به نام خداوند جان و خرد کزین برتر اندیشه برنگذرد

خداوند نام و خداوند جای خداوند روزی ده رهنمای

خداوند کیهان و گردون سپهر فروزندهٔ ماه و ناهید و مهر

TOP PRACTICE CHANGING IN ONCOLOGY 2021

دکترعلیرضا باری
هماتولوژیست-اونکولوژیست

CheckMate 577 Update: Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer After Neoadjuvant Chemotherapy

CheckMate 577 Update: Background

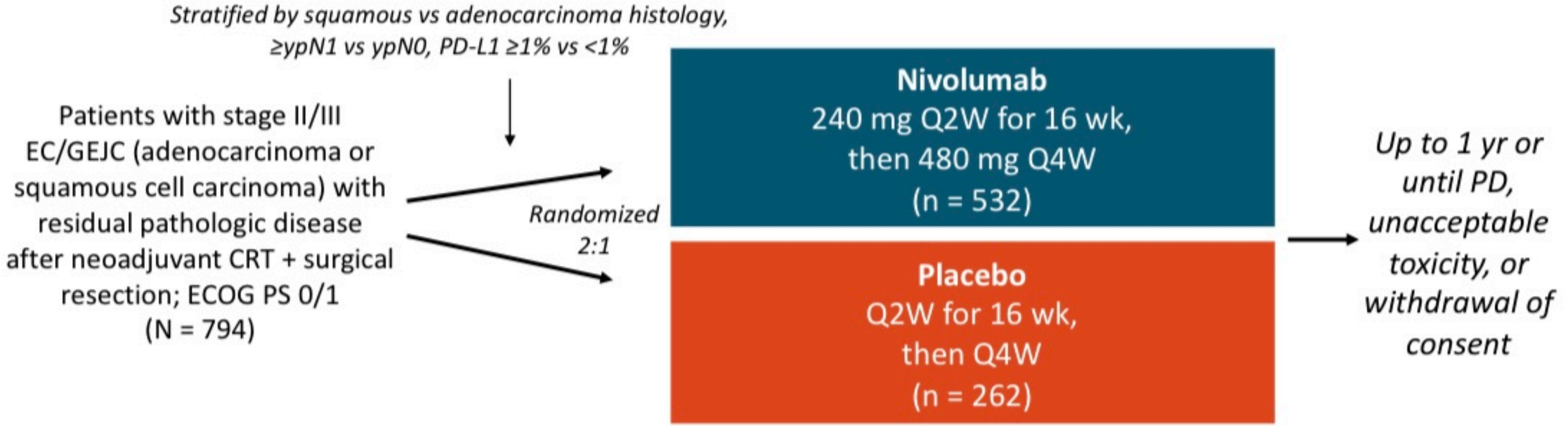
- High risk of recurrence after standard trimodality therapy (neoadjuvant chemoradiotherapy followed by surgery) for locally advanced EC/GEJC, especially those with residual disease
- No established adjuvant therapy in this setting
- Phase III CheckMate 577 trial evaluated safety and efficacy of adjuvant nivolumab vs placebo in patients with resected EC/GEJC and residual pathologic disease after neoadjuvant chemoradiotherapy
  - Primary endpoint analysis showed significant DFS improvement with nivolumab compared with placebo[1]
  - Current analysis presents updated efficacy, safety, and quality-of-life data[2]

. Kelly. NEJM. 2021;384:1191. 2. Kelly. ASCO 2021. Abstr 4003.

Slide credit: clinicaloptions.com

CheckMate 577 Update: Study Design

- Randomized, international, double-blind, placebo-controlled phase III study



- **Primary endpoint:** DFS
- **Secondary endpoints:** OS, OS rate at Yr 1, 2, and 3
- **Exploratory endpoints:** safety, DMFS, PFS2, QoL
- Median follow-up: 24.4 mo (range: 6.2-44.9)

Kelly. NEJM. 2021;384:1191. 2. Kelly. ASCO 2021. Abstr 4003.

Slide credit: clinicaloptions.com

CheckMate 577 Update: Efficacy and QoL

Outcome	Nivolumab (n = 532)	Placebo (n = 262)	HR (95% CI)	*P* Value
Median DFS, mo (95% CI) ▪ 6-mo DFS, % (95% CI)	22.4 (16.6-34.0) 72 (68-76)	11.0 (8.3-14.3) 63 (57-69)	0.69 (0.56-0.86)	.0003
Median distant metastasis–free survival, mo (95% CI)	28.3 (21.3-NE)	17.6 (12.5-25.4)	0.74 (0.60-0.92)	--
Recurrence, % ▪ Distant ▪ Locoregional	 29 12	 39 17	--	--
Median PFS2, mo (95% CI)	NR (34.0-NE)	32.1 (24.2-NE)	0.77 (0.60-0.99)	--

- DFS benefit with nivolumab seen across multiple subgroups, including tumor location, histology, PD-L1 expression, lymph node status, tumor status, time from resection to randomization, and radiotherapy dosage
- Patient-reported quality of life improved with treatment in both arms and maintained after treatment ended (FACT-E G7 and esophageal cancer subscale)

Kelly. ASCO 2021. Abstr 4003.

Slide credit: clinicaloptions.com

CheckMate 577 Update: Conclusions

- In updated results from CheckMate 577, adjuvant nivolumab significantly prolonged DFS compared with placebo in patients with resected EC/GEJC after neoadjuvant chemotherapy
  - 31% reduction in risk of recurrence with doubled median DFS (11.0 mo to 22.4 mo)
  - Nivolumab led to clinically meaningful reduction in distant and locoregional recurrence and prolonged PFS2 and DMFS
- Adjuvant nivolumab safety profile acceptable and QoL maintained
  - QoL improved on treatment in both treatment arms and maintained after treatment ended
- Investigators indicate the data provide more support that adjuvant nivolumab should be new standard of care for patients with resected EC/GEJC and residual pathologic disease after neoadjuvant chemoradiotherapy

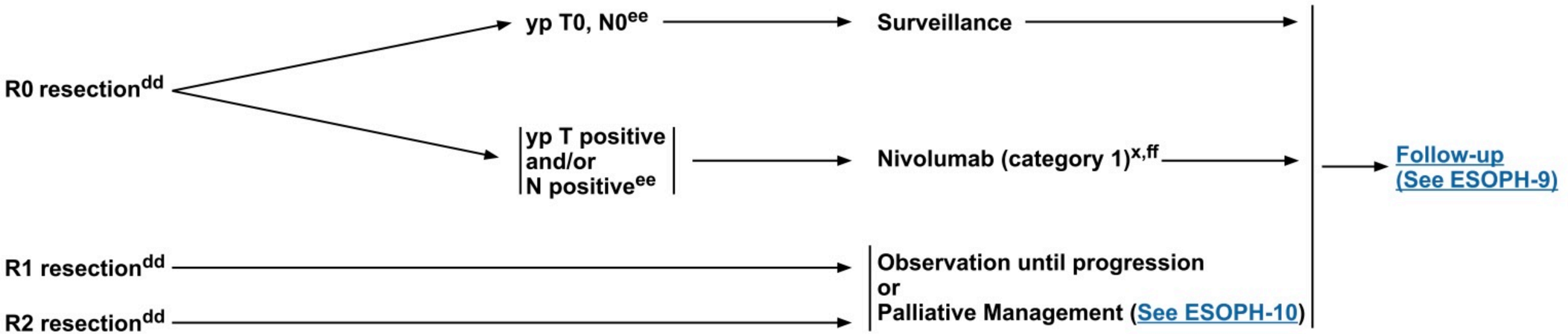
Kelly. ASCO 2021. Abstr 4003.

Slide credit: clinicaloptions.com

SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS FOR SQUAMOUS CELL CARCINOMA
(Patients Have Received Preoperative Chemoradiation)

TUMOR CLASSIFICATION[g,dd]

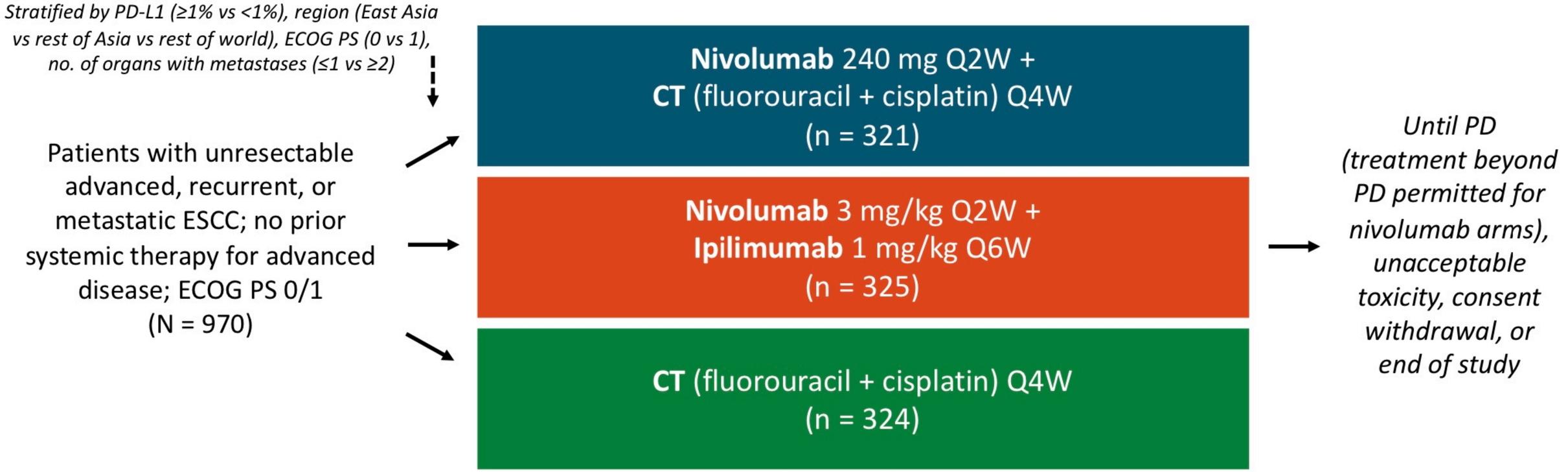
POSTOPERATIVE MANAGEMENT



CheckMate 648: Nivolumab + Ipilimumab or Chemotherapy vs Chemotherapy Alone for First-line Treatment of Advanced Esophageal Squamous Cell Carcinoma

CheckMate 648: Study Design

- International, randomized, open-label phase III trial



- Coprimary endpoints: OS and PFS in patients with tumor cell PD-L1 ≥1%
- Secondary endpoints: OS and PFS in all randomized patients, ORR in all randomized patients and those with tumor cell PD-L1 ≥1%

Chau. ASCO 2021. Abstr LBA4001.

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CheckMate 648: Baseline Characteristics

Characteristic	Nivolumab + CT (n = 321)	Nivolumab + Ipilimumab (n = 325)	CT (n = 324)
Median age, yr (range)	64 (40-90)	63 (28-81)	64 (26-81)
Male, %	79	83	85
Asian/non-Asian, %	70/30	70/30	70/30
ECOG PS 1, %	54	54	53
ESCC, %	97	99	98
Tumor cell PD-L1 expression, %			
▪ ≥1%	49	49	48
▪ <1%	51	51	52
Disease status at entry, %			
▪ De novo metastatic	57	60	58
▪ Recurrent locoregional	7	8	8
▪ Recurrent distant	22	22	19
▪ Unresectable advanced	14	10	16
No. of organs with metastases, %			
▪ ≤1	49	49	49
▪ ≥2	51	51	51
Current/former smoker, %	79	82	79

Chau. ASCO 2021. Abstr LBA4001.

Slide credit: clinicaloptions.com

CheckMate 648: OS

Survival Outcome	Patients With Tumor Cell PD-L1 ≥1%			All Randomized Patients		
	Nivolumab + CT (n = 158)	Nivolumab + Ipilimumab (n = 158)	CT (n = 157)	Nivolumab + CT (n = 321)	Nivolumab + Ipilimumab (n = 325)	CT (n = 324)
Median OS, mo (95% CI)	15.4 (11.9-19.5)	13.7 (11.2-17.0)	9.1 (7.7-10.0)	13.2 (11.1-15.7)	12.8 (11.3-15.5)	10.7 (9.4-11.9)
▪ HR (99.5% CI)	0.54 (0.37-0.80)	0.64 (0.46-0.90)		0.74 (0.58-0.96)	0.78 (0.62-0.98)	
▪ *P* value	<.0001	.0010		.0021	.0110	
12-mo OS, %	58	57	37	54	54	44

- Nivolumab + CT and nivolumab + ipilimumab improved OS vs CT alone in most prespecified subgroups

Chau. ASCO 2021. Abstr LBA4001.

Slide credit: clinicaloptions.com

CheckMate 648: Response

Response per BICR	Patients With Tumor Cell PD-L1 ≥1%			All Randomized Patients		
	Nivo + CT (n = 158)	Nivo + Ipi (n = 158)	CT (n = 157)	Nivo + CT (n = 321)	Nivo + Ipi (n = 325)	CT (n = 324)
ORR, % (95% CI)	53 (45-61)	35 (28-43)	20 (14-27)	47 (42-53)	28 (23-33)	27 (22-32)
▪ CR, %	16	18	5	13	11	6
▪ PR, %	37	18	15	34	17	21
▪ SD, %	25	27	46	32	32	46
▪ PD, %	14	30	15	13	32	12
Median DoR, mo (95% CI)	8.4 (6.9-12.4)	11.8 (7.1-27.4)	5.7 (4.4-8.7)	8.2 (6.9-9.7)	11.1 (8.3-14.0)	7.1 (5.7-8.2)

Chau. ASCO 2021. Abstr LBA4001.

Slide credit: clinicaloptions.com

CheckMate 648: Conclusions

- In patients with untreated advanced ESCC, nivolumab + either CT or ipilimumab significantly increased OS vs CT alone
  - Significant OS benefit observed in patients with PD-L1 expression ≥1% and in overall study population
  - PFS significantly improved with nivolumab + CT vs CT alone
  - DoR longer in nivolumab arms vs CT alone
- Safety consistent with previous data
- Investigators concluded that nivolumab + CT and nivolumab + ipilimumab constitute potential new first-line treatment standards in advanced ESCC

US FDA approves Keytruda® combined with trastuzumab and chemotherapy for gastric cancer

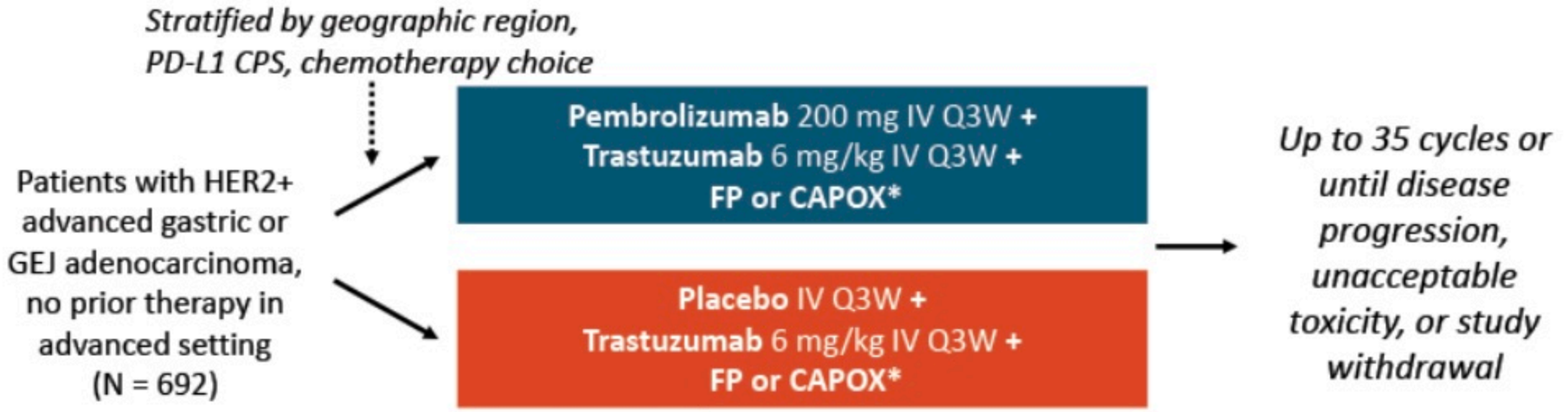
KEYNOTE-811 Interim Analysis: Background

- Trastuzumab with chemotherapy (fluoropyrimidine and platinum) is standard first-line therapy for HER2+ metastatic gastric or gastroesophageal junction cancer
- Phase II results suggest that addition of pembrolizumab to trastuzumab/chemotherapy has manageable safety and antitumor activity in this setting[1,2]
- Phase III KEYNOTE-811 trial is evaluating safety and efficacy of adding pembrolizumab to trastuzumab/chemotherapy in unresectable or metastatic HER2+ gastric or gastroesophageal junction cancer[3]
  - Presented here is the protocol-specified first interim analysis that assessed ORR after first 260 patients had follow-up ≥8.5 mo; superiority boundary $P = .002$ (1 sided)

1. Janjigian. Lancet Oncol. 2020;21:821. 2. Rha. ASCO 2020. Abstr 3081. 3. Janjigian ASCO 2021. Abstr 4013.

KEYNOTE-811: Pembrolizumab + Trastuzumab + CT for HER2+ Advanced Gastroesophageal Cancer

- Randomized, double-blind, placebo-controlled phase III study



*Trastuzumab 8 mg/kg loading dose.
FP: 5-fluorouracil 800 mg/m² IV Days 1-5 Q3W + cisplatin 80 mg/m² IV Q3W
CAPOX: capecitabine 1000 mg/m² BID Days 1-14 Q3W + oxaliplatin 130 mg/m² IV Q3W

- Efficacy analysis: first 264 patients enrolled; safety analysis: 433 patients who received ≥1 dose of study medication
- **Primary endpoints:** OS, PFS per RECIST v1.1 by BICR
- **Secondary endpoints:** ORR and DoR per RECIST v1.1 by BICR, safety

Janjigian ASCO 2021. Abstr 4013.

KEYNOTE-811 Interim Analysis: Efficacy

Outcome	Efficacy Population	
	Pembrolizumab (n = 133)	Placebo (n = 131)
ORR, % (95% CI)	74.4 (66.2-81.6)	51.9 (43.0-60.7)
ORR difference*	22.7 (11.2-33.7); *P* = .00006	
DCR, % (95% CI)	96.2 (91.4-98.8)	89.3 (82.7-94.0)
Best response, n (%)		
▪ CR	15 (11)	4 (3)
▪ PR	84 (63)	64 (49)
▪ SD	29 (22)	49 (37)
▪ PD	5 (4)	7 (5)
▪ Not evaluable	0	2 (2)
▪ Not assessed	0	5 (4)
Duration of response†	(n = 99)	(n = 68)
▪ Median, mo (range)	10.6 (1.1+ to 16.5+)	9.5 (1.4+ to 15.4+)
▪ ≥6 mo duration, %	70.3	61.4
▪ ≥9 mo duration, %	58.4	51.1
Size reduction from baseline, n (%)	(n = 124)‡	(n = 122)‡
▪ Any decrease	97	90
▪ ≥80% decrease	32	15

*Calculated using Mietten and Nurminen method; stratified by randomization stratification factors. †Calculated in patients with CR or PR as best response.
‡Calculated in patients with measurable disease at baseline and at least 1 post baseline measurement.

njigian ASCO 2021. Abstr 4013.

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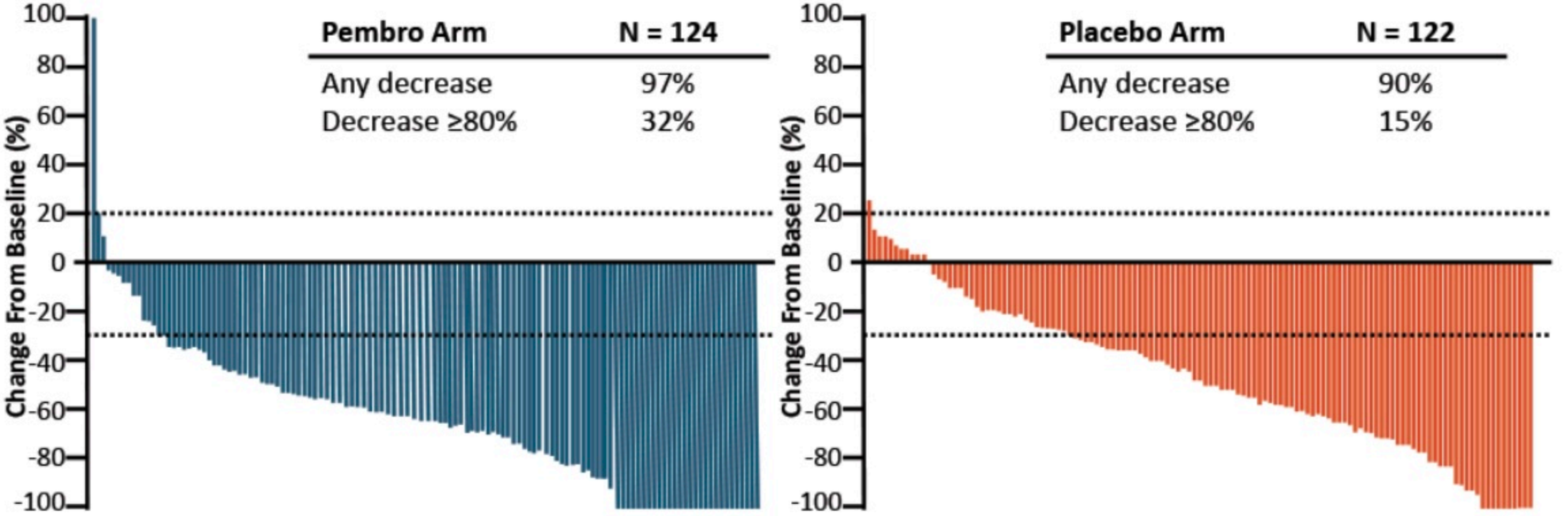
KEYNOTE-811 Interim Analysis: Target Lesion Change From Baseline



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KEYNOTE-811 Interim Analysis: Conclusions

- Adding pembrolizumab to trastuzumab/CT led to a 22.7% improvement in ORR vs placebo + trastuzumab/CT as first-line treatment for patients with advanced HER2+ gastric or gastroesophageal junction cancer
- Responses with pembrolizumab + trastuzumab/CT were deeper and more durable than those achieved with placebo + trastuzumab/CT
- Safety profile was similar between treatment arms with no unexpected safety concerns associated with pembrolizumab
- Investigators suggest pembrolizumab + trastuzumab/chemotherapy may be a possible new treatment option for previously untreated, unresectable or metastatic HER2+ gastric or gastroesophageal junction cancer

anjigian ASCO 2021. Abstr 4013.

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PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy
- Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

Preferred Regimens
- HER2 overexpression positive adenocarcinoma[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,11]
- HER2 overexpression negative[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1)[g,h,12]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[13-15]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[13,16-18]

Other Recommended Regimens
- HER2 overexpression positive adenocarcinoma[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab[a] and pembrolizumab[g,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] and pembrolizumab[g,h,19]
- Fluorouracil[b,i] and irinotecan[j,20]
- Paclitaxel with or without cisplatin or carboplatin[j,21-25]
- Docetaxel with or without cisplatin[j,26-29]
- Fluoropyrimidine[j,17,30,31] (fluorouracil[b] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b,j,32,33]
- Docetaxel, carboplatin, and fluorouracil (category 2B)[j,34]

Useful in Certain Circumstances
- HER2 overexpression negative[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS 1-4) (category 2B)[g,h,12]

KEYNOTE-177: Phase III Trial of First-line Pembrolizumab vs Chemotherapy in MSI-H/dMMR Metastatic CRC

KEYNOTE-177: Background

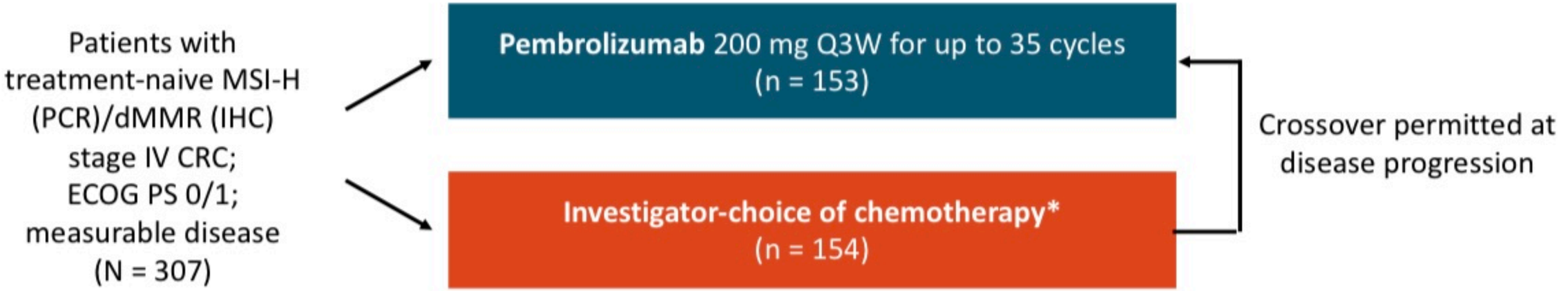
- Deficiencies in dMMR can lead to MSI-H, which is found in ~ 5% of patients with mCRC[1,2]
  - This disease type typically responds poorly to chemotherapy
  - Unique biology of MSI-H/dMMR mCRC well suited to immune checkpoint inhibition: features high tumor mutation burden, high levels of tumor neoantigens, and increased immune cell infiltration
- Prior phase II studies demonstrated durable antitumor activity and acceptable safety with use of pembrolizumab in previously treated MSI-H mCRC[3,4]
  - Pembrolizumab approved for previously treated MSI-H metastatic tumors regardless of tumor type or site[5]
- Current phase III study compared efficacy and safety of first-line pembrolizumab vs standard therapy in patients with MSI-H mCRC[6]

1. Innocenti. JCO. 2019;37:1217. 2. Venderbosch. Clin Cancer Res. 2014;20:5322. 3. Le. NEJM. 2015;372:2509.
4. Le. J Clin Oncol. 2020;38:11. 5. Pembrolizumab PI. 6. Andre. ASCO 2020. Abstr LBA4.

