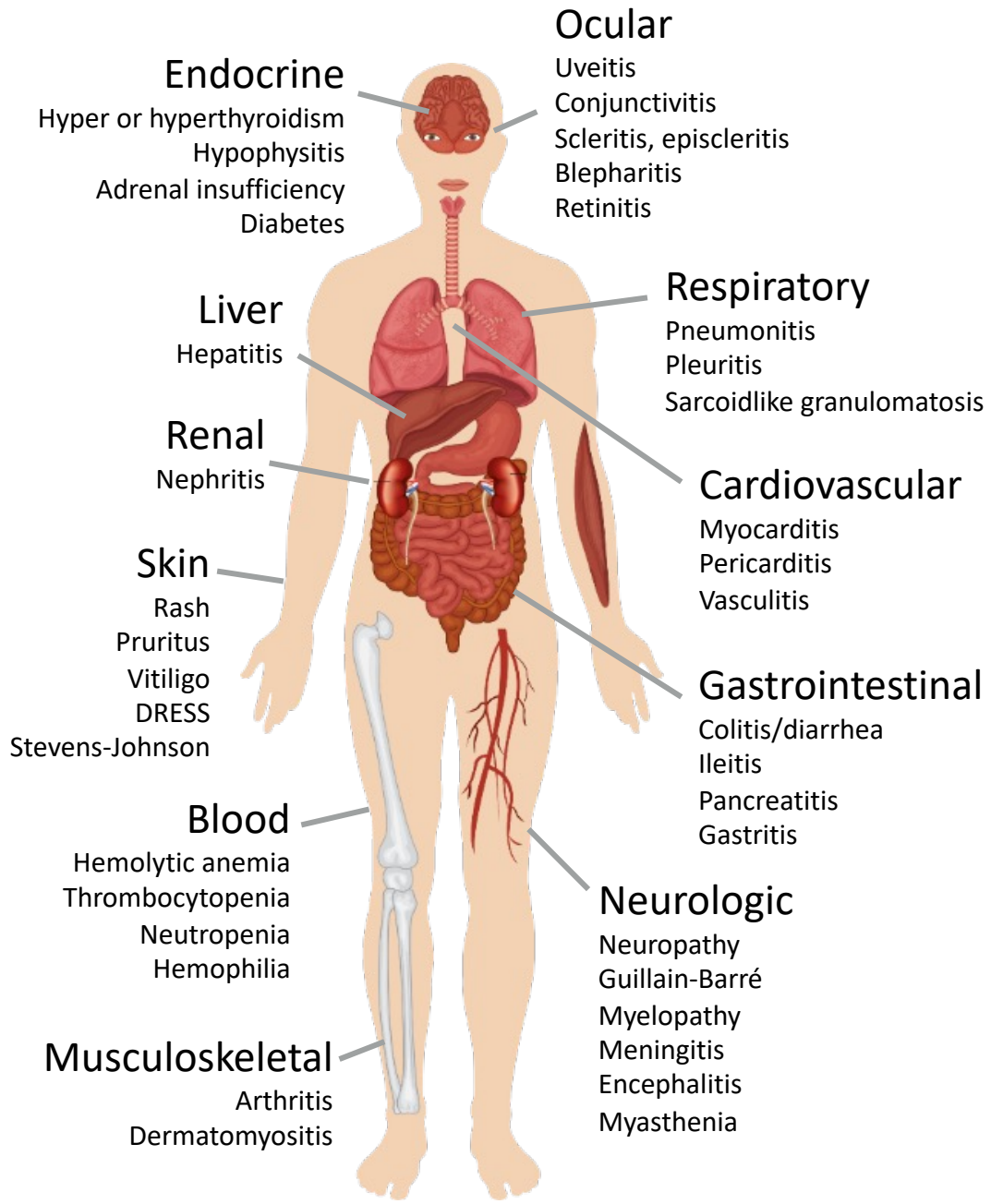
No. at Risk

Durva + Gem + Cis	341	331	324	309	294	278	268	252	238	208	174	151	135	118	93	79	74	57	49	39	29	24	15	12	9	8	4	1
Placebo + Gem + Cis	344	337	329	317	299	283	261	242	220	183	159	143	125	97	78	65	52	40	29	21	15	10	8	4	4	3	0	0