Slide credit: clinicaloptions.com

KEYNOTE-177: Study Design

- Randomized, open-label phase III trial



*Chemotherapy options included mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab.
†Blinded independent central review per RECIST v1.1.

- Dual primary endpoints: PFS,† OS
  - Trial positive if pembrolizumab superior to chemotherapy for either primary endpoint
- Secondary endpoints: ORR,† safety
- Data cutoff: February 29, 2020
- Median follow-up: 28.4 mos in pembrolizumab arm, 27.2 mos in comparator arm

Andre. ASCO 2020. Abstr LBA4.

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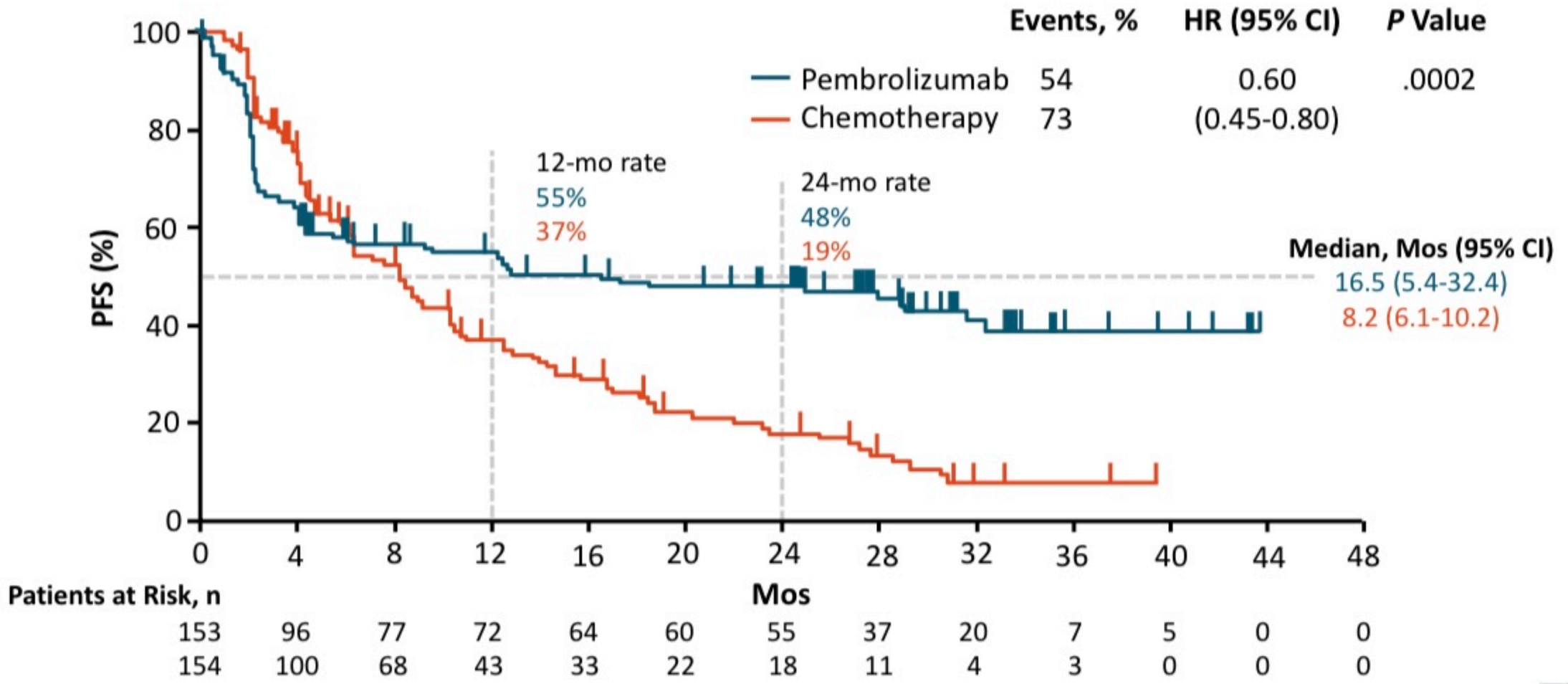
KEYNOTE-177: PFS (Primary Endpoint; ITT)



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KEYNOTE-177: Other Efficacy Endpoints

Efficacy Outcomes (ITT)	Pembrolizumab (n = 153)	Chemotherapy (n = 154)	*P* Value
ORR, %	43.8	33.1	.0275
DCR (CR + PR + SD), %	64.7	75.3	
Best overall response, %			
▪ CR	11.1	3.9	
▪ PR	32.7	29.2	
▪ SD	20.9	42.2	
▪ PD	29.4	12.3	
▪ Not evaluable	2.0	1.3	
▪ No assessment	3.9	11.0	
Median time to response, mos (range)	2.2 (1.8-18.8)	2.1 (1.7-24.9)	

- 36% of patients in chemotherapy arm crossed over to receive pembrolizumab; 23% received anti–PD-1/PD-L1 therapy outside of study
- OS analysis ongoing

Andre. ASCO 2020. Abstr LBA4.

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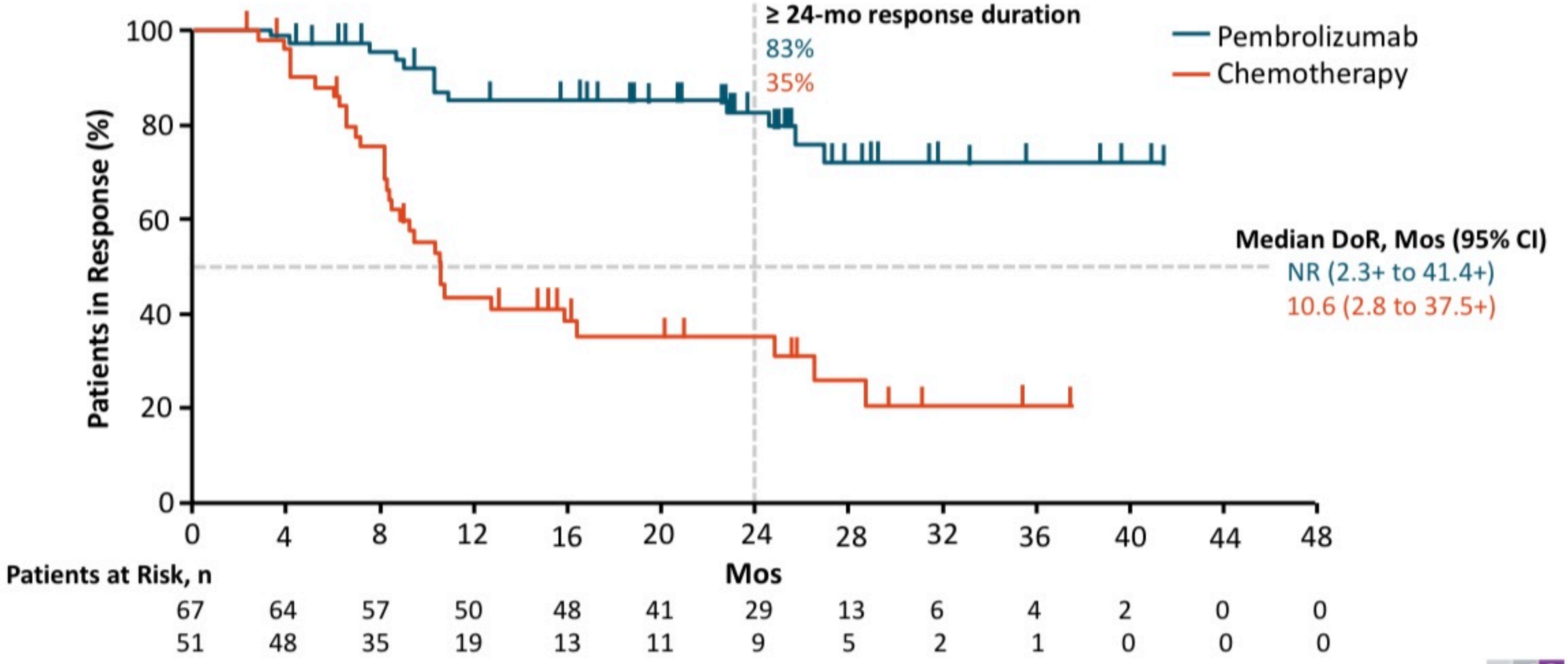
KEYNOTE-177: Duration of Response



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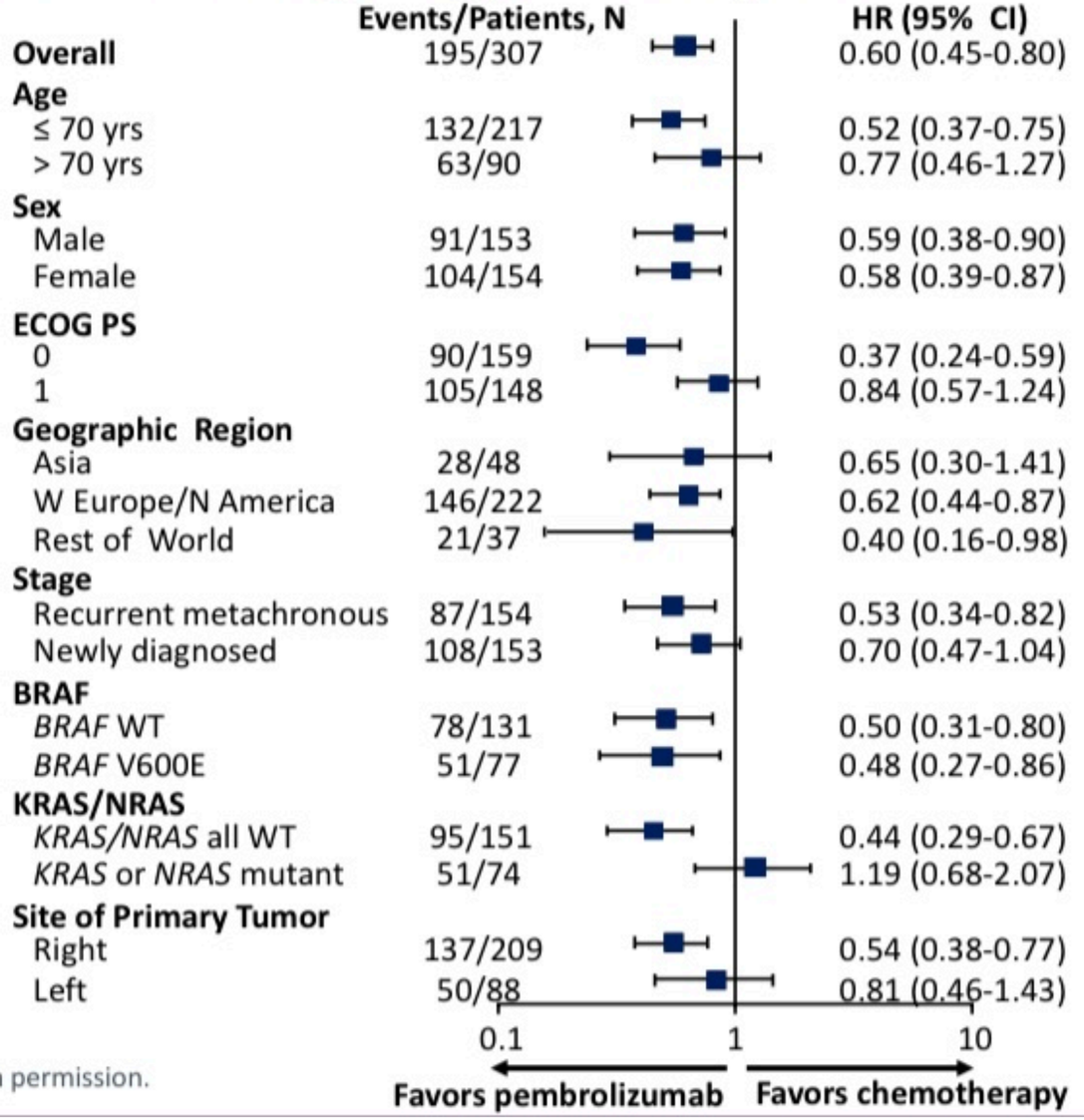
KEYNOTE-177: PFS Subgroup Analysis



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Conclusions

- Pembrolizumab produced significant and clinically meaningful improvements in outcomes vs standard therapy in treatment-naive patients with MSI-H mCRC
  - Median PFS: 16.5 vs 8.2 mos (HR: 0.60, 95% CI 0.45-0.80; *P* = .0002)
  - ORR: 43.8% vs 33.1% (*P* = .0275)
  - Median DoR: not reached vs 10.6 mos
- Pembrolizumab associated with favorable safety profile vs chemotherapy
  - Grade ≥ 3 treatment-related AEs: 22% vs 66%
- KEYNOTE-177 deemed a positive study based on PFS outcomes; OS outcomes still awaited
- Investigators concluded that single-agent pembrolizumab should be the new first-line standard of care for patients with MSI-H mCRC

Andre. ASCO 2020. Abstr LBA4.

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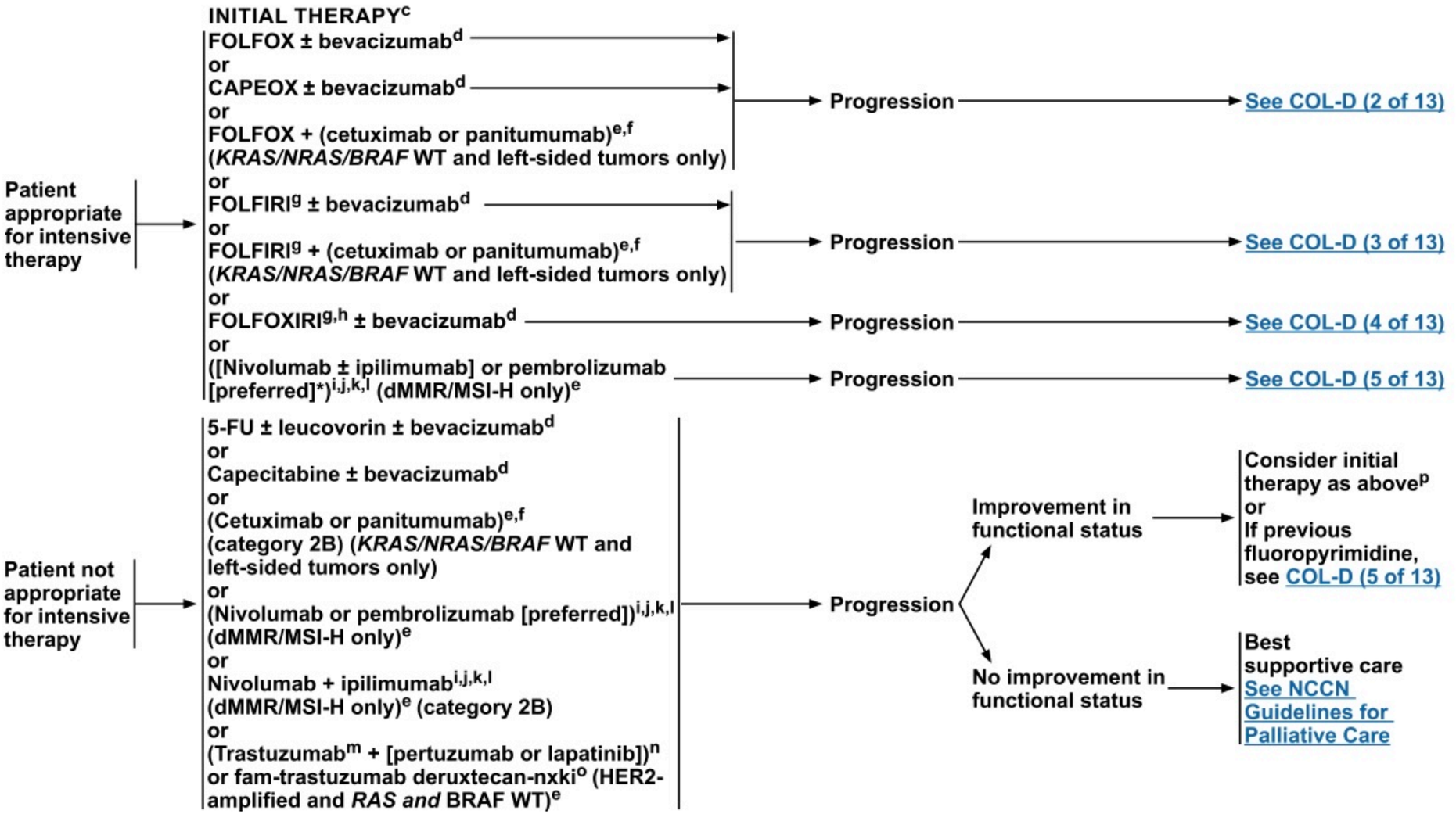
CONTINUUM OF CARE - SYSTEMATIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]



KRAS G12C confirmed as a therapeutic target for advanced NSCLC

-KRASG12C mutations occur in around 14% of patients with lung adenocarcinomas

-For many years, researchers considered KRAS an “undruggable” target

The New England Journal of Medicine

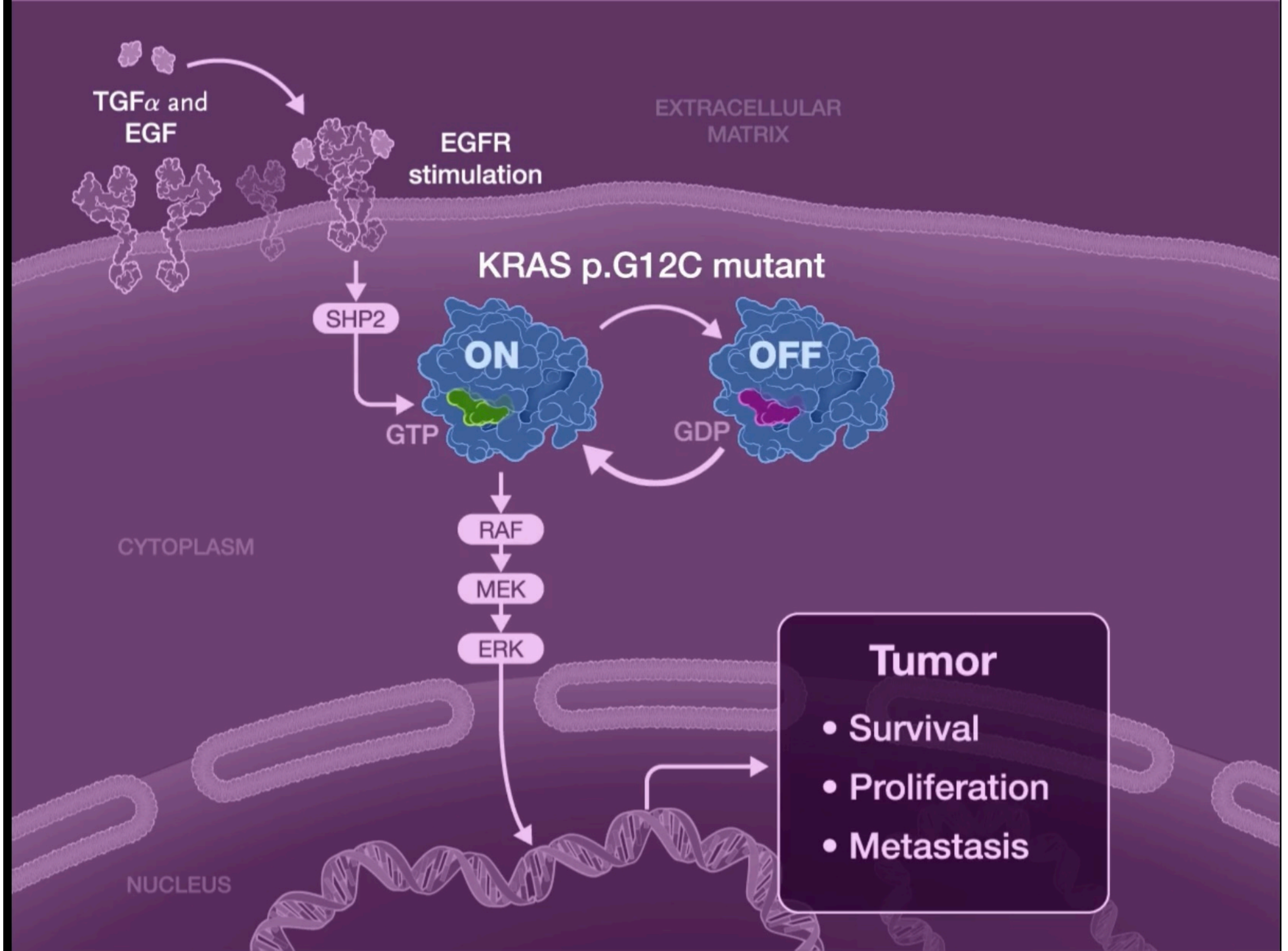
Sotorasib for Lung Cancers with KRAS Mutation

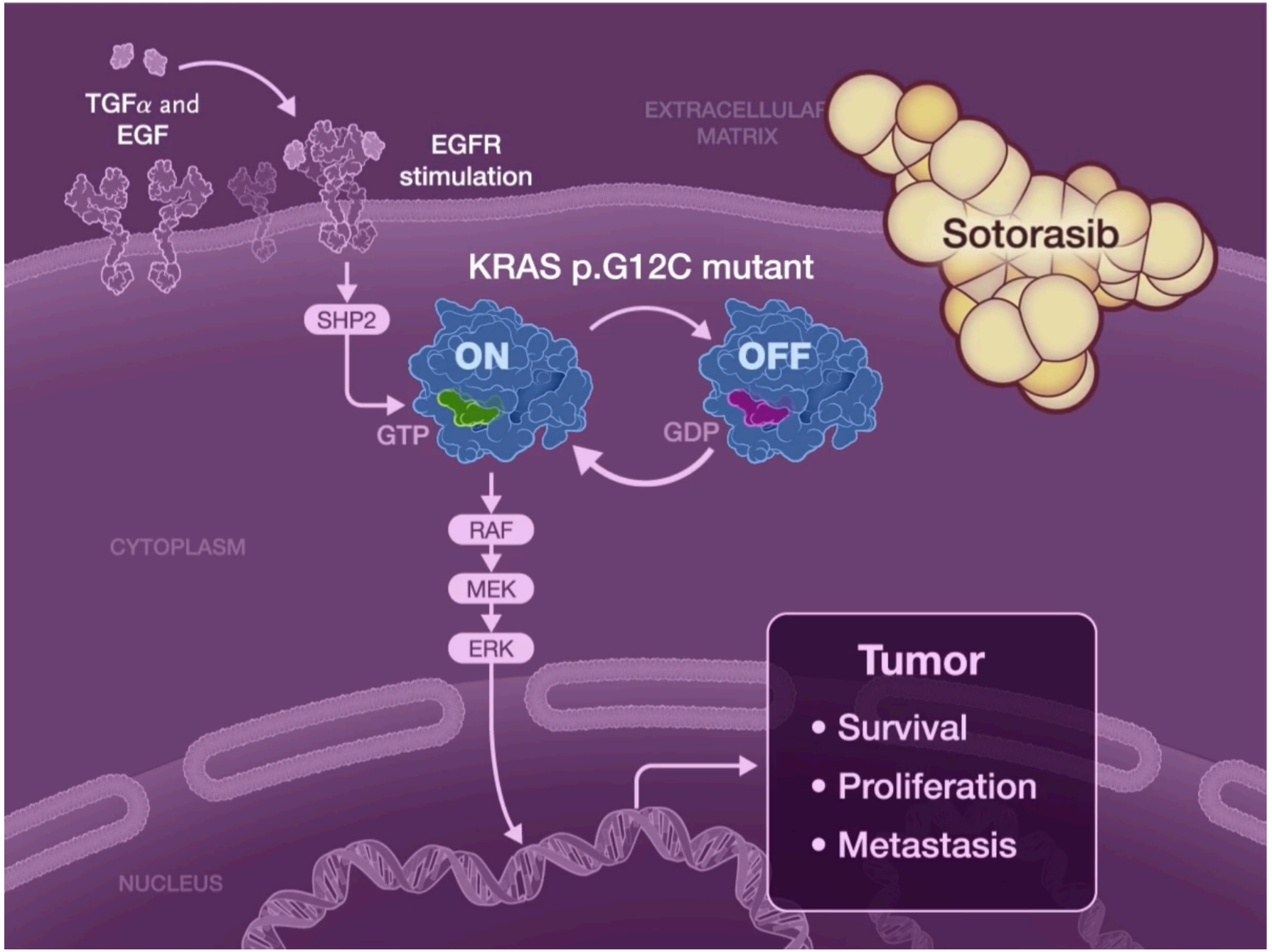
KEY POINTS FROM

Sotorasib for Lung Cancers with KRAS p.G12C Mutation

by F. Skoulidis et al.

JUNE 24, 2021


TGFα and EGF
EGFR stimulation
EXTRACELLULAR MATRIX
KRAS p.G12C mutant
SHP2
ON
OFF
GTP
GDP
RAF
MEK
ERK
CYTOPLASM
NUCLEUS
Tumor
• Survival
• Proliferation
• Metastasis


TGFα and
EGF
EGFR
stimulation
EXTRACELLULAR
MATRIX
Sotorasib
KRAS p.G12C mutant
SHP2
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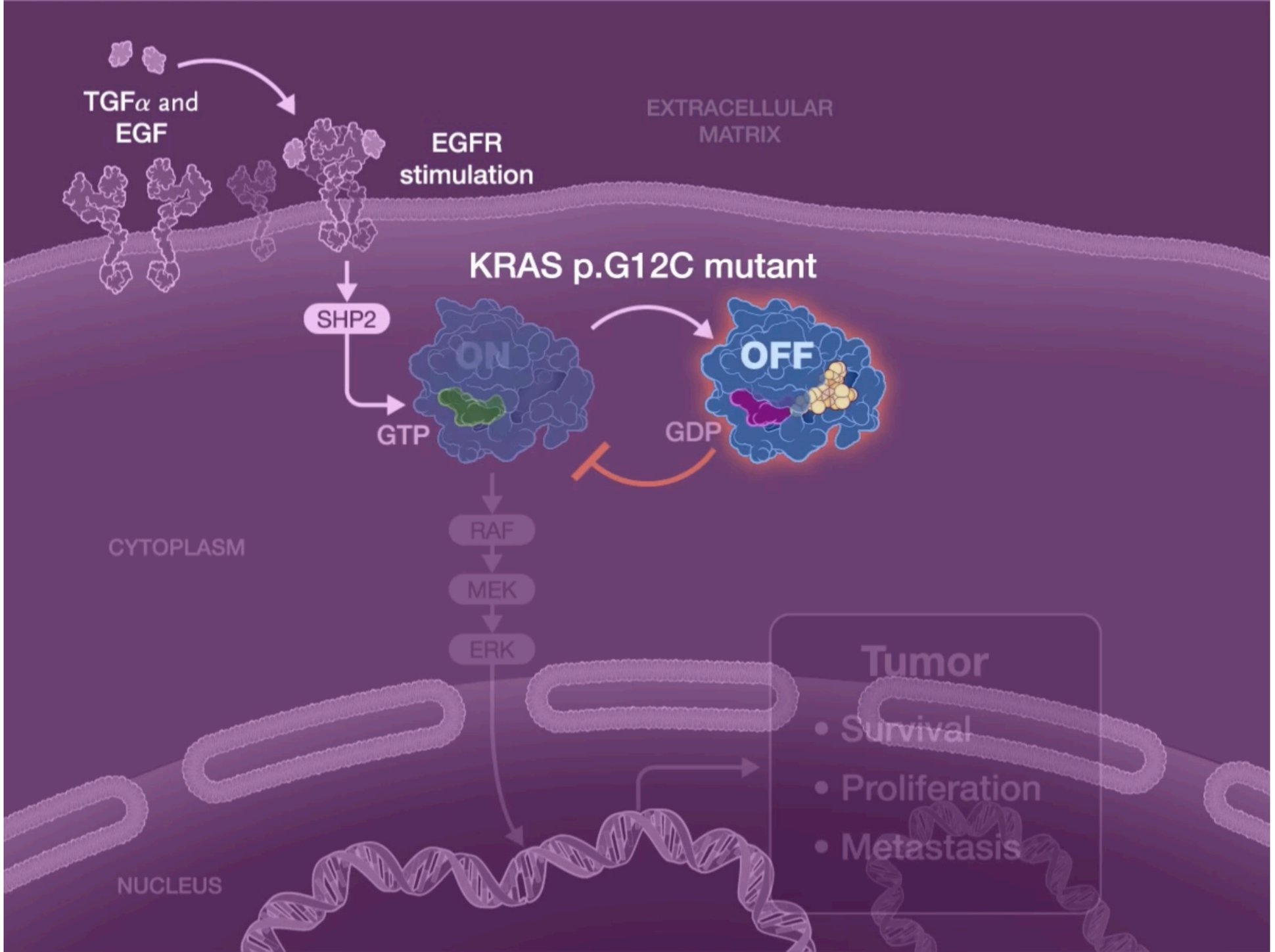
GDP
RAF
MEK
ERK
CYTOPLASM
NUCLEUS
Tumor
• Survival
• Proliferation
• Metastasis


TGFα and
EGF
EGFR
stimulation
EXTRACELLULAR
MATRIX
KRAS p.G12C mutant
SHP2
ON
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Tumor
• Survival
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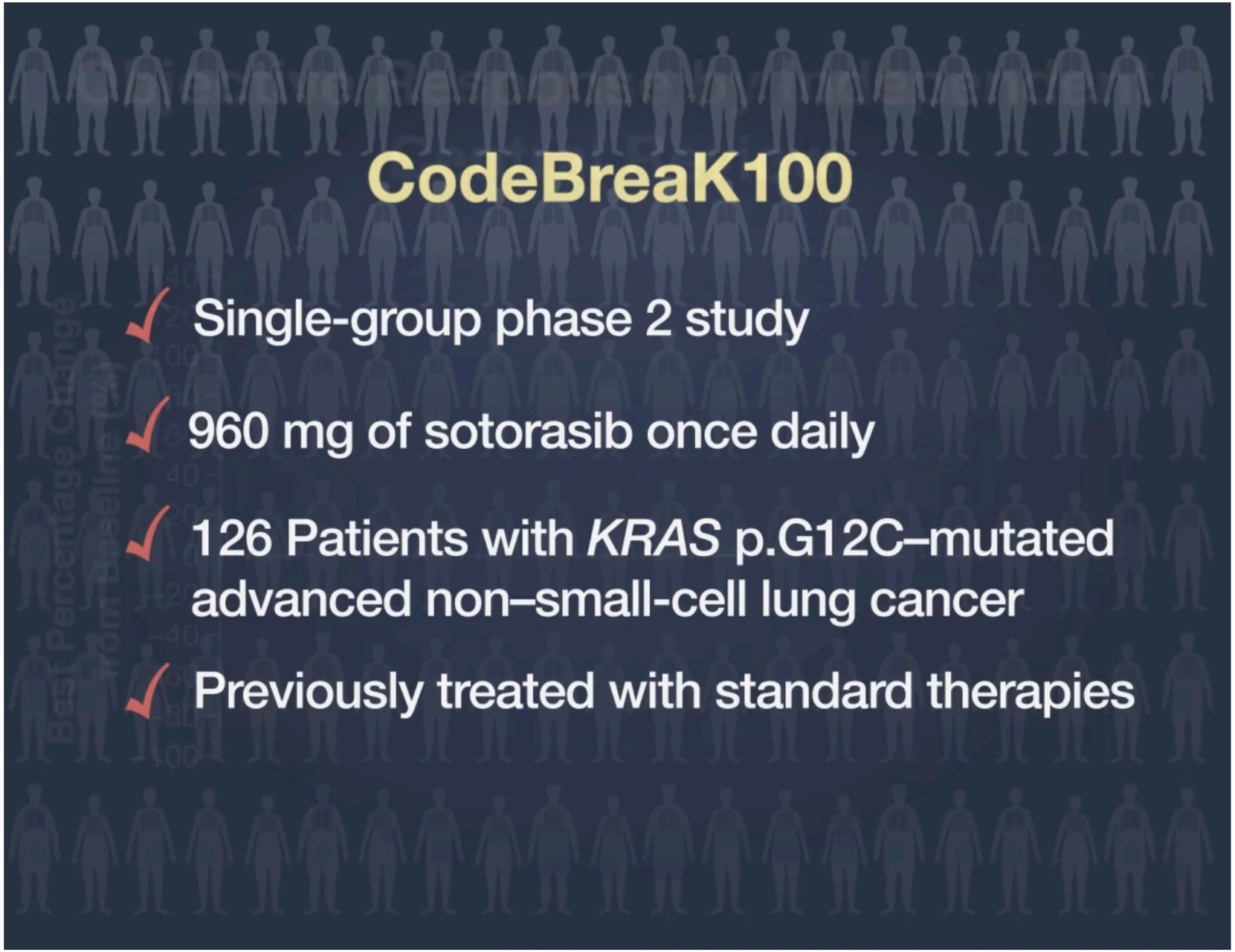
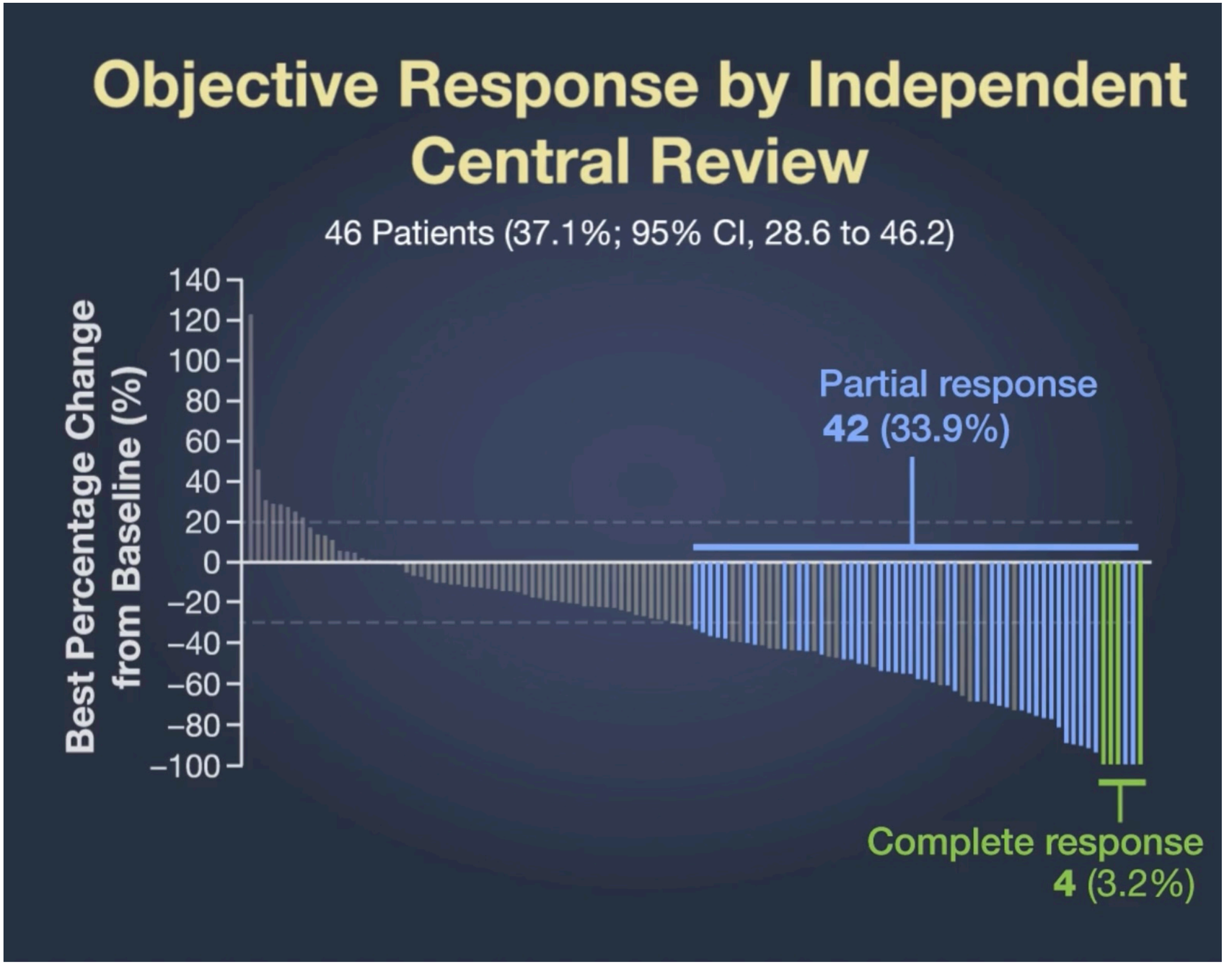
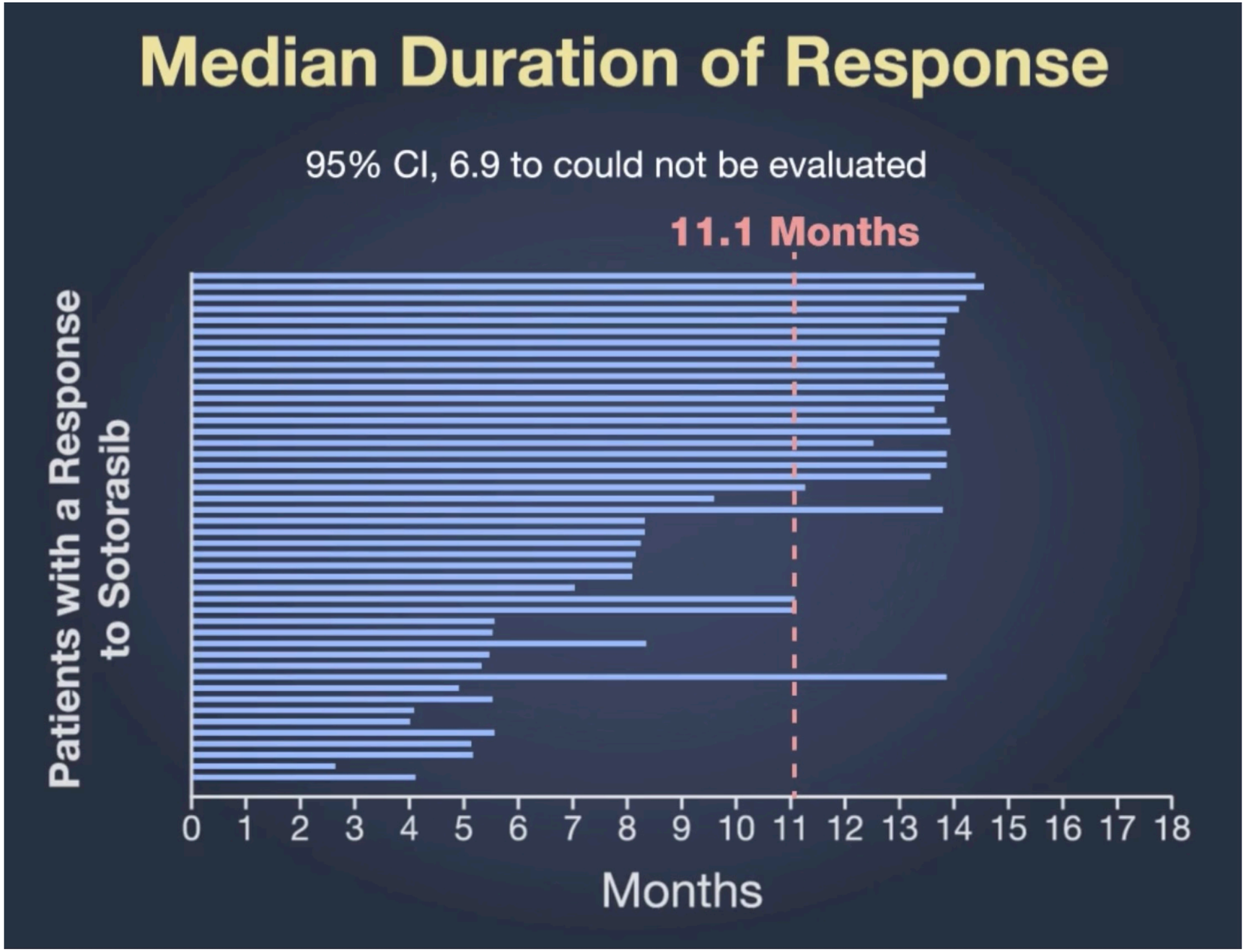
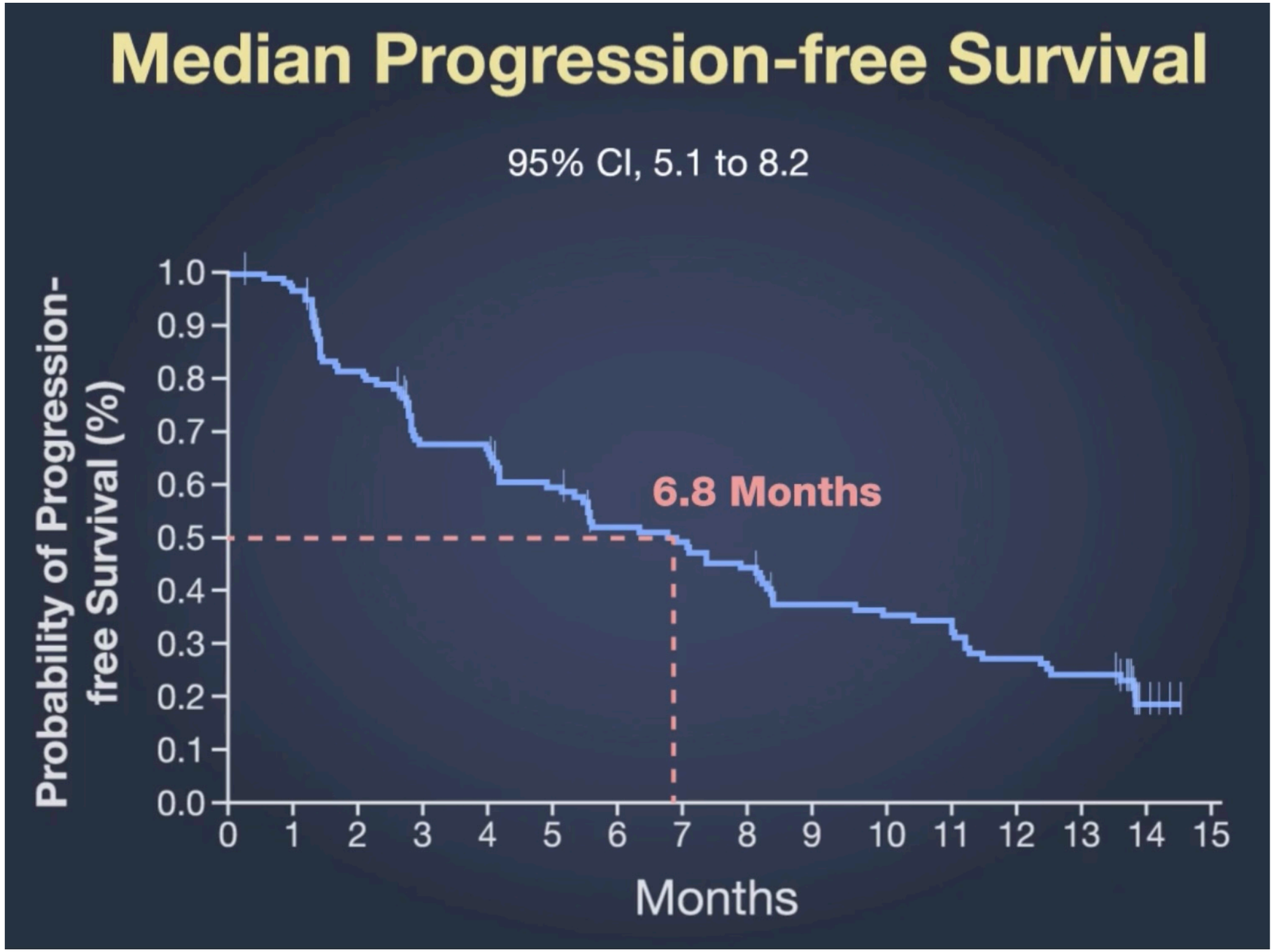
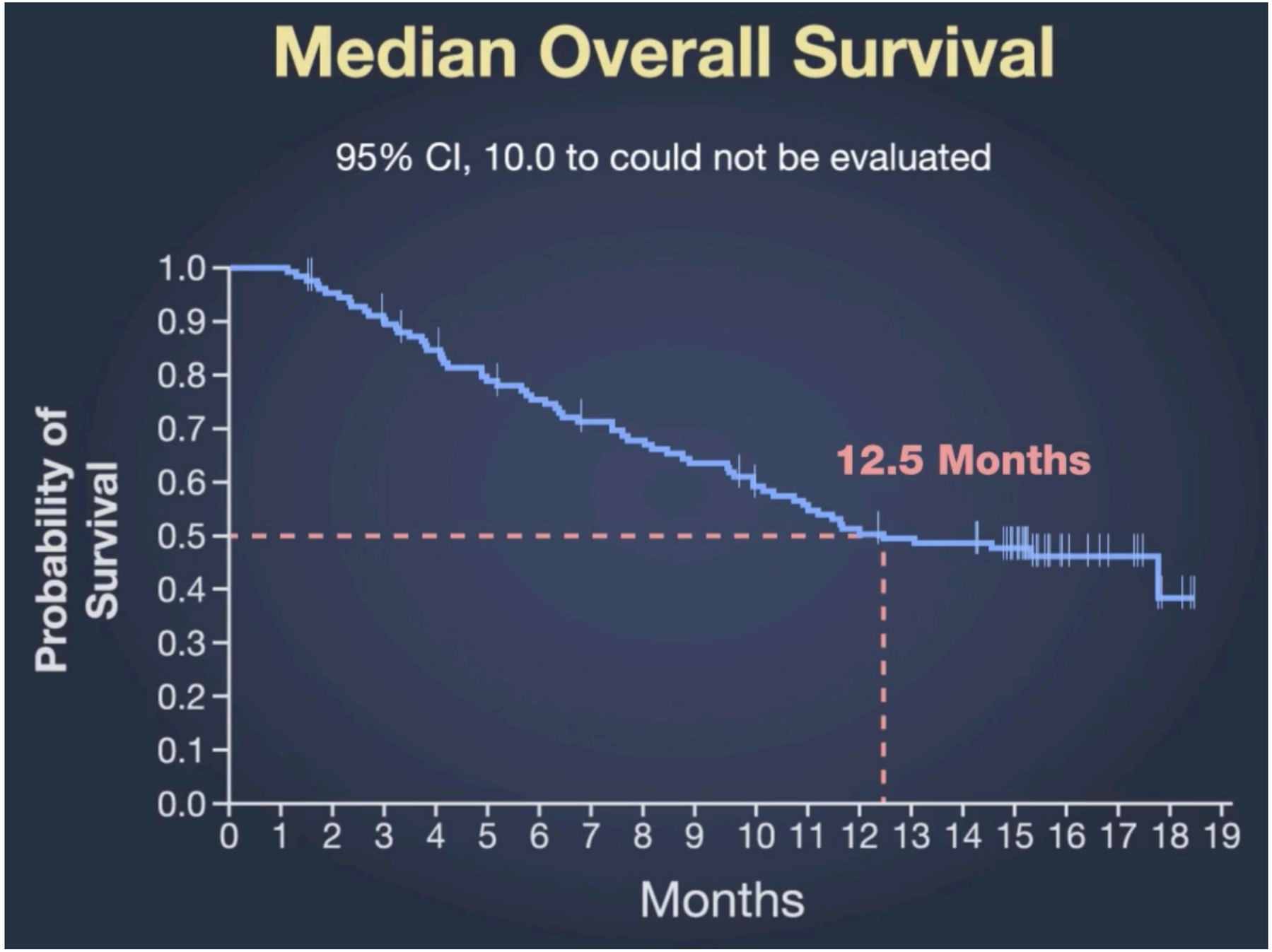
NUCLEUS


CodeBreaK100
Single-group phase 2 study
960 mg of sotorasib once daily
126 Patients with *KRAS* p.G12C–mutated advanced non–small-cell lung cancer
Previously treated with standard therapies

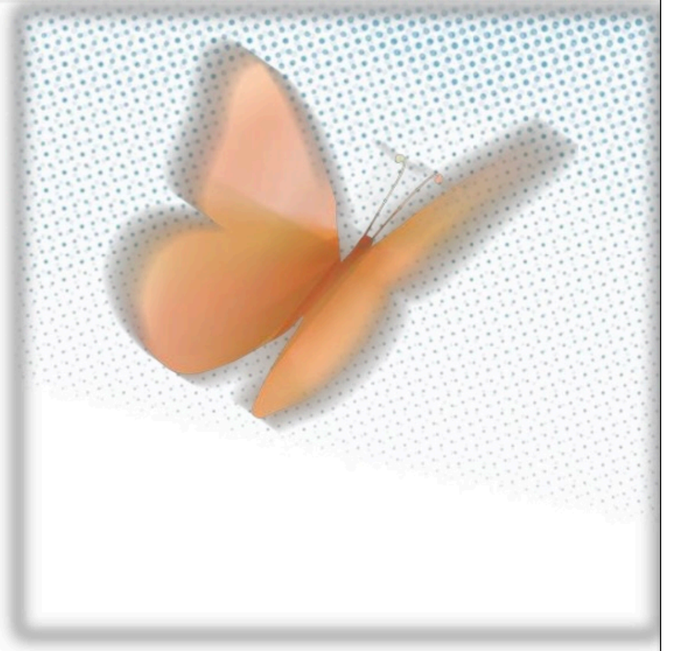

Objective Response by Independent Central Review
46 Patients (37.1%; 95% CI, 28.6 to 46.2)
Best Percentage Change from Baseline (%)
140
120
100
80
60
40
20
0
−20
−40
−60
−80
−100
Partial response
42 (33.9%)
Complete response
4 (3.2%)