Oh DY et al. NEJM Evid 2022;1(8):1-11

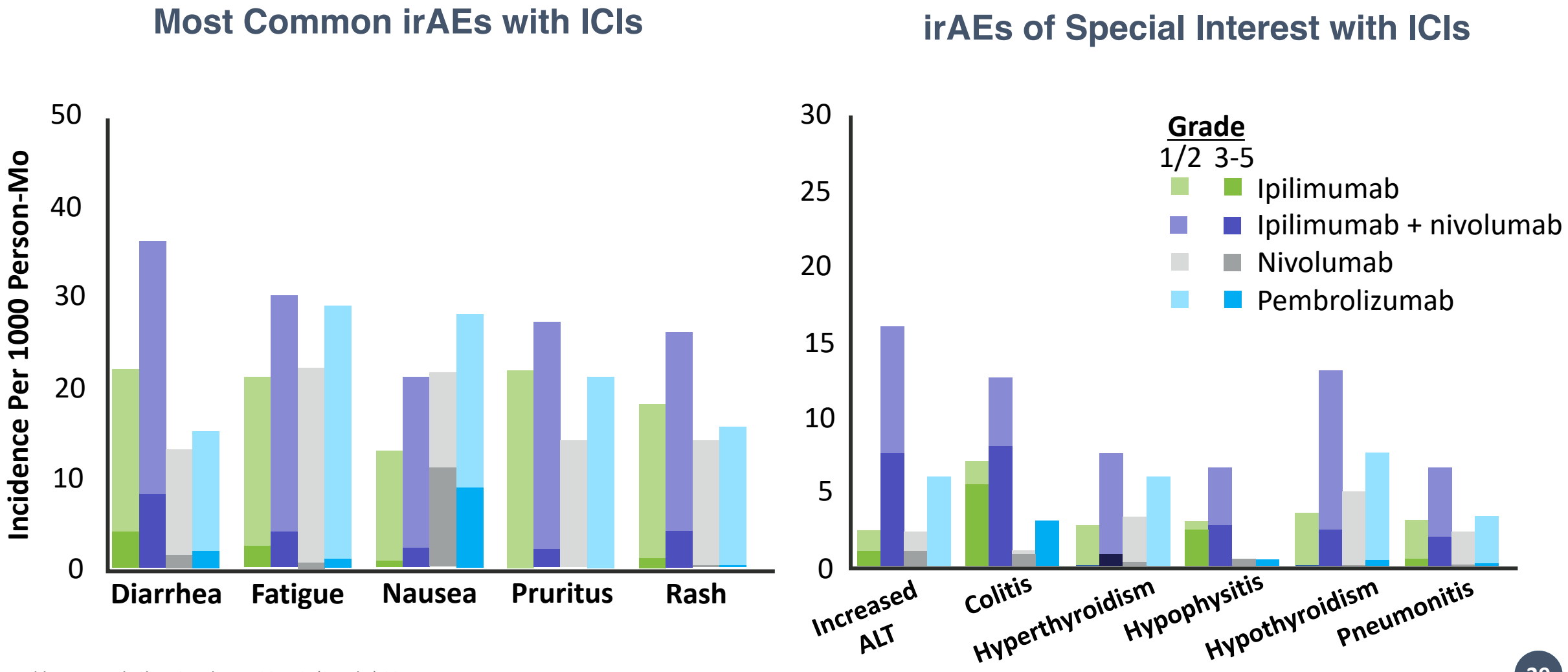
Spectrum of Immune-related Toxicity

- Immunotherapies present with a novel spectrum of AEs that differ in important ways from those associated with chemotherapy and targeted agents
  - Immune-related AEs or immune-mediated AEs
  - Occur through an imbalance of tolerance and drug-induced immunity



Champiat S et al. *Ann Oncol.* 2016;27(4):559-574.
Michot JM et al. *Eur J Cancer.* 2016;54:139-148.
Steven NM et al. *Rheumatology (Oxford).* 2019;58(Suppl 7):vii29-vii39.
Winer A et al. *J Thorac Dis*. 2018;10(Suppl 3):S480-S489.
Robert. Presented at: ASCO 2017.
Education session: Checkpoint inhibitor immunotherapy.

Safety Profile of ICIs



Madden KM et al. *Clin J Oncol Nurs*. 2017;21(Suppl 4):30-41.

Conclusions

- Immunotherapy has changed the landscape of treatment for gastrointestinal malignancies

- Standard option for the following GI cancer settings
  - 1L MMR deficient CRC
  - Neoadjuvant therapy for MMRd rectal cancer
  - 1L therapy with chemotherapy for gastroesophageal cancer
  - 1L therapy with chemotherapy for biliary tract cancers
  - 1L therapy for hepatocellular cancer

- Management of Immunotherapy associated toxicities