Median Duration of Response
95% CI, 6.9 to could not be evaluated
11.1 Months
Patients with a Response to Sotorasib
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Months


Median Progression-free Survival
95% CI, 5.1 to 8.2
Probability of Progression-free Survival (%)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
6.8 Months
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Months


Median Overall Survival
95% CI, 10.0 to could not be evaluated
Probability of Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
12.5 Months
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Months

elcc European Lung Cancer Virtual Congress



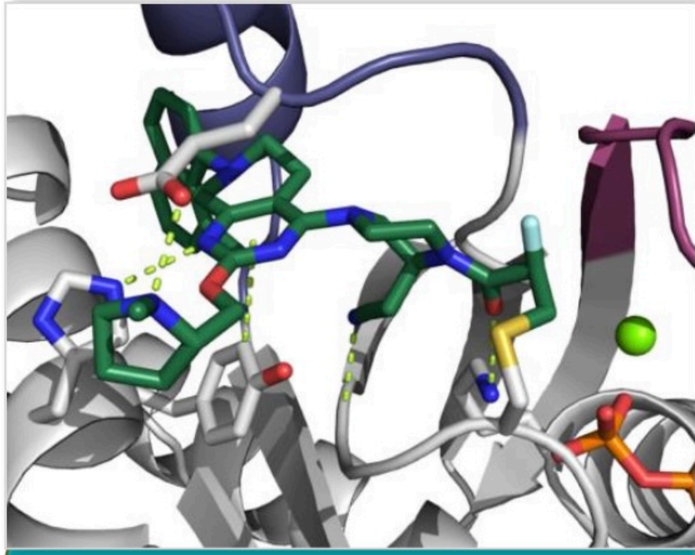
KRYSTAL-1: ACTIVITY AND PRELIMINARY PHARMACODYNAMIC (PD) ANALYSIS OF ADAGRASIB (MRTX849) IN PATIENTS (PTS) WITH ADVANCED NON–SMALL-CELL LUNG CANCER (NSCLC) HARBORING KRAS^{G12C} MUTATION

Gregory J. Riely[1], Sai-Hong Ignatius Ou[2], Igor I. Rybkin[3], Alexander I. Spira[4], Kyriakos P. Papadopoulos[5], Joshua K. Sabari[6], Melissa L. Johnson[7], Rebecca S. Heist[8], Lyudmila Bazhenova[9], Minal Barve[10], Jose M. Pacheco[11], Ticiana A. Leal[12], Karen Velastegui[13], Cornelius Cilliers[13], Peter Olson[13], James G. Christensen[13], Thian Kheoh[13], Richard C. Chao[13], Pasi A. Jänne[14]

[1]Thoracic Oncology Service, Division of Solid Tumor, Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA; [2]University of California, Irvine, Chao Family Comprehensive Cancer Center, Orange, CA, USA; [3]Henry Ford Cancer Institute, Detroit, MI, USA; [4]Virginia Cancer Specialists, Fairfax, VA, USA; US Oncology Research, The Woodlands, TX, USA; [5]START Center for Cancer Care, San Antonio, TX, USA; [6]Perlmutter Cancer Center, New York University Langone Health, New York, NY, USA; [7]Sarah Cannon Research Institute Tennessee Oncology, Nashville, TN, USA; [8]Massachusetts General Hospital, Boston, MA, USA; [9]Moores Cancer Center, University of California San Diego, La Jolla, CA, USA; [10]Mary Crowley Cancer Research, Dallas, TX, USA; [11]Division of Medical Oncology, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [12]University of Wisconsin Carbone Cancer Center, Madison, WI, USA; [13]Mirati Therapeutics, Inc., San Diego, CA, USA; [14]Dana-Farber Cancer Institute, Boston, MA, USA.

Adagrasib (MRTX849) Is a Differentiated, Selective Inhibitor of KRAS^{G12C}

- KRAS^{G12C} mutations act as oncogenic drivers and occur in approximately 14% of NSCLC (adenocarcinoma)[1-3]
- The KRAS protein cycles between GTP-on and GDP-off states and has a protein resynthesis half-life of ~24 h[4,5]
- Adagrasib is a covalent inhibitor of KRAS^{G12C} that irreversibly and selectively binds KRAS^{G12C} in its inactive, GDP-bound state[6]
- Adagrasib was optimized for desired properties of a KRAS^{G12C} inhibitor:
  - Potent covalent inhibitor of KRAS^{G12C} (cellular IC_{50}: ~5 nM)
  - High selectivity (>1000X) for the mutant KRAS^{G12C} protein vs wild-type KRAS
  - Favorable PK properties, including oral bioavailability, long half-life (~24 h), and extensive tissue distribution



Adagrasib Crystal Structure

Hypothesis: Maintaining continuous exposure of adagrasib above a target threshold enables inhibition of KRAS-dependent signaling for the complete dosing interval and maximizes depth and duration of antitumor activity.

Adagrasib in Patients With NSCLC: ORR in Pooled Dataset

Efficacy Outcome[a], n (%)	Phase 1/1b, NSCLC 600 mg BID (n=14)	Phase 1/1b and 2, NSCLC 600 mg BID (n=51)
Objective Response Rate	6 (43%)	23 (45%)[b]
Best Overall Response		
Complete Response (CR)	0 (0%)	0 (0%)
Partial Response (PR)	6 (43%)	23 (45%)
Stable Disease (SD)	8 (57%)	26 (51%)
Progressive Disease (PD)	0 (0%)	1 (2%)
Not Evaluable (NE)	0 (0%)	1 (2%)[c]
Disease Control	14 (100%)	49 (96%)

[a]Based on investigator assessment of the clinically evaluable patients (measurable disease with ≥1 on-study scan); 14/18 patients (Phase 1/1b) and 51/79 patients (Phase 1/1b and 2 pooled) met these criteria. [b]At the time of the 30 August 2020 data cutoff, 5 patients had unconfirmed PRs. All 5 PRs were confirmed by scans that were performed after the 30 August 2020 data cutoff. [c]One patient had tumor reimaging too early for response assessment.
Data as of 30 August 2020. The pooled dataset includes data from the NSCLC Phase 1/1b and Phase 2 600 mg BID cohorts.

Incidence of Treatment-Related Adverse Events

	All Cohorts Pooled, 600 mg BID[a] (n=110)		
TRAEs[b,c], %	**Any Grade**	**Grades 3-4**	**Grade 5**
Any TRAEs	85%	30%	2%
Most frequent TRAEs[a,d], %			
Nausea	54%	2%	0%
Diarrhea	51%	0%	0%
Vomiting	35%	2%	0%
Fatigue	32%	6%	0%
Increased ALT	20%	5%	0%
Increased AST	17%	5%	0%
Increased blood creatinine	15%	0%	0%
Decreased appetite	15%	0%	0%
QT prolongation	14%	3%	0%
Anemia	13%	2%	0%

- Grade 5 TRAEs included pneumonitis in a patient with recurrent pneumonitis (n=1) and cardiac failure (n=1)
- 4.5% of TRAEs led to discontinuation of treatment

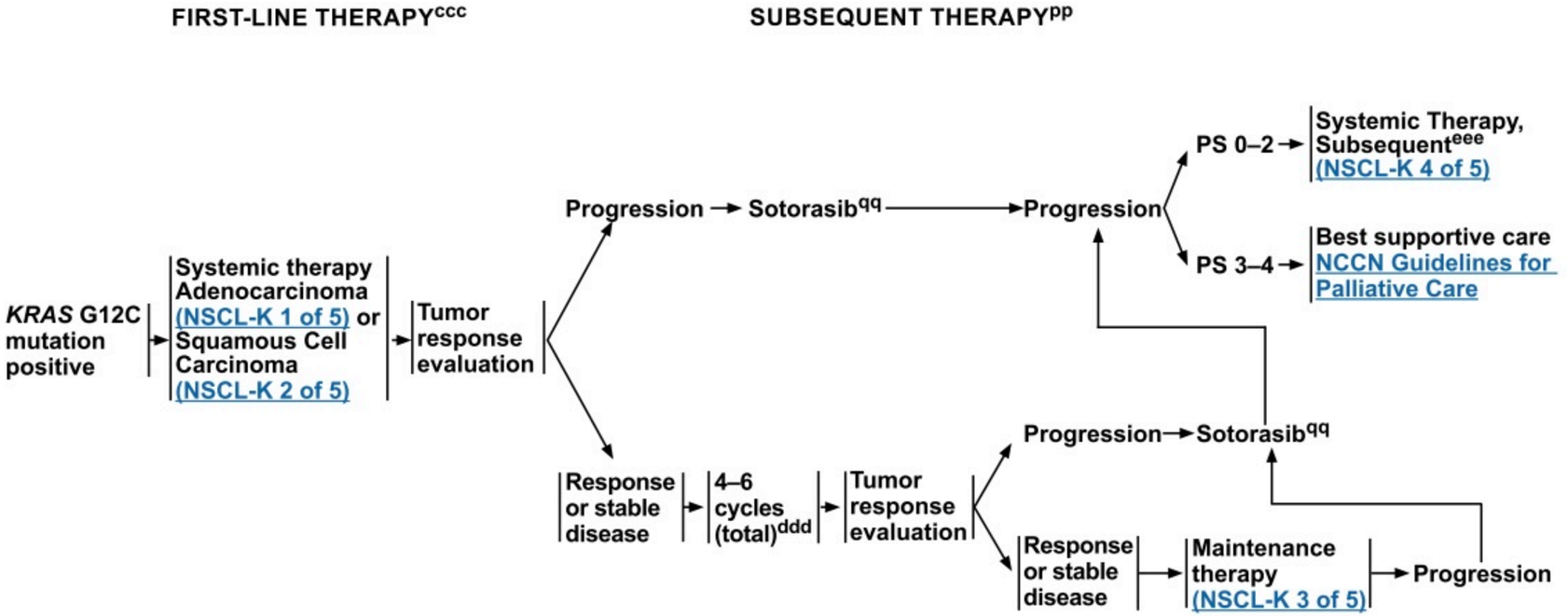
[a]Includes patients pooled from Phase 1/1b and Phase 2 NSCLC (n=79), and CRC and Phase 2 other tumor cohorts (n=31). [b]Includes events reported between the first dose and 30 August 2020. [c]The most common treatment-related SAEs reported (2 patients each) reported were diarrhea (grade 1, grade 2) and hyponatremia (both grade 3). [d]Occurred in ≥10%. Data as of 30 August 2020.

Conclusions

- Adagrasib is a KRAS^{G12C}-selective covalent inhibitor with a long half-life and extensive predicted target coverage throughout the dosing interval
- Adagrasib is well tolerated and provides durable responses and broad disease control to patients with NSCLC harboring KRAS^{G12C} mutations
- In an exploratory genomic analysis, ORR was higher in patients with tumors harboring KRAS^{G12C} and STK11 co-mutations
- Initial biomarker analyses post-treatment with adagrasib indicate downregulation of KRAS/MAPK pathway genes and an increase in immune transcripts in patients with STK11 co-mutations
- Adagrasib is being evaluated as 1L monotherapy in patients with NSCLC with KRAS^{G12C} and STK11 co-mutations in a new cohort of KRYSTAL-1

Presented at the European Lung Cancer Conference (ELCC), March 25-27, 2021

KRAS G12C MUTATION POSITIVE[mm]



[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.
[ccc] Monitoring During Initial Therapy: Response assessment after 2 cycles, then every 2–4 cycles with CT of known or high-risk sites of disease with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.
[ddd] In general, 4 cycles of initial systemic therapy (ie, with carboplatin or cisplatin) are administered prior to maintenance therapy. However, if patient is tolerating therapy well, consideration can be given to continue to 6 cycles.
[eee] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

IMpower010: Phase III Trial of Adjuvant Atezolizumab vs BSC in Resected Stage IB-IIIA NSCLC After Adjuvant Chemotherapy

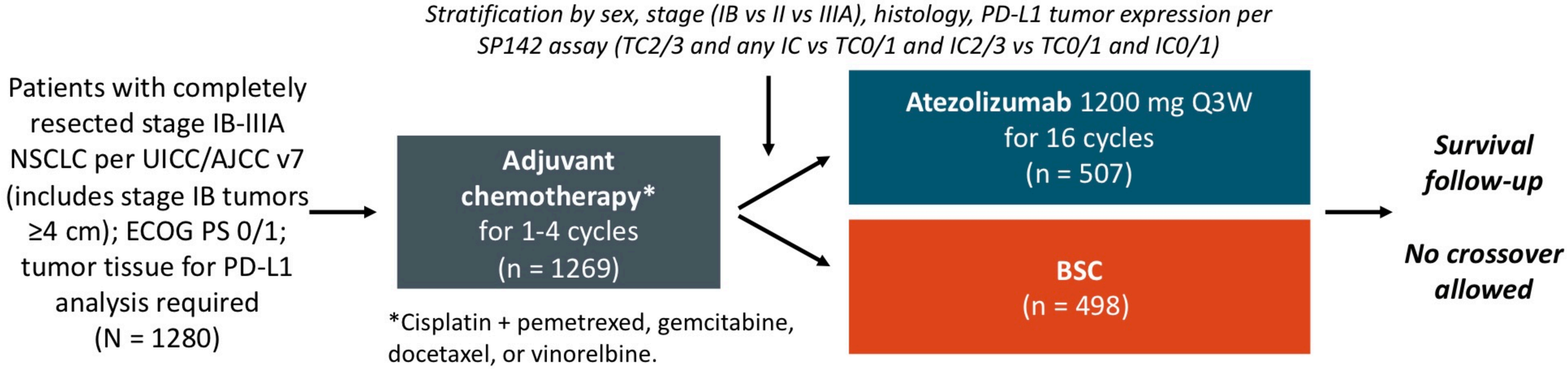
IMpower010: Background

- Adjuvant platinum-based chemotherapy has long been the standard of care for completely resected early-stage NSCLC (stage IB-IIIA) based on an absolute improvement in 5-yr OS of 4%-5%[1-4]
- Use of adjuvant osimertinib in patients with resectable, early-stage NSCLC following standard adjuvant chemotherapy has been shown to confer a substantial DFS benefit to patients with tumors harboring *EGFR*-activating mutations[5]
- However, patients with resectable, early-stage NSCLC lacking *EGFR* mutations still face a high unmet need for improved adjuvant treatment
- IMpower010: randomized phase III trial evaluating the efficacy and safety of adjuvant atezolizumab vs BSC in patients with completely resected NSCLC after adjuvant chemotherapy[6]
  - Primary results from a preplanned interim analysis are presented here[7]

1. Pignon. JCO. 2008;26:3552. 2. NCCN Clinical Practice Guidelines in Oncology. Non-small cell lung Cancer. V8.2020.
3. Postmus. Ann Oncol. 2017;28:iv1. 4. Vansteenkiste. Ann Oncol. 2019;30:1244. 5. Wu. NEJM. 2020;383:1711.
6. NCT02486718. 7. Wakelee. ASCO 2021. Abstr 8500.

IMpower010: Study Design

- Randomized, open-label phase III trial (data cutoff for interim analysis: January 21, 2021)



- Primary endpoint: hierarchical evaluation of investigator-assessed DFS in 3 populations
  - Stage II-IIIA with PD-L1 TC ≥1% (by PD-L1 SP264 IHC assay) → all randomized stage II-IIIA → ITT population (stage IB-IIIA)
- Key secondary endpoints: OS (ITT); DFS in stage II-IIIA with PD-L1 TC ≥50 (by PD-L1 SP264 IHC assay); 3-yr and 5-yr DFS in all 3 populations; safety

Wakelee. ASCO 2021. Abstr 8500.

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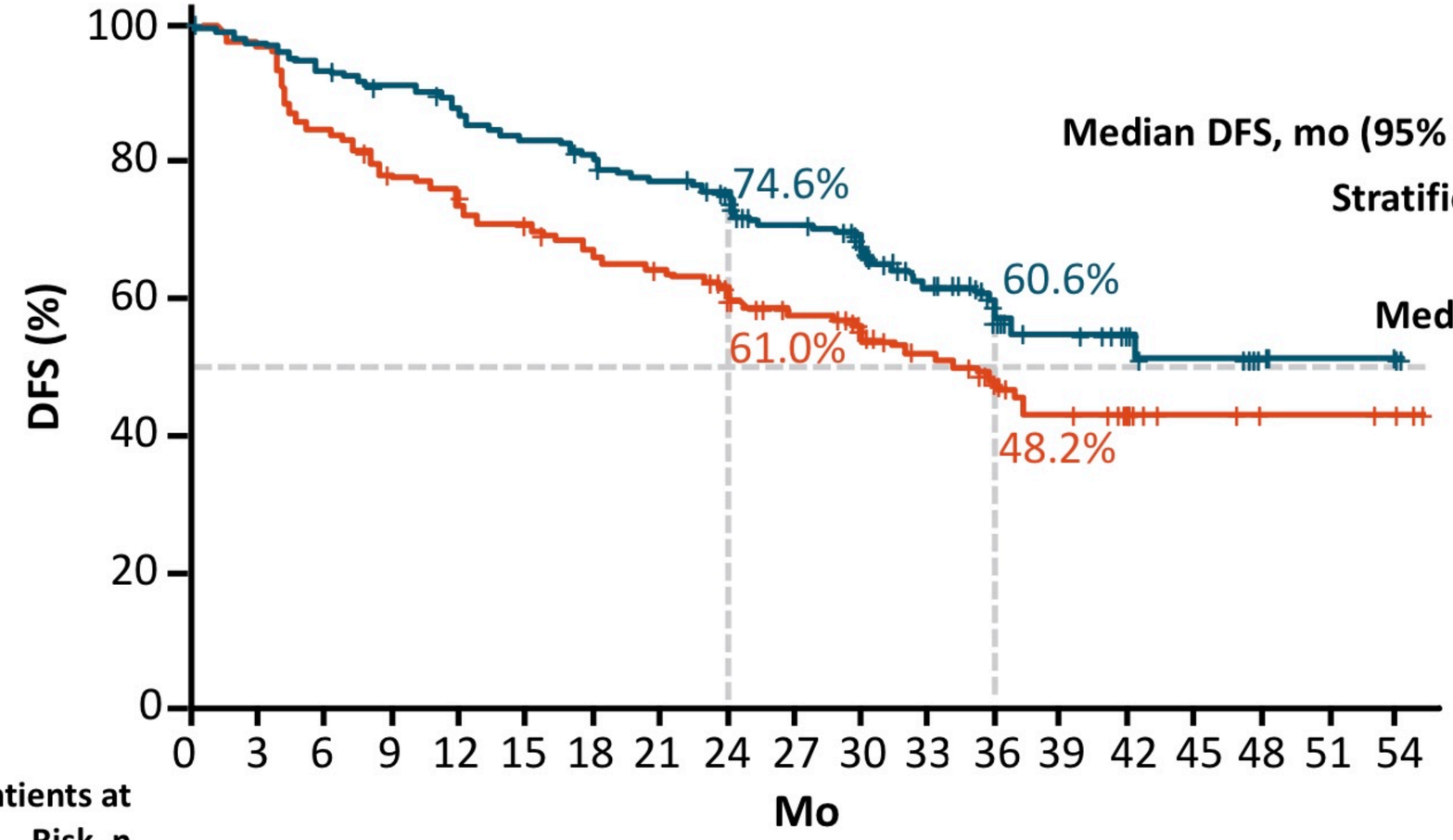
IMpower010: DFS in Stage II-IIIA NSCLC With PD-L1 TC ≥1% (Primary Endpoint)



	Atezolizumab (n = 248)	BSC (n = 228)
Median DFS, mo (95% CI)	NE (36.1-NE)	35.3 (29.0-NE)

Stratified HR: 0.66 (95% CI: 0.50-0.88; *P* = .004)
(crossed significance boundary)

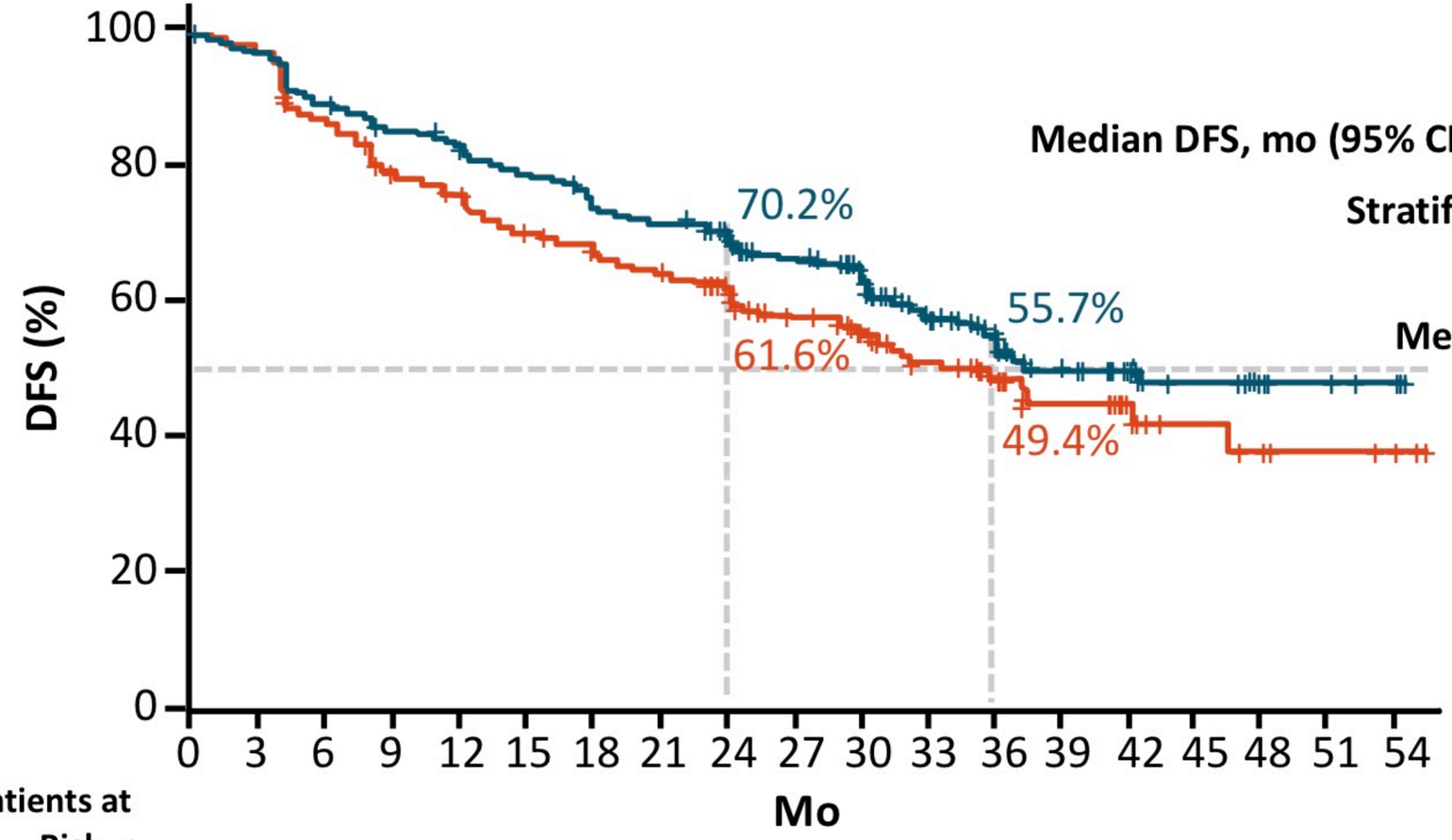
Median follow up: 32.8 mo (range: 0.1-57.5)

Patients at Risk, n

Atezolizumab	248	235	225	217	206	198	190	181	159	134	111	76	54	31	22	12	8	3	3
BSC	228	212	186	169	160	151	142	135	117	97	80	59	38	21	14	7	6	4	3

PD-L1 expression by SP263 assay.

IMpower010: DFS in All Randomized Stage II-IIIA NSCLC (Primary Endpoint)



	Atezolizumab (n = 442)	BSC (n = 440)
Median DFS, mo (95% CI)	42.3 (36.0-NE)	35.3 (30.4-46.4)

Stratified HR: 0.79 (95% CI: 0.64-0.96; *P* = .02)
(crossed significance boundary)

Median follow up: 32.2 mo (range: 0-57.5)

Patients at Risk, n																			
Atezolizumab	442	418	384	367	352	337	319	305	269	225	185	120	84	48	34	16	11	5	3
BSC	440	412	366	331	314	292	277	263	230	182	146	102	71	35	22	10	8	4	3

Wakelee. ASCO 2021. Abstr 8500. Reproduced with permission.

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NCCN Guidelines Version 1.2022
Non-Small Cell Lung Cancer

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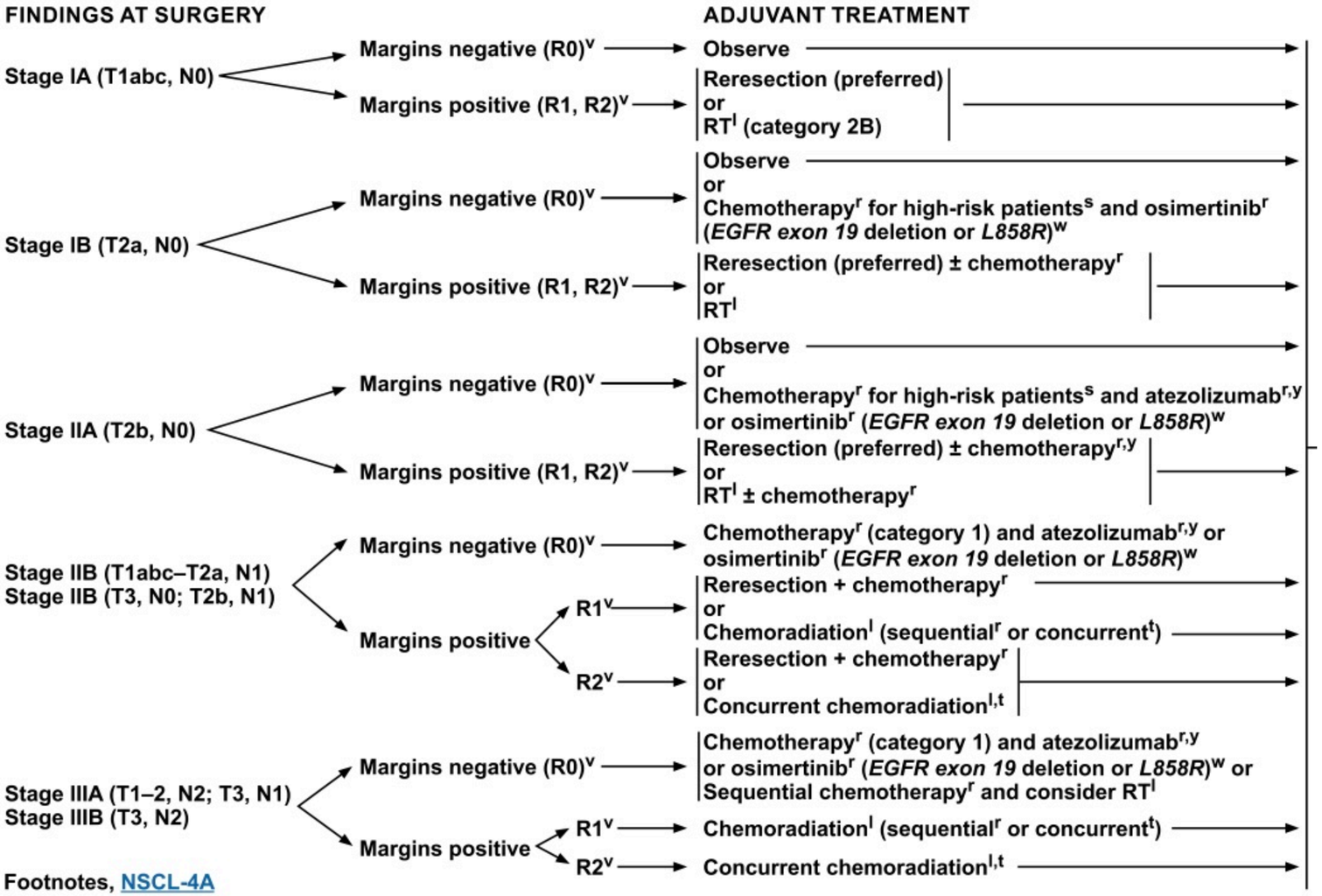


Footnotes, NSCL-4A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

KEYNOTE-564: Adjuvant Pembrolizumab vs Placebo After Nephrectomy for Renal Cell Carcinoma

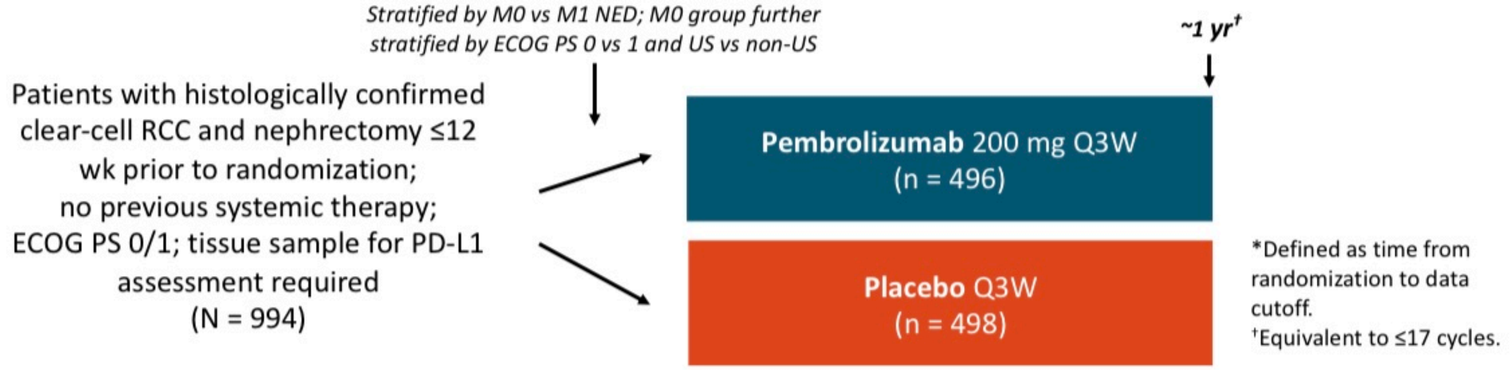
KEYNOTE-564: Background

- Globally, 179,000 deaths due to kidney cancer in 2020[1]
- Standard of care treatment for locoregional RCC is nephrectomy[2,3]
  - Standard adjuvant therapy supported by high levels of evidence not yet established
  - Studies of adjuvant VEGF-targeted therapy and immunotherapy with cytokines have produced equivocal and negative results, respectively[4,5]
- Disease recurrence in ~50% of patients after surgery[4-7]
  - Risk factors for recurrence include tumor stage/size, nodal involvement, nuclear grade
  - M1 stage with no evidence of disease after resection also at elevated risk of recurrence
- Current study evaluated adjuvant pembrolizumab vs placebo for patients with clear-cell RCC after nephrectomy[8]

1. Sung. CA Cancer J Clin. 2020;71:209. 2. NCCN Kidney cancer. 2021;v4. 3. Escudier. Ann Oncol. 2019;30:706.
4. Sun. Eur Urol. 2018;74:611. 5. Smaldone. Hematol Oncol Clin North Am. 2011;25:765. 6. Correa. J Clin Oncol. 2019;37:2062. 7. Appleman. ASCO 2019. Abstr 4502. 8. Choueiri. ASCO 2021. Abstr LBA5.

KEYNOTE-564: Study Design

- Randomized, double-blind phase III trial of adjuvant therapy; data cutoff: December 14, 2020; median follow-up*: 24.1 mo (range: 14.9-41.5)



- Primary endpoint: DFS per investigator
  - *P* value boundary for statistical significance: .0114
- Secondary endpoints: OS, safety

Choueiri. ASCO 2021. Abstr LBA5. NCT03142334.

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KEYNOTE-564: Baseline Characteristics

Characteristic	Pembrolizumab (n = 496)	Placebo (n = 498)
Median age, yr (range)	60 (27-81)	60 (25-84)
Male, n (%)	347 (70.0)	359 (72.1)
ECOG PS, n (%)		
▪ 0	421 (84.9)	426 (85.5)
▪ 1	75 (15.1)	72 (14.5)
Disease risk category, n (%)		
▪ M0 intermediate-high*	427 (86.1)	433 (86.9)
▪ M0 high†	40 (8.1)	36 (7.2)
▪ M1 NED‡	29 (5.8)	29 (5.8)

Characteristic, n (%)	Pembrolizumab (n = 496)	Placebo (n = 498)
Geographic location		
▪ North America	113 (26.8)	125 (25.1)
▪ European Union	188 (37.9)	187 (37.6)
▪ Rest of world	175 (35.3)	186 (37.3)
PD-L1 status§		
▪ CPS <1	124 (25.0)	113 (22.7)
▪ CPS ≥1	365 (73.6)	383 (76.9)
▪ Missing	7 (1.4)	2 (0.4)
Sarcomatoid features		
▪ Present	52 (10.5)	59 (11.8)
▪ Absent	417 (84.1)	415 (83.3)
▪ Unknown	27 (5.4)	24 (4.8)

*pT2, grade 4 or sarcomatoid, N0 M0; or pT3, any grade, N0 M0.
†pT4, any grade, N0 M0; or pT any stage, any grade, N+ M0.
‡No evidence of disease after complete resection of primary tumor and soft tissue metastases ≤1 year from nephrectomy.
§PD-L1 IHC 22C3 pharmDx assay.

Choueiri. ASCO 2021. Abstr LBA5.

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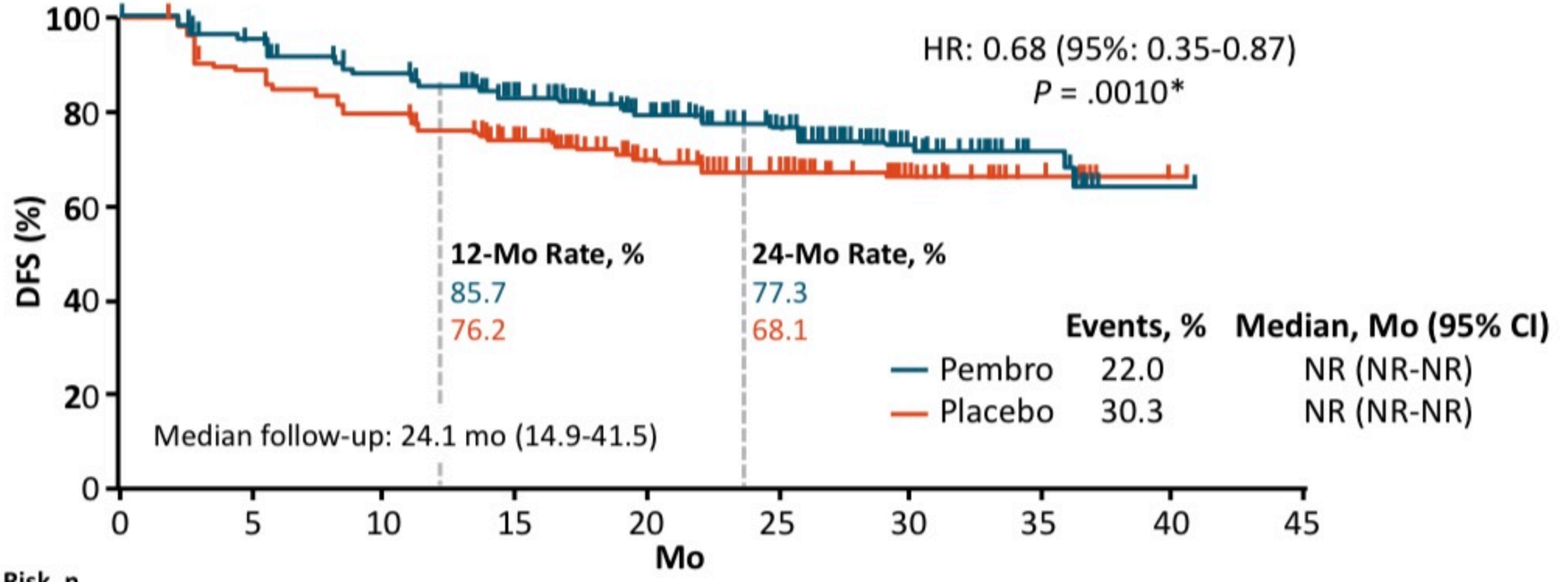
KEYNOTE-564: DFS (Primary Endpoint)



*Crossed *P* value boundary for statistical significance of .0114.

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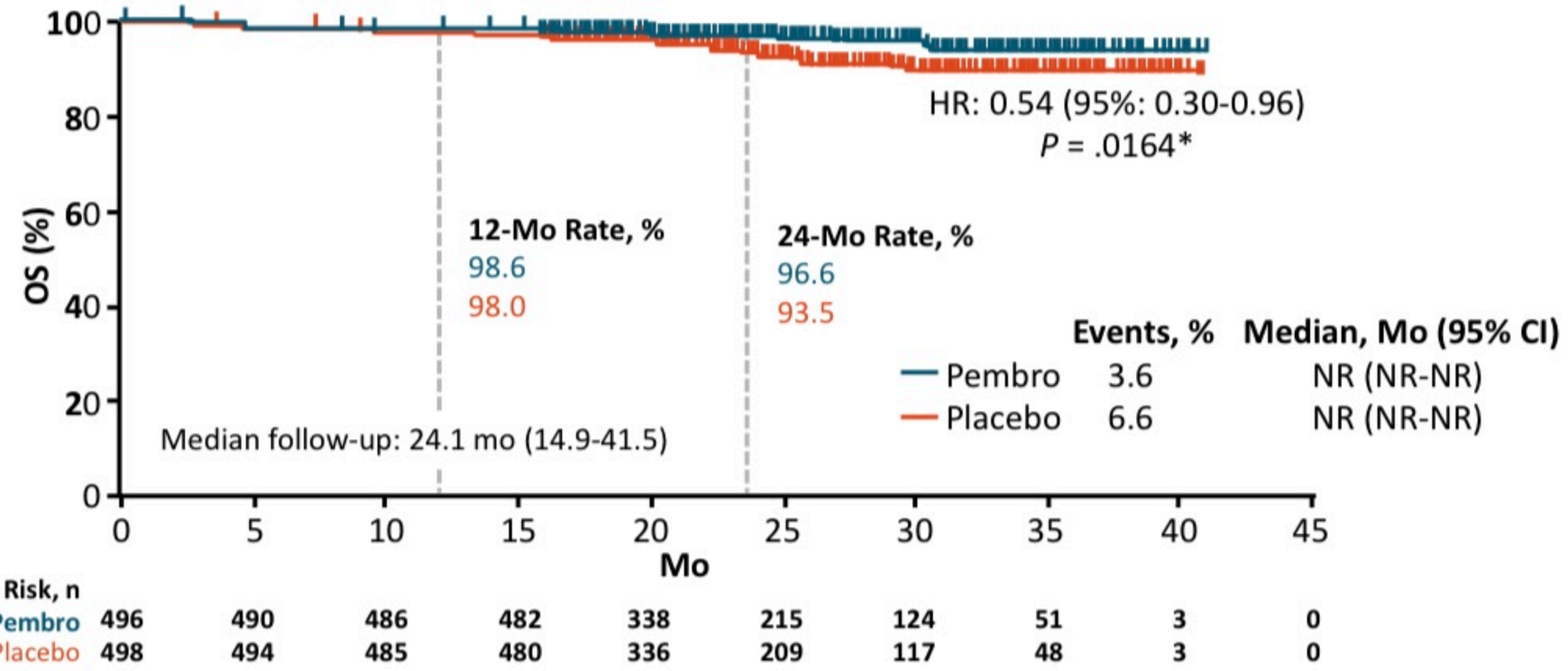
KEYNOTE-564: Interim OS



*Did not cross *P* value boundary for statistical significance of .0000093 for 51 OS events; final OS analysis to occur after ~200 OS events.

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KEYNOTE-564: Immune-Mediated AEs

imAEs in As-Treated Patients, n (%)	Pembro (n = 488)	Placebo (n = 496)
Any grade		
▪ Hypothyroidism	103 (21.1)	18 (3.6)
▪ Hyperthyroidism	58 (11.9)	1 (0.2)
▪ Pneumonitis	11 (2.3)	5 (1.0)
▪ Adrenal insufficiency	10 (2.0)	1 (0.2)
▪ Type 1 diabetes	9 (1.8)	0
▪ Colitis	8 (1.6)	1 (0.2)
▪ Severe skin reaction	8 (1.6)	2 (0.4)
▪ Thyroiditis	6 (1.2)	1 (0.2)
▪ Hepatitis	5 (1.0)	0
▪ Sarcoidosis	4 (0.8)	0
▪ Myasthenic syndrome	3 (0.6)	0
▪ Nephritis	3 (0.6)	0
▪ Hypophysitis	2 (0.4)	0
▪ Myositis	2 (0.4)	1 (0.2)
▪ Vasculitis	2 (0.4)	0
▪ Encephalitis	1 (0.2)	0
▪ Myocarditis	1 (0.2)	0
▪ Uveitis	0	1 (0.2)

- Use of high-dose (≥40 mg/day) systemic corticosteroid treatment for imAEs
  - Pembrolizumab, n = 36 (7.4%)
  - Placebo, n = 3 (0.6%)
- Grade 3/4 imAEs were uncommon (<2% incidence for any grade), with severe skin reaction and type 1 diabetes being most frequent
- No deaths due to imAEs

Choueiri. ASCO 2021. Abstr LBA5.

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KEYNOTE-564: Conclusions

- In the first prespecified interim analysis of the phase III KEYNOTE-564 trial, adjuvant pembrolizumab achieved a statistically significant and clinically meaningful DFS improvement in patients with RCC post nephrectomy
  - HR for DFS: 0.68 (95% CI: 0.53-0.87; *P* = .0010)
  - DFS benefit consistent across subgroups examined, including for patients with M1 metastatic staging and no evidence of disease
- OS data immature, additional follow-up planned
- Safety profile with pembrolizumab consistent with previous reports
  - High-dose corticosteroid treatment for immune-mediated AEs infrequent
- Investigators conclude that pembrolizumab may be considered a possible new standard of care for patients with RCC in the adjuvant setting

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NCCN Guidelines Version 4.2022
Kidney Cancer

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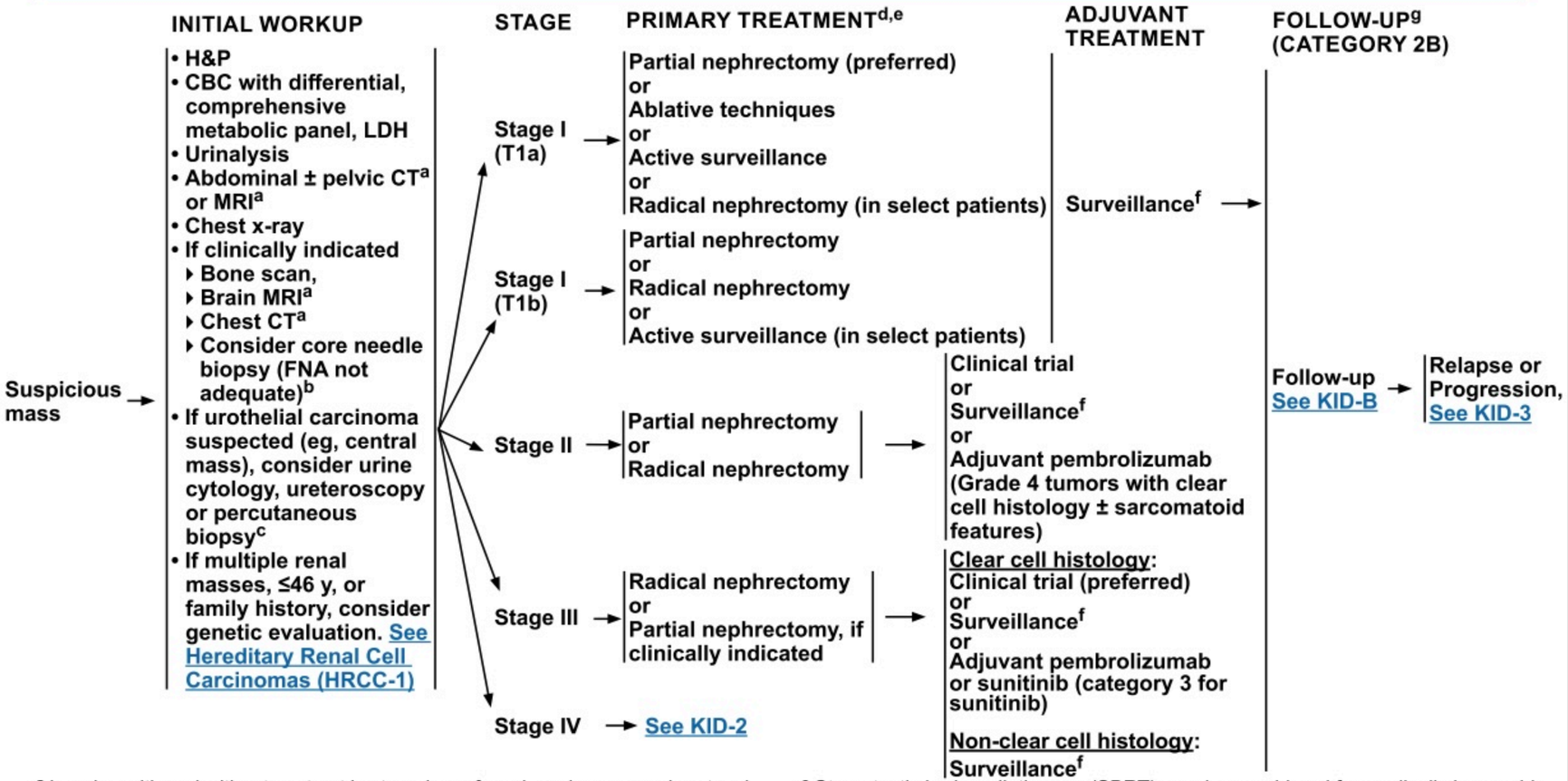


[a] Imaging with and without contrast is strongly preferred, such as a renal protocol.
[b] Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance or ablative techniques, cryosurgery, and radiofrequency ablation strategies.
[c] If metastatic disease is present or the patient cannot tolerate ureteroscopy.
[d] See Principles of Surgery (KID-A).
[e] Stereotactic body radiotherapy (SBRT) may be considered for medically inoperable patients with Stage I kidney cancer (category 2B), with Stage II/III kidney cancer (both category 3).
[f] See Follow-up (KID-B).
[g] No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

VISION: 177Lu-PSMA-617 in Previously Treated Metastatic Castration-Resistant Prostate Cancer

VISION: Background

- PSMA is highly expressed in prostate cancer, including metastatic disease, and offers potential target for molecular therapy and PET imaging[1]
  - Normal physiologic PSMA expression is relatively restricted (eg, cells of the salivary and lacrimal glands)
- ^{177}Lu-PSMA-617: targeted high-affinity radioligand that delivers β particle emission to PSMA-expressing cells and their microenvironment[2]
- Current report from the VISION study evaluated efficacy of ^{177}Lu-PSMA-617 in men with PSMA-positive mCRPC previously treated with both next-generation androgen receptor pathway inhibitor and taxane regimens[3]

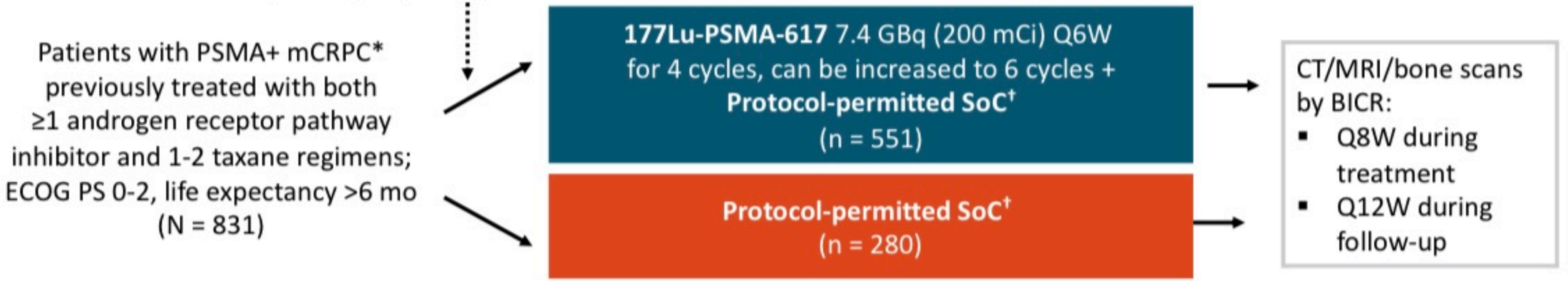
1. Heston. Urology 1997;49:104. 2. Benesova. J Nucl Med 2015;56:914. 3. Morris. ASCO 2021. Abstr LBA4.

Slide credit: clinicaloptions.com

VISION: Study Design

- Randomized, open-label phase III study

Stratified by ECOG (0/1 vs 2), LDH (high vs low), liver mets (yes vs no), androgen receptor pathway inhibitors in SoC (yes vs no)



*≥1 PSMA-positive metastatic lesion with ^{68}Ga uptake >liver and no PSMA-negative lesions in bone with soft tissue component ≥1 cm, lymph nodes ≥2.5 cm, or solid organ ≥1 cm. †Protocol-permitted SoC excludes chemotherapy, immunotherapy, radium-223, and investigational drugs

- **Alternate primary endpoints:** radiographic PFS per PCWG3, OS
- **Key secondary endpoints:** ORR and DCR per RECIST v1.1 by BICR, time to first symptomatic skeletal event; **other secondary endpoints:** safety and tolerability, biomarkers including PSA, HRQoL
- 2 analysis sets: OS analysis in full randomized population, radiographic PFS in subset after dropout reduction measures implemented

Morris. ASCO 2021. Abstr LBA4.

Slide credit: clinicaloptions.com

VISION: Survival

Outcome	rPFS Analysis Set			All Randomized Patients		
	^{177}Lu-PSMA-617 + SoC (n = 385)	SoC Alone (n = 196)	HR (95% CI)	^{177}Lu-PSMA-617 + SoC (n = 551)	SoC Alone (n = 280)	HR (95% CI)
Median OS, mo	14.6	10.4	0.63 (0.51-0.79)	15.3	11.3	0.62 (0.52-0.74) *P* <.001 (1 sided)
Median rPFS, mo	8.7	3.4	0.40 (99.2% CI: 0.29-0.57) *P* <.001 (1 sided)	8.8	3.6	0.43 (99.2% CI: 0.32-0.58)

- OS, rPFS generally consistent across prespecified subgroups, including LDH, liver metastases, ECOG PS, age, race, and whether SoC included androgen receptor pathway inhibitors
  - Subsets with small numbers of patients had larger CIs

Morris. ASCO 2021. Abstr LBA4.

Slide credit: clinicaloptions.com

VISION: Other Efficacy Outcomes

Response,* n (%)	Patients With Measurable Disease	
	^{177}Lu-PSMA-617 + SoC (n = 184)	SoC Alone (n = 64)
CR	9.2	0
PR	41.8	3.1
SD	35.3	46.9
PD	13.0	45.3
Unknown	0.5	4.7

*By RECIST v1.1.

PSA Response, n (%)	Evaluable Patients	
	^{177}Lu-PSMA-617 + SoC (n = 333)	SoC Alone (n = 138)
Confirmed ≥50% decrease	177 (46.0)	14 (7.1)
Confirmed ≥80% decrease	127 (33.0)	4 (2.0)

Morris. ASCO 2021. Abstr LBA4.

Slide credit: clinicaloptions.com

VISION: Safety

Adverse Event, n (%)	^{177}Lu-PSMA-617 + SoC (n = 529)		SoC Alone (n = 205)	
	Any Grade	Grades 3-5	Any Grade	Grades 3-5
Any TEAE	451 (85.3)	150 (28.4)	59 (28.8)	8 (3.9)
▪ Serious	49 (9.3)	43 (8.1)	5 (2.4)	5 (2.4)
▪ Grade 5	--	5 (0.9)	--	0
Fatigue	260 (49.1)	60 (29.3)	37 (7.0)	5 (2.4)
Bone marrow suppression	251 (47.4)	36 (17.6)	124 (23.4)	14 (6.8)
▪ Leukopenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)
▪ Lymphopenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
▪ Anemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
▪ Thrombocytopenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Dry mouth	208 (39.3)	2 (1.0)	0	0
Nausea and vomiting	208 (39.3)	35 (17.1)	8 (1.5)	1 (0.5)
Renal effects	46 (8.7)	12 (5.9)	18 (3.4)	6 (2.9)
Second primary malignancies	11 (2.1)	2 (1.0)	4 (0.8)	1 (0.5)
Intracranial hemorrhage	7 (1.3)	3 (1.5)	5 (0.9)	2 (1.0)

Morris. ASCO 2021. Abstr LBA4.

Slide credit: clinicaloptions.com

VISION: Conclusions

- In the phase III VISION trial, addition of ^{177}Lu-PSMA-617 to SoC in men with previously treated PSMA-positive mCRPC prolonged OS and radiographic PFS and improved response rates compared with standard of care alone
- ^{177}Lu-PSMA-617 was generally well tolerated and combined safely with standard of care therapy
  - Higher rate of TRAEs with ^{177}Lu-PSMA-617, including 5 grade 5 AEs
  - However, patients who received ^{177}Lu-PSMA-617 remained on therapy for longer and received more cycles of standard of care therapy
- Investigators suggest the findings warrant adoption of ^{177}Lu-PSMA-617 as a new treatment option in patients with mCRPC previously treated with androgen receptor inhibition and taxane therapy

Morris. ASCO 2021. Abstr LBA4.

Slide credit: clinicaloptions.com

Phase III OlympiA: Interim Analysis of Adjuvant Olaparib vs Placebo in BRCA-Mutated, HER2-Negative, High-Risk Early Breast Cancer

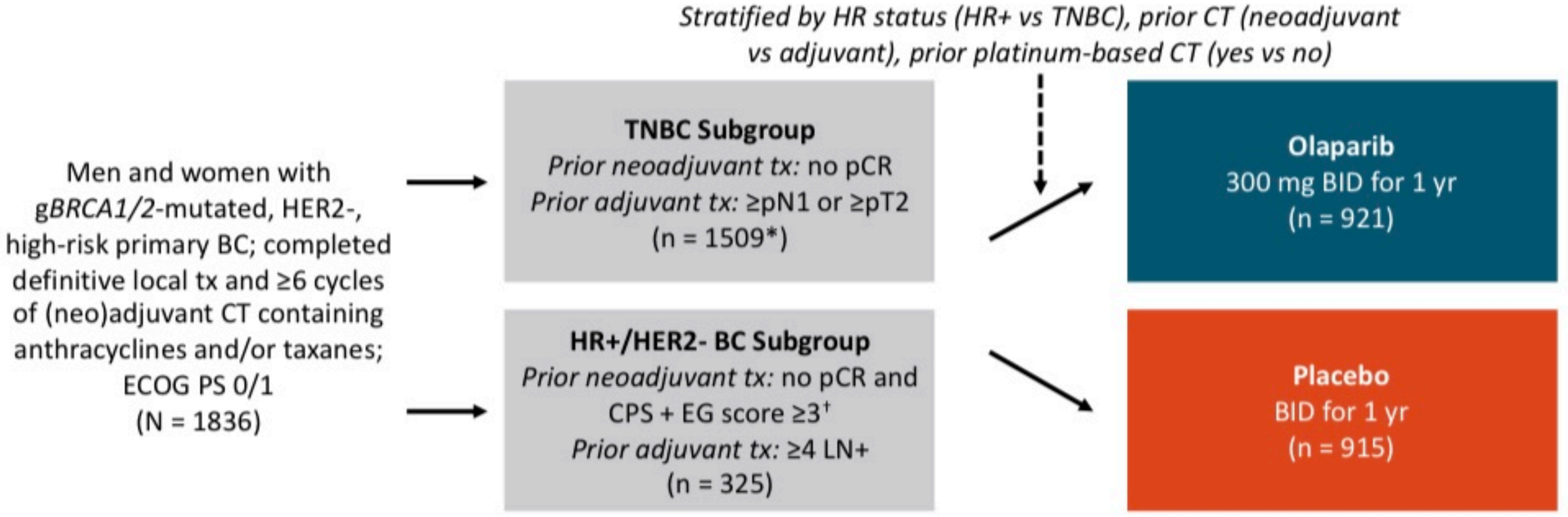
OlympiA: Background

- Inhibition of PARP enzymes leads to synthetic lethality in cells deficient in homologous recombination repair, such as those with *BRCA1/2* mutations[1,2]
- Germline mutations in *BRCA1* increase risk of developing TNBC; germline mutations in *BRCA2* increase risk of developing estrogen receptor–positive breast cancer[3,4]
- Olaparib: PARP inhibitor approved by FDA for multiple indications, including treatment of adults with (suspected) deleterious g*BRCA*-mutated, HER2-negative MBC previously treated with CT in (neo)adjuvant/metastatic setting; those with hormone receptor–positive disease must be previously treated with ET or ineligible for ET[5]
- Current interim analysis of phase III OlympiA trial compares efficacy and safety of adjuvant olaparib vs placebo in patients with *BRCA1/2*-mutated, HER2-negative early breast cancer at high risk of recurrence[6,7]

1. Farmer. Nature. 2005;434:917. 2. Fong. NEJM. 2009;361:123. 3. Mavaddat. Cancer Epidemiol Biomarkers Prev. 2012;21:134. 4. Atchley. JCO. 2008;26:4282. 5. Olaparib PI. 6. Tutt. ASCO 2021. Abstr LBA1. 7. Tutt. NEJM. 2021;[Epub].

OlympiA: Study Design

- Prespecified interim analysis of international, randomized, double-blind phase III trial (data cutoff: Mar 27, 2020)



- **Primary endpoint:** iDFS
- **Secondary endpoints:** distant DFS, OS, safety

*Excluded n = 2 (both in olaparib arm) due to unconfirmed HER2- status.
†Staging system for BC-specific survival after neoadjuvant tx incorporating pretreatment clinical stage, ER status, nuclear grade, pathologic stage (range: 0-6).

- Prespecified interim analysis of ITT population triggered when 165 invasive disease or death events occurred in first 900 patients enrolled (mature cohort); type I error rate controlled with superiority boundaries per hierarchical multiple-testing procedure

Tutt. NEJM. 2021;[Epub]. NCT02032823.

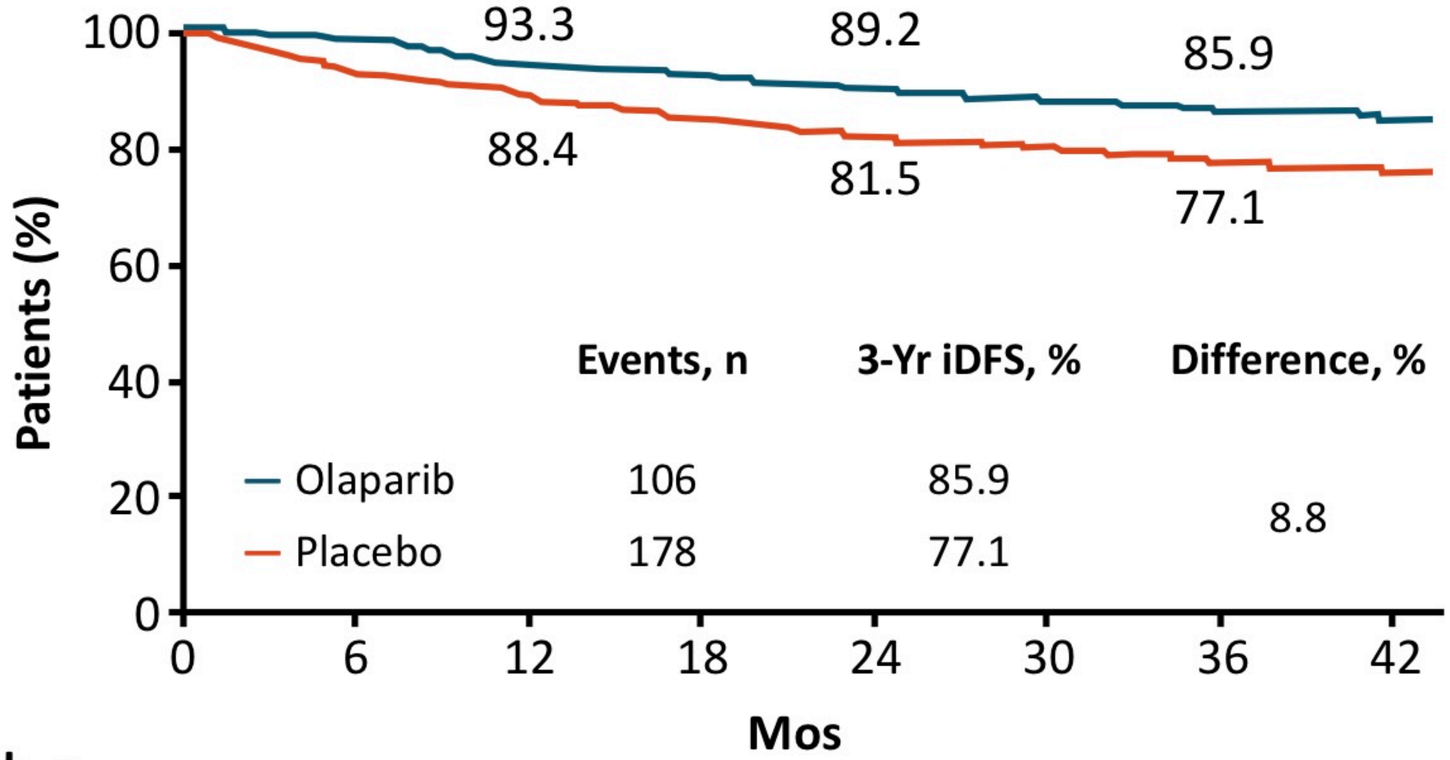
3.3 CALCULATION FOR THE CPS&EG STAGING SYSTEM

The CPS&EG score is a staging system for disease specific survival in patients with breast cancer treated with neoadjuvant chemotherapy.[1] This incorporates pretreatment clinical stage, estrogen receptor status, nuclear grade and post-neoadjuvant chemotherapy pathological stage.

Calculation instructions: Add the points for Clinical Stage + Pathologic Stage + ER status + Nuclear grade to derive a sum (CPS&EG score) between 0 and 6.

Stage/feature		Points
Clinical Stage (AJCC staging [1])	0	0
	IIA	0
	IIB	1
	IIIA	1
	IIIB	2
	IIIC	2
Pathologic Stage (AJCC staging [1])	0	0
	I	0
	IIA	1
	IIB	1
	IIIA	1
	IIIB	1
	IIIC	2
Receptor status	ER negative [2]	1
Nuclear grade [3]	Nuclear grade 3	1

OlympiA: iDFS (Primary Endpoint)



	Events, n	3-Yr iDFS, %	Difference, %	Stratified HR for Invasive Disease/Death (99.5% CI)
Olaparib	106	85.9	8.8	0.58 (0.41-0.82; *P* <.001)
Placebo	178	77.1		

Patients at Risk, n

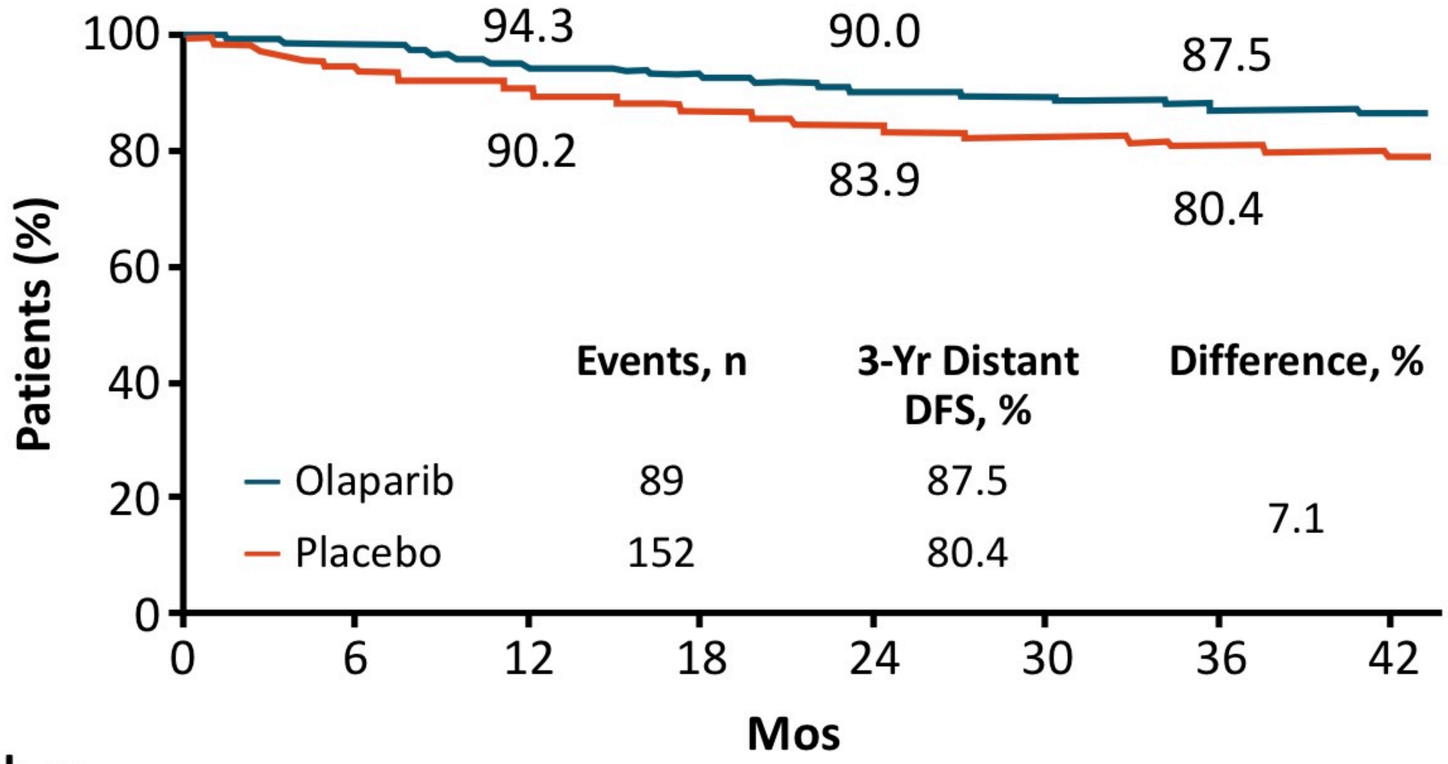
Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173

- In this prespecified interim analysis, adjuvant olaparib significantly improved iDFS vs placebo (*P* <.001, crossing early-reporting efficacy boundary of *P* <.005)

utt. NEJM. 2021;[Epub].

Slide credit: clinicaloptions.com

OlympiA: Distant DFS



Patients at Risk, n

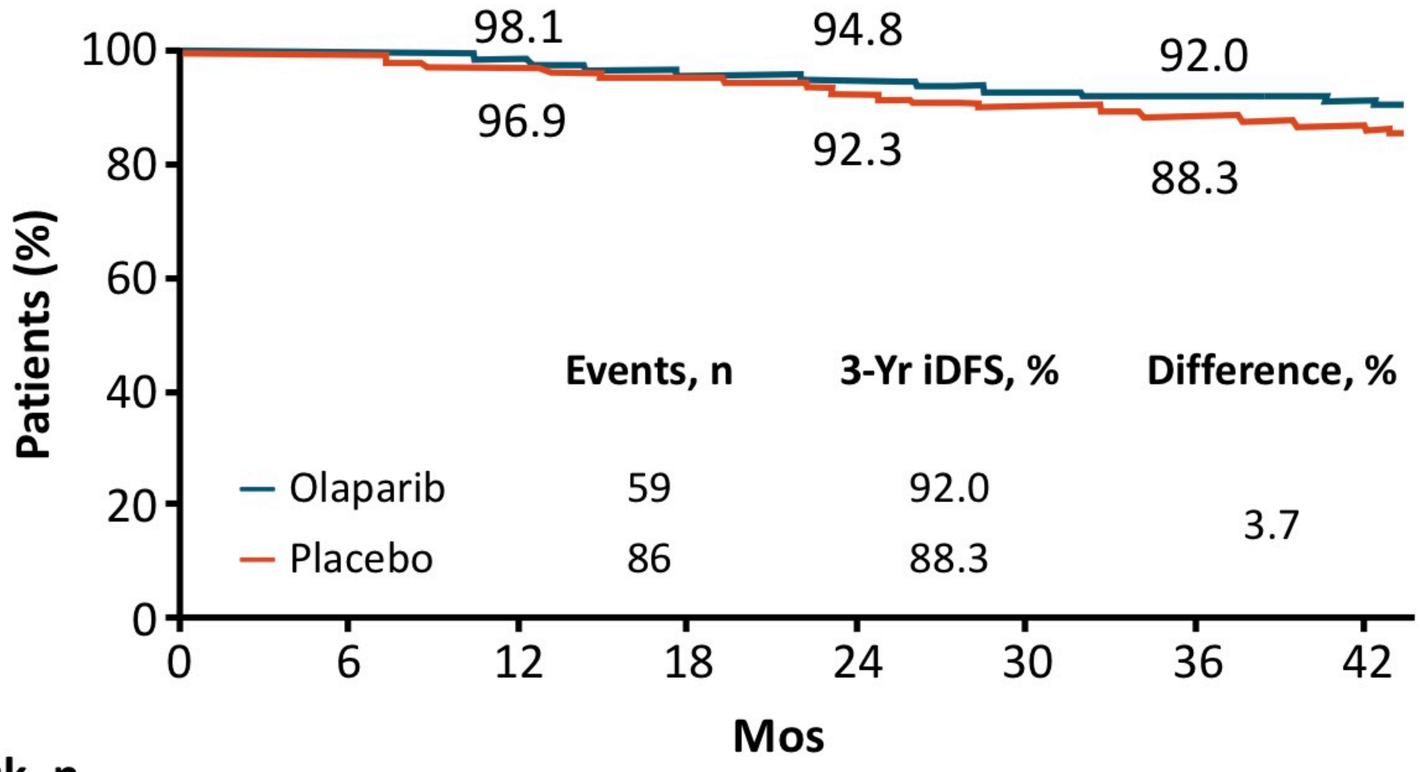
Olaparib	921	823	744	612	479	364	279	187
Placebo	915	817	742	594	461	359	263	179

- Adjuvant olaparib significantly improved distant DFS vs placebo (*P* <.001, crossing early-reporting efficacy boundary of *P* <.005)

Tutt. NEJM. 2021;[Epub].

Slide credit: clinicaloptions.com

OlympiA: Overall Survival



	Events, n	3-Yr iDFS, %	Difference, %	Stratified HR for Death (99% CI)
Olaparib	59	92.0	3.7	0.68 (0.44-1.05; *P* = .02)
Placebo	86	88.3		

Patients at Risk, n

Olaparib	921	856	801	659	531	400	310	205
Placebo	915	865	801	659	516	397	292	199

- Adjuvant olaparib did not significantly improve OS vs placebo (*P* = .02 did not cross early-reporting efficacy boundary of *P* = .01)
- Main cause of death was BC: olaparib, 55/59 deaths; placebo, 82/86 deaths

Tutt. NEJM. 2021;[Epub].

Slide credit: clinicaloptions.com

OlympiA: AEs, Treatment Exposure, QoL

AE in ≥10% of Patients, n (%)	Olaparib (n = 911)		Placebo (n = 904)	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3
Nausea	518 (56.9)	7 (0.8)	211 (23.3)	0
Fatigue	365 (40.1)	16 (1.8)	245 (27.1)	4 (0.4)
Anemia	214 (23.5)	79 (8.7)	35 (3.9)	3 (0.3)
Vomiting	206 (22.6)	6 (0.7)	74 (8.2)	0
Headache	180 (19.8)	2 (0.2)	152 (16.8)	1 (0.1)
Diarrhea	160 (17.6)	3 (0.3)	124 (13.7)	3 (0.3)
Decreased neutrophil count	146 (16.0)	44 (4.8)	59 (6.5)	7 (0.8)
Decreased WBC count	143 (15.7)	27 (3.0)	52 (5.8)	3 (0.3)
Decreased appetite	119 (13.1)	2 (0.2)	53 (5.9)	0
Dysgeusia	107 (11.7)	0	38 (4.2)	0
Dizziness	104 (11.4)	1 (0.1)	67 (7.4)	1 (0.1)
Arthralgia	84 (9.2)	2 (0.2)	107 (11.8)	2 (0.2)

- In the olaparib arm, anemia was the most frequent AE at grade ≥3 in >1% patients
  - Transfusions: olaparib, 5.8%; placebo, 0.9%
- Median percentage of intended dose received: olaparib, 94.8%; placebo, 98.9%
- For the olaparib vs placebo arms:
  - Dose reductions: 25.0% vs 5.2%
  - Discontinuations due to AEs: 9.9% vs 4.2% (with olaparib, most commonly due to nausea, 2.0%; anemia, 1.8%; fatigue, 1.3%; decreased neutrophil count, 1.0%)
- No declines or clinically significant differences observed between arms in global health quality during tx

Tutt. NEJM. 2021;[Epub].

OlympiA: Safety

Safety Outcome, n (%)	Olaparib (n = 911)	Placebo (n = 904)
Any AE	835 (91.7)	753 (83.3)
Serious AE	79 (8.7)	76 (8.4)
AE of special interest	30 (3.3)	46 (5.1)
▪ MDS/AML	2 (0.2)	3 (0.3)
▪ Pneumonitis	9 (1.0)	11 (1.2)
▪ New primary malignancy	19 (2.1)	32 (3.5)
Grade ≥3 AE	221 (24.3)	102 (11.3)
Grade 4 AE	17 (1.9)	4 (0.4)
AE leading to permanent discontinuation	90 (9.9)	38 (4.2)

- AEs leading to death: olaparib, n = 1 (cardiac arrest); placebo, n = 2 (AML, ovarian cancer)

Tutt. NEJM. 2021;[Epub].

Slide credit: clinicaloptions.com

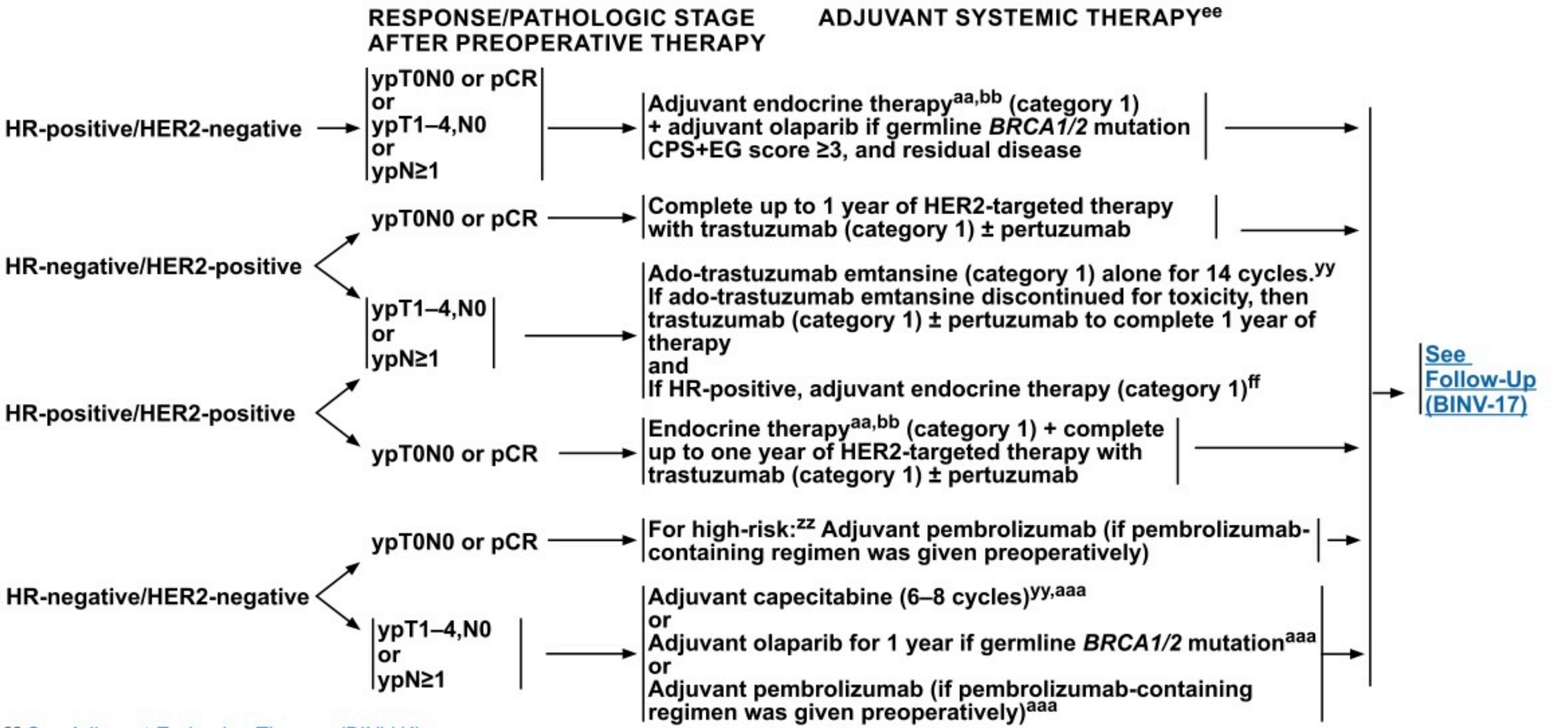
OlympiA: Conclusions

- In this prespecified interim analysis of the phase III OlympiA trial, adjuvant olaparib significantly improved the primary endpoint of iDFS vs placebo in patients with g*BRCA1/2*-mutated, HER2-, high-risk EBC
  - 3-yr iDFS rate: 85.9% vs 77.1%; difference: 8.8% (HR: 0.58; 95% CI: 0.41-0.82; *P* <.001)
  - Distant DFS also significantly improved (HR: 0.57; *P* <.001)
- Despite fewer deaths occurring with olaparib vs placebo, OS was not significantly improved in this analysis (HR: 0.68; *P* = .02 not crossing early-reporting efficacy boundary of *P* = .01)
  - Blinded follow-up continuing
- Safety profile of olaparib consistent with prior reports, did not affect global health quality
- Investigators concluded that positive results from this trial support use of g*BRCA1/2* sequencing to select optimal systemic therapy for patients with EBC

Tutt. NEJM. 2021;[Epub].

Slide credit: clinicaloptions.com

ADJUVANT SYSTEMIC THERAPY AFTER PREOPERATIVE SYSTEMIC THERAPY[ee]



[aa] See Adjuvant Endocrine Therapy (BINV-K).
[bb] See Preoperative/Adjuvant Therapy Regimens (BINV-L).
[ee] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.
[ff] Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab or ado-trastuzumab emtansine is unknown.
[yy] Recommendations do not apply to residual DCIS (ypTis).
[zz] High-risk criteria include stage II–III TNBC. The use of adjuvant pembrolizumab (category 2A) may be individualized.
[aaa] There are no data on sequencing or to guide selection of an adjuvant therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ASCENT: Patient Subgroup Analyses of Sacituzumab Govitecan vs Single-Agent CT in Metastatic TNBC After ≥2 Prior CT Regimens

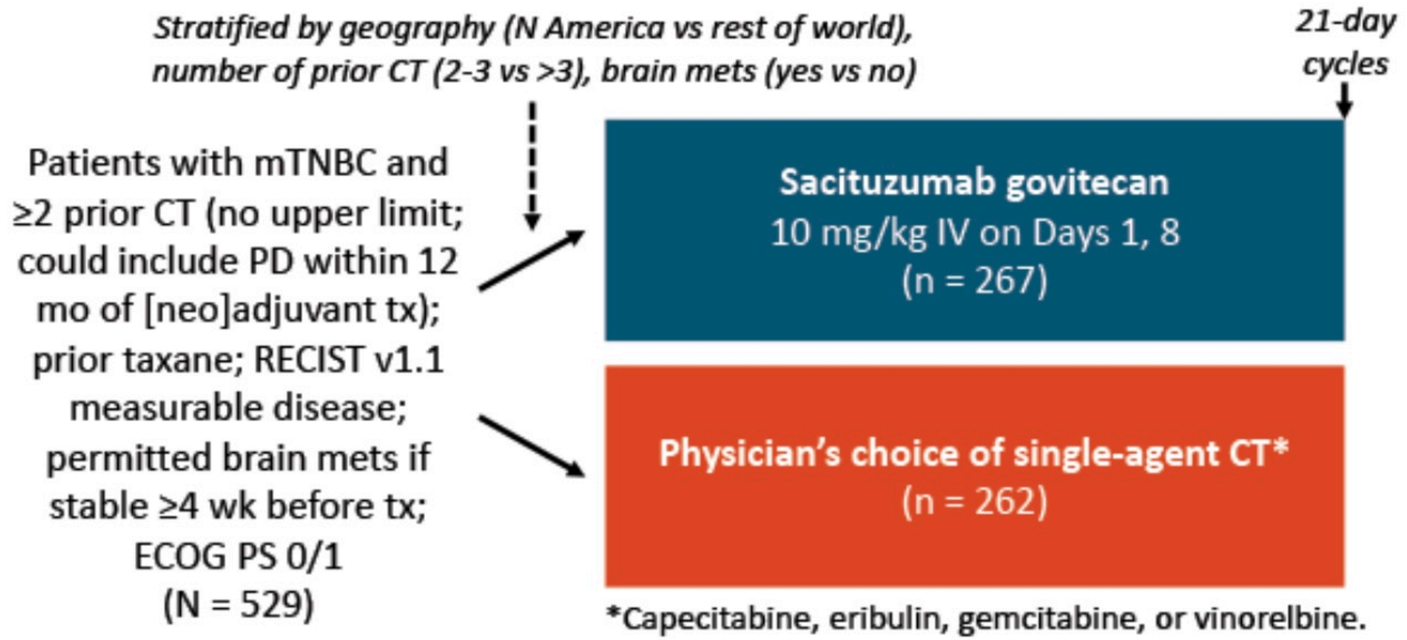
ASCENT Subgroup Analyses: Background

- Sacituzumab govitecan: antibody–drug conjugate consisting of anti–TROP-2 Ab conjugated via hydrolyzable linker to the topoisomerase I inhibitor SN-38[1]
  - FDA-approved indications for SG include treatment of adults with unresectable locally advanced or metastatic TNBC previously treated with ≥2 prior systemic tx (≥1 tx must have been for metastatic disease)[2]
- In April 2021, FDA granted regular approval to SG in this TNBC setting based on the ASCENT trial[3]
- ASCENT: phase III trial comparing SG vs single-agent CT among patients with unresectable locally advanced or metastatic TNBC previously treated with ≥2 prior systemic tx[1]
  - Primary analysis of SG vs CT in those without baseline brain mets showed significantly prolonged mPFS (5.6 vs 1.7 mo; HR: 0.41; 95% CI: 0.32-0.52; *P* <.001) and mOS (12.1 vs 6.7 mo; HR: 0.48; 95% CI: 0.38-0.59; *P* <.001)
  - Trial halted early due to efficacy per unanimous recommendation of DSMC
- Current subgroup analyses of ASCENT report on efficacy and safety of SG vs CT among those aged <65 yr vs ≥65 yr,[4] those in the second-line setting with TNBC recurrence ≤12 mo after (neo)adjuvant tx,[5] and by individual CT agent[6]

1. Bardia. NEJM. 2021;384:1529. 2. Sacituzumab govitecan PI. 3. FDA. FDA grants regular approval to sacituzumab govitecan for triple-negative breast cancer. 4. Kalinsky. ASCO 2021. Abstr 1011. 5. Carey. ASCO 2021. Abstr 1080. 6. O'Shaughnessy. ASCO 2021. Abstr 1077.

ASCENT Subgroup Analyses: Study Design

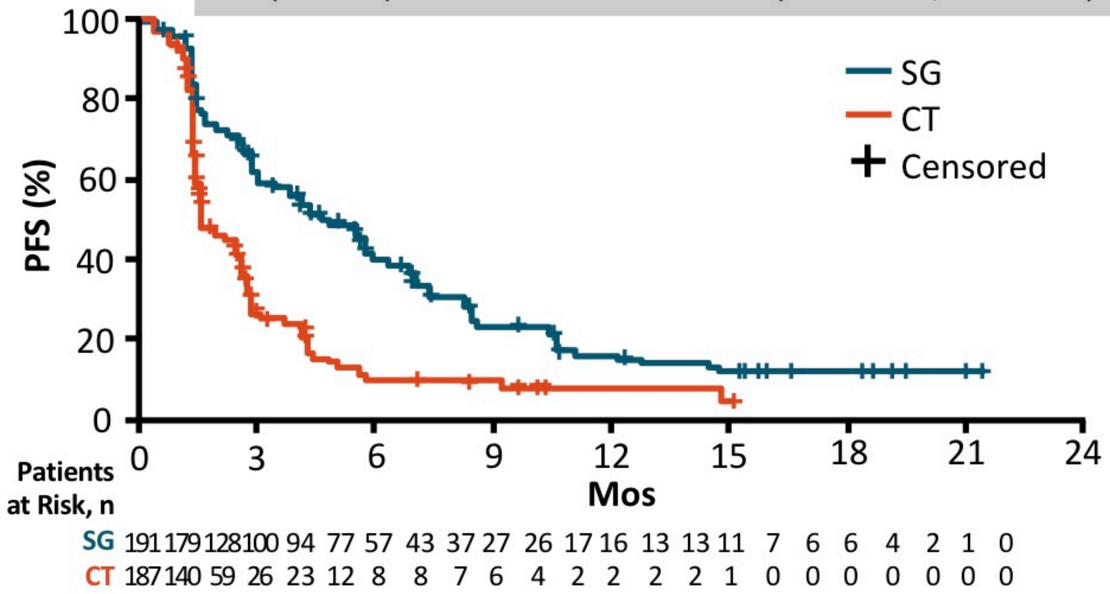
- International, randomized, open-label phase III trial



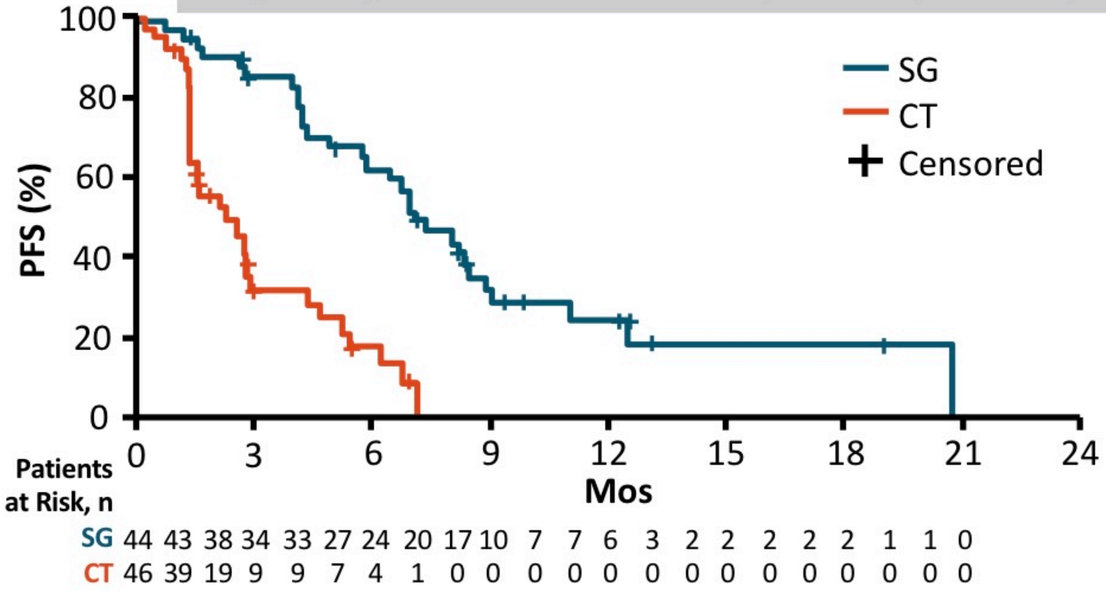
- **Primary endpoint:** PFS by BICR in patients without brain mets
- **Secondary endpoints:** investigator-assessed PFS, OS, ORR, DoR, TTR, safety

ASCENT Subgroup Analyses: PFS in Patients Without Brain Mets Aged <65 Yr vs ≥65 Yr

PFS BICR Analysis	Aged <65 Yr	
	SG (n = 191)	CT (n = 187)
No. events	136	117
Median PFS, mo (95% CI)	4.6 (3.7-5.7)	1.7 (1.5-2.5)
HR (95% CI)	0.46 (0.35-0.59; *P* <.0001)	



PFS BICR Analysis	Aged ≥65 Yr	
	SG (n = 44)	CT (n = 46)
No. events	30	33
Median PFS, mo (95% CI)	7.1 (5.8-8.9)	2.4 (1.4-2.9)
HR (95% CI)	0.22 (0.12-0.40; *P* <.0001)	



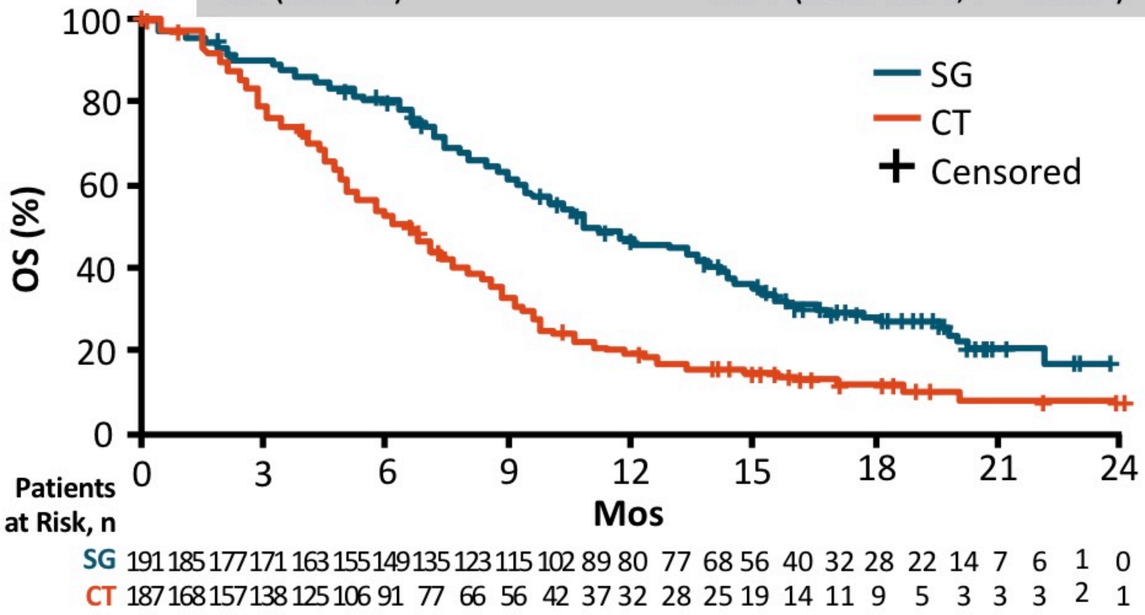
- In those aged ≥65 yr, median PFS benefit with SG vs CT was similar to benefit in overall population (overall population: 5.6 vs 1.7 mo)

Kalinsky. ASCO 2021. Abstr 1011. Reproduced with permission.

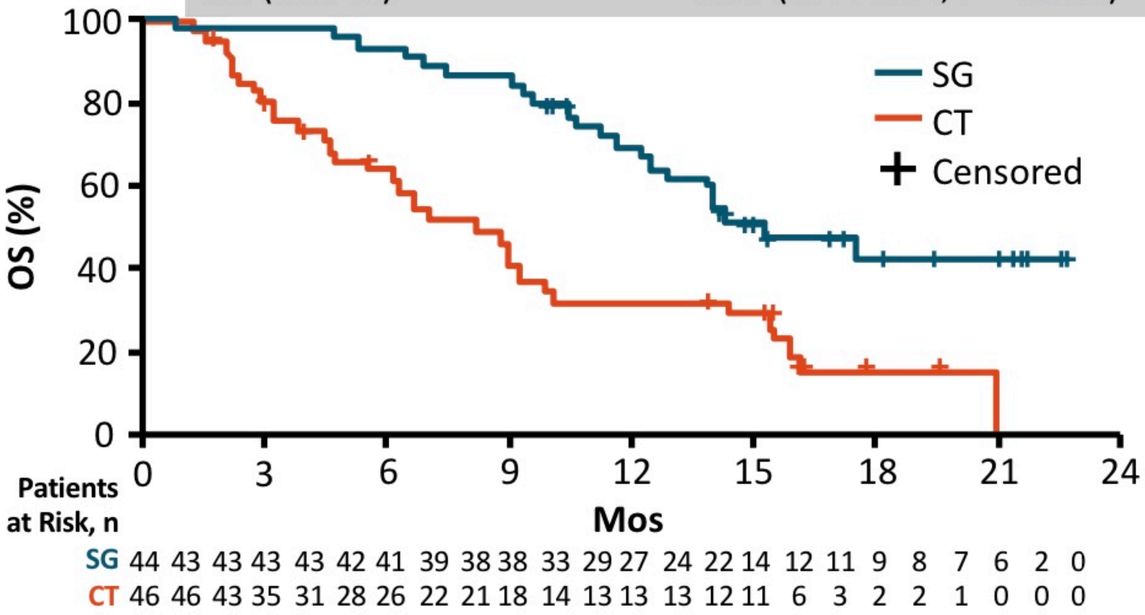
Slide credit: clinicaloptions.com

ASCENT Subgroup Analyses: OS in Patients Without Brain Mets Aged <65 Yr vs ≥65 Yr

OS BICR Analysis	Aged <65 Yr	
	SG (n = 191)	CT (n = 187)
No. events	133	150
Median OS, mo (95% CI)	11.2 (9.9-13.4)	6.6 (5.3-7.4)
HR (95% CI)	0.50 (0.40-0.64; *P* <.0001)	



OS BICR Analysis	Aged ≥65 Yr	
	SG (n = 44)	CT (n = 46)
No. events	22	35
Median OS, mo (95% CI)	15.3 (12.4-NE)	8.2 (5.6-9.8)
HR (95% CI)	0.37 (0.22-0.64; *P* = .0003)	



- In those aged ≥65 yr, median OS benefit with SG vs CT was similar to benefit in overall population (overall population: 12.1 vs 6.7 mo)

Kalinsky. ASCO 2021. Abstr 1011. Reproduced with permission.

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ASCENT Subgroup Analyses: Responses in Patients Without Brain Mets Aged <65 Yr vs ≥65 Yr

Response	Patients Without Brain Mets (n = 468)			
	Aged <65 Yr		Aged ≥65 Yr	
	SG (n = 191)	CT (n = 187)	SG (n = 44)	CT (n = 46)
ORR, n (%)	60 (31)	11 (6)	22 (50)	0
▪ CR	7 (4)	2 (1)	3 (7)	0
▪ PR	53 (28)	9 (5)	19 (43)	0
CBR,* n (%)	78 (41)	16 (9)	27 (61)	4 (9)
Median DoR, mo (95% CI)	5.8 (5.4-7.9)	3.6 (2.8-NE)	7.1 (4.4-12.3)	NE

*Confirmed best overall response of CR, PR, and SD ≥6 mo.

- Among those aged ≥75 yr, 2/7 receiving SG achieved a best response of PR vs 0/11 receiving CT achieved a response

Kalinsky. ASCO 2021. Abstr 1011.

Slide credit: clinicaloptions.com

ASCENT Subgroup Analyses: Safety by Age Group

Event in Safety Population,* n (%)[1]	SG (n = 258)		CT (n = 224)	
	Aged <65 Yr (n = 209)	Aged ≥65 Yr (n = 49)	Aged <65 Yr (n = 176)	Aged ≥65 Yr (n = 48)
Any TEAE	208 (99.5)	49 (100)	171 (97)	48 (100)
▪ Grade ≥3	153 (73)	33 (67)	115 (65)	30 (63)
▪ Leading to dose reduction	39 (19)	17 (35)	43 (24)	16 (33)
▪ Leading to study drug d/c	11 (5)	1 (2)	11 (6)	1 (2)
Any TRAE	204 (98)	48 (98)	152 (86)	40 (83)
▪ Grade ≥3	135 (65)	31 (63)	79 (45)	26 (54)
▪ Leading to dose reduction	39 (19)	17 (35)	41 (23)	16 (33)
▪ Leading to study drug d/c	4 (2)	1 (2)	6 (3)	0
▪ Leading to death	0	0	1 (1)	0

- 1 death observed due to TRAE (neutropenic sepsis related to eribulin)[2]
- In the SG arm, numerically higher rates of grade ≥3 TEAEs and TRAEs for those aged <65 yr vs ≥65 yr; higher rate of TRAE leading to dose reduction among those aged ≥65 yr, yet similar to CT arm[1]
- Among those aged ≥65 yr, key TRAEs leading to dose reduction with SG vs CT were neutropenia (10% vs 25%), fatigue/asthenia (10% vs 4%), diarrhea (6% vs 0%), febrile neutropenia (6% vs 0%), nausea (4% vs 0%)[1]
- Frequency of AEs in patients aged ≥75 yr comparable to those aged ≥65 yrs[1]

1. Kalinsky. ASCO 2021. Abstr 1011.
2. O'Shaughnessy. ASCO 2021. Abstr 1077.
*All patients who received ≥1 dose of study drug, regardless of brain mets status.

ASCENT Subgroup Analyses: Efficacy of SG vs Individual CT Agent in Patients Without Brain Mets

Outcome	SG (n = 235)	CT (n = 233)				HR for SG vs CT (95% CI)
		Eribulin (n = 126)	Vinorelbine (n = 47)	Cape (n = 31)	Gem (n = 29)	
PFS events, n	166	86	29	20	15	
Median PFS, mo	5.6	2.1	1.6	1.6	2.7	0.41 (0.32-0.52; *P* <.001)
OS events, n	155	103	36	23	23	
Median OS, mo	12.1	6.9	5.9	5.2	8.4	0.48 (0.38-0.59; *P* <.001)
ORR, n (%)	82 (35)	6 (5)	2 (4)	2 (6)	1 (3)	
Best overall response, n (%)						
▪ CR	10 (4)	2 (2)	0	0	0	
▪ PR	72 (31)	4 (3)	2 (4)	2 (6)	1 (3)	

- In this analysis of patients without brain mets (n = 468), SG demonstrated improved PFS, OS, and ORR vs each individual agent used in the CT arm
  - Baseline characteristics generally balanced between SG arm and individual CT agents

O'Shaughnessy. ASCO 2021. Abstr 1077.

Slide credit: clinicaloptions.com

ASCENT Subgroup Analyses: SG vs CT in Patients With Recurrent TNBC After Recent (Neo)adjuvant Therapy

Outcome		SG (n = 33)	CT (n = 32)
PFS	▪ Events, n	21	23
	▪ Median, mo	5.7	1.5
	▪ HR (95% CI)	0.41 (0.22-0.76)	
OS	▪ Events, n	22	24
	▪ Median, mo	10.9	4.9
	▪ HR (95% CI)	0.51 (0.28-0.91)	

Response	SG (n = 33)	CT (n = 32)
ORR, n (%)	10 (30)	1 (3)
Best overall response, n (%)		
▪ CR	1 (3)	0
▪ PR	9 (27)	1 (3)
▪ SD	13 (39)	7 (22)
• SD >6 mo	4 (12)	1 (3)
▪ PD	9 (27)	18 (56)
▪ NE	1 (3)	6 (19)
CBR,* n (%)	14 (42)	2 (6)
Median DoR, mo	6.7	NE

*Confirmed best overall response of CR, PR, and SD ≥6 mo.

- In this exploratory subgroup analysis of patients without brain mets whose TNBC recurred within 12 mo of (neo)adjuvant therapy and were previously treated with 1 line of therapy for metastatic disease, SG demonstrated improved efficacy vs CT consistent with the overall study population
- Baseline characteristics of this subgroup comparable to overall study population

Carey. ASCO 2021. Abstr 1080.

Slide credit: clinicaloptions.com

ASCENT Subgroup Analyses: Conclusions

- In these subgroup analyses of the phase III ASCENT trial, SG maintained PFS, OS, and ORR benefit vs single-agent CT:
  - Among patients aged ≥65 yr vs <65 yr[1]
  - Among patients in the second-line setting with TNBC recurrence ≤12 mo after (neo)adjuvant tx[2]
  - When compared with individual CT agents[3]
- Safety profile of SG was consistent and manageable across these subgroups[1-3]
  - Dose reductions due to TEAEs more common among those aged ≥65 yr in both SG and CT arms[1]
- Investigators concluded that these data support SG as new standard of care in setting of pretreated metastatic TNBC, including those with early relapse who may be chemotherapy resistant[2,3]
  - Recommend proactive toxicity monitoring and management to optimize SG use in older patients[1]
- Ongoing studies are evaluating SG in earlier settings for TNBC (NeoSTAR, SASCIA)[4,5]

1. Kalinsky. ASCO 2021. Abstr 1011. 2. Carey. ASCO 2021. Abstr 1080. 3. O'Shaughnessy. ASCO 2021. Abstr 1077. 4. NCT04230109. 5. NCT04595565.

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a,b,c]

HER2-Negative

Preferred Regimens		Other Recommended Regimens[g]	Useful in Certain Circumstances[g]
• Anthracyclines ▸ Doxorubicin ▸ Liposomal doxorubicin • Taxanes ▸ Paclitaxel • Anti-metabolites ▸ Capecitabine ▸ Gemcitabine • Microtubule inhibitors ▸ Vinorelbine ▸ Eribulin • Sacituzumab govitecan-hziy (for TNBC)[d]	• For germline *BRCA1/2* mutations[d] see additional targeted therapy options (BINV-R)[e] • Platinum (for TNBC and germline *BRCA1/2* mutation)[e] ▸ Carboplatin ▸ Cisplatin • For PD-L1–positive TNBC see additional targeted therapy options (BINV-R)[f]	• Cyclophosphamide • Docetaxel • Albumin-bound paclitaxel • Epirubicin • Ixabepilone	• AC (doxorubicin/cyclophosphamide) • EC (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/ methotrexate/fluorouracil) • Docetaxel/capecitabine • GT (gemcitabine/paclitaxel) • Gemcitabine/carboplatin • Carboplatin + paclitaxel or albumin-bound paclitaxel

HER2-Positive Disease, see BINV-Q (2 of 8)

[a] Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m^2.

[b] Consider scalp cooling to reduce incidence of chemotherapy-induced alopecia for patients receiving chemotherapy. Results may be less effective with anthracycline-containing regimens.

[c] For treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.

[d] For adult patients with metastatic TNBC who received at least two prior therapies, with at least one line for metastatic disease.

[e] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy.

[f] See Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease (BINV-R).

[g] Sequential single agents are preferred, but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

RELATIVITY-047: Phase II/III Trial of First-line Relatlimab + Nivolumab vs Nivolumab Alone in Advanced Melanoma

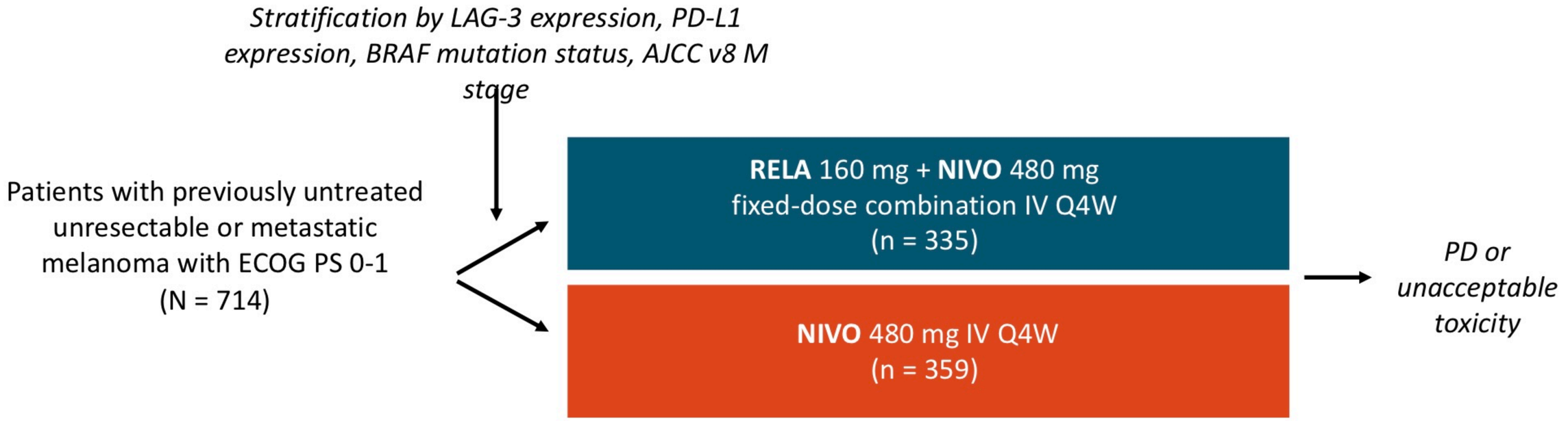
RELATIVITY-047: Background

- Therapy with immune checkpoint inhibitors has revolutionized the treatment of advanced melanoma, but new combinatorial strategies are needed to further improve outcomes
- LAG-3 is an immune checkpoint protein upregulated in melanoma and other tumor types that inhibits T-cell activity[1-4]
- Relatlimab is a human mAb targeting LAG-3 that restores the effector function of exhausted T-cells[5]
- Dual targeting of PD-1 and LAG-3 with relatlimab + nivolumab represents an attractive treatment approach
  - Synergistic antitumor activity observed in preclinical models[6]
  - Active and well-tolerated in patients with melanoma relapsed/refractory to anti–PD-1 therapy[7,8]
- Current study reports initial efficacy and safety of relatlimab + nivolumab vs nivolumab alone in the first-line setting among patients with advanced melanoma in the RELATIVITY-047 phase II/III trial[9]

1. Durham. PLoS One. 2014;9:e109080. 2. Workman. J Immunol. 2004;172:5450-5455. 3. Grosso. J Clin Invest. 2007;117:3383-3392.
4. Hemon. J Immunol. 2011;186:5173–5183. 5. Lipson. SITC 2016. Abstr P232. 6. Woo. Cancer Res. 2012;72:917-927.
7. Ascierto. ASCO 2017. Abstr 9520. 8. Ascierto. ESMO 2017. Abstr LBA18. 9. Lipson. ASCO 2021. Abstr 9503.

RELATIVITY-047: Study Design

- Global, randomized, double-blind phase II/III trial



- Primary endpoint: PFS by BICR
- Key secondary endpoints: OS, ORR by BICR
  - Hierarchical statistical testing: PFS then OS then ORR

Lipson. ASCO 2021. Abstr 9503.

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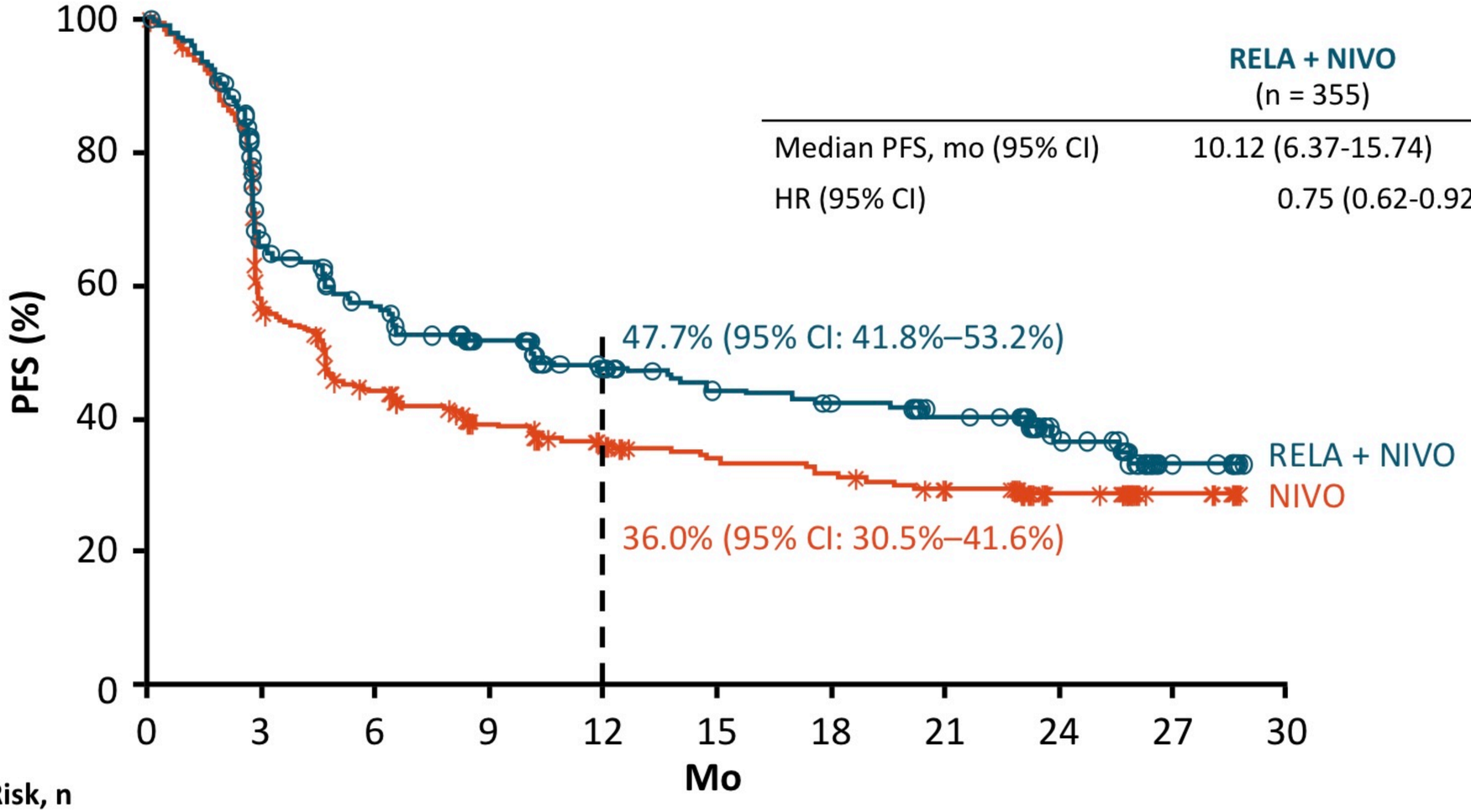
RELATIVITY-047: PFS by BICR (Primary Endpoint)

	RELA + NIVO (n = 355)	NIVO (n = 359)
Median PFS, mo (95% CI)	10.12 (6.37-15.74)	4.63 (3.38-5.62)
HR (95% CI)	0.75 (0.62-0.92), *P* = .0055	



Patients at Risk, n

RELA + NIVO	355	201	163	132	99	81	75	67	30	6	0
NIVO	359	174	124	94	72	61	57	49	27	6	0

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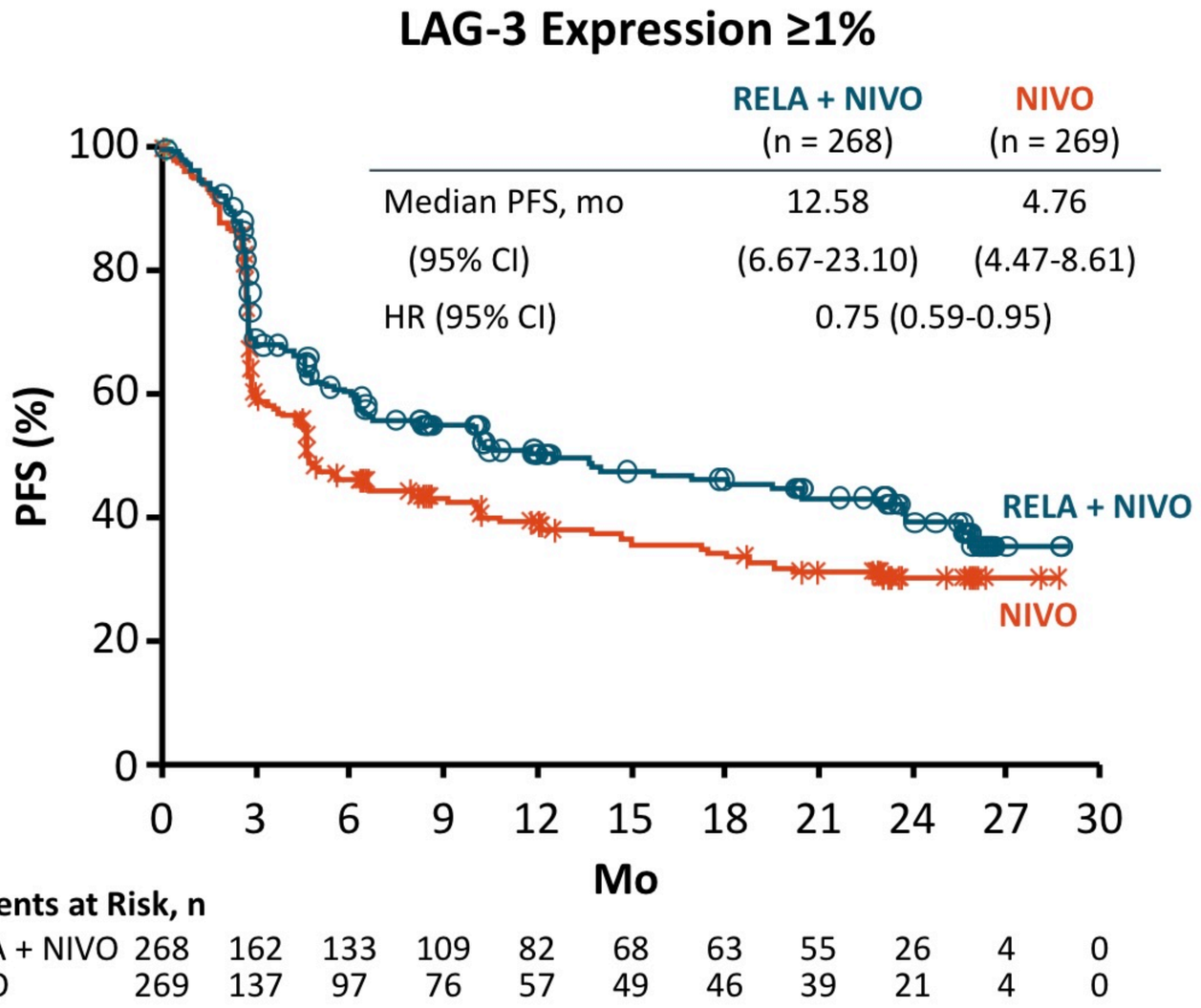
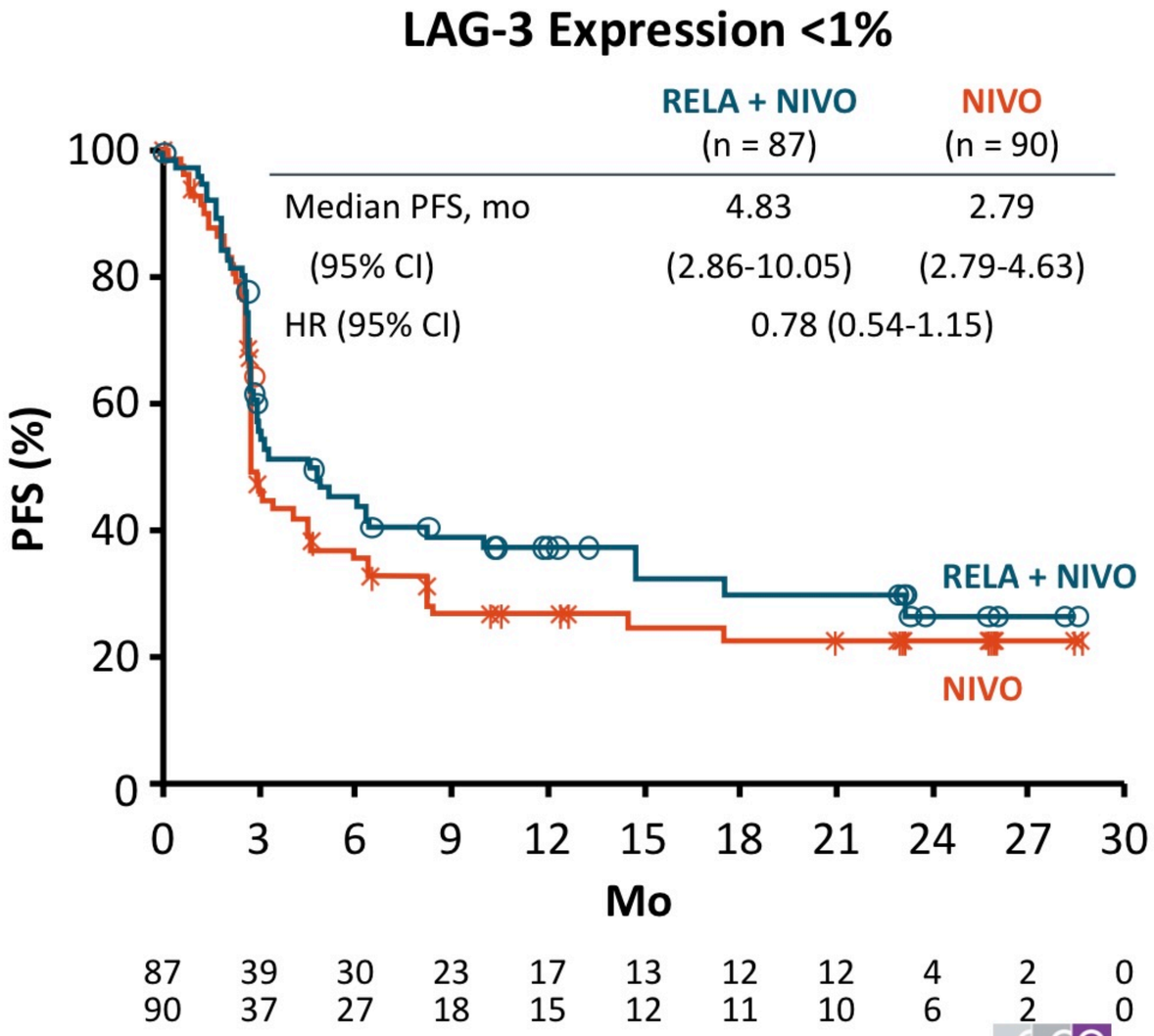
RELATIVITY-047: PFS by LAG-3 Expression Level





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RELATIVITY-047: Safety

AEs, n (%)	RELA + NIVO (n = 355)		NIVO (n = 359)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any AE	345 (97.2)	143 (40.3)	339 (94.4)	120 (33.4)
Any TRAE	288 (81.1)	67 (18.9)	251 (69.9)	35 (9.7)
TRAEs ≥10%				
▪ Pruritus	83 (23.4)	0	57 (15.9)	2 (0.6)
▪ Fatigue	82 (23.1)	4 (1.1)	46 (12.8)	1 (0.3)
▪ Rash	55 (15.5)	3 (0.8)	43 (12.0)	2 (0.6)
▪ Arthralgia	51 (14.4)	3 (0.8)	26 (7.2)	1 (0.3)
▪ Hypothyroidism	51 (14.4)	0	43 (12.0)	0
▪ Diarrhea	48 (13.5)	3 (0.8)	33 (9.2)	2 (0.6)
▪ Vitiligo	37 (10.4)	0	35 (9.7)	0
TRAEs leading to discontinuation	52 (14.6)	30 (8.5)	24 (6.7)	11 (3.1)

- 3 treatment-related deaths with RELA + NIVO: hemophagocytic lymphohistiocytosis, acute edema of the lung, pneumonitis
- 2 treatment-related deaths with NIVO: sepsis and myocarditis, worsening pneumonia

Lipson. ASCO 2021. Abstr 9503.

RELATIVITY-047: Immune-Mediated AEs

Immune-Mediated AEs, n (%)	RELA + NIVO (n = 355)		NIVO (n = 359)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hypothyroidism/thyroiditis	64 (18.0)	0	50 (13.9)	0
Rash	33 (9.3)	2 (0.6)	24 (6.7)	5 (1.4)
Diarrhea/colitis	24 (6.8)	4 (1.1)	11 (3.1)	5 (1.4)
Hyperthyroidism	22 (6.2)	0	24 (6.7)	0
Hepatitis	20 (5.6)	14 (3.9)	9 (2.5)	4 (1.1)
Adrenal insufficiency	15 (4.2)	5 (1.4)	3 (0.8)	0
Pneumonitis	13 (3.7)	2 (0.6)	6 (1.7)	2 (0.6)
Hypophysitis	9 (2.5)	1 (0.3)	3 (0.8)	1 (0.3)
Nephritis and renal dysfunction	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)
Hypersensitivity	4 (1.1)	0	4 (1.1)	0

- Other AE of interest: myocarditis (any grade) occurred in 5 (1.7%) patients with RELA + NIVO and 2 (0.6%) patients with NIVO (troponin monitoring performed for first 2 months of treatment per protocol)

Lipson. ASCO 2021. Abstr 9503.

RELATIVITY-047: Conclusions

- Fixed-dose combination of RELA + NIVO demonstrated superior PFS by BICR compared with NIVO alone in previously untreated patients with advanced melanoma
  - Median PFS 10.12 vs 4.63 months (HR: 0.75; 95% CI: 0.62-0.92; *P* = .0055)
  - PFS favored RELA + NIVO across key prespecified subgroups, regardless of LAG-3 expression
  - OS and ORR remain blinded per protocol
- RELA + NIVO showed manageable safety profile compared with NIVO alone, and no unexpected safety signals were observed
  - Grade 3/4 TRAEs: 18.9% vs 9.7%
- Investigators indicate that RELATIVITY-047 is the first phase III study to validate dual LAG-3 and PD-1 inhibition and conclude that RELA + NIVO is a potential new treatment option for patients with advanced melanoma

Lipson. ASCO 2021. Abstr 9503.

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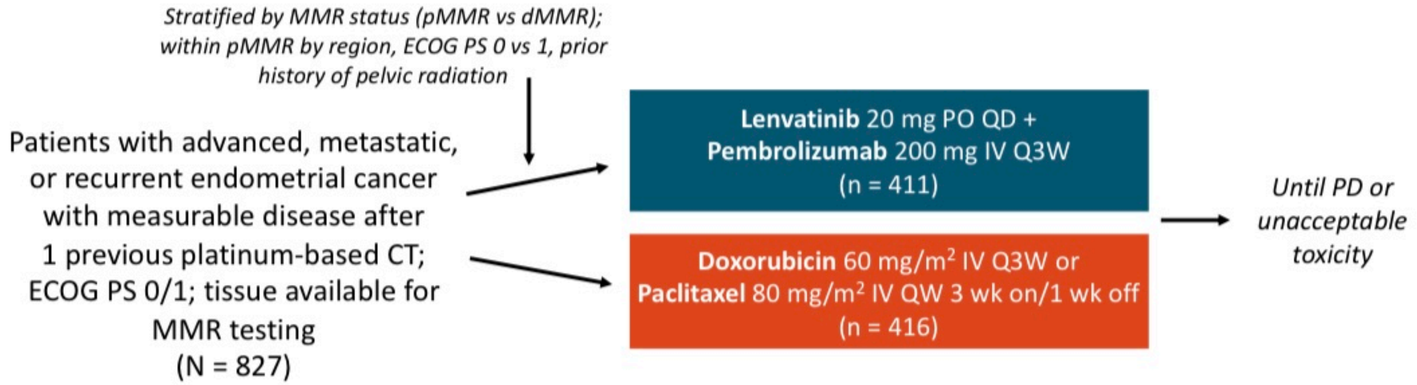
Phase III KEYNOTE-775: Second-line Pembrolizumab + Lenvatinib vs Chemotherapy in Advanced EC

Study 309/KEYNOTE-775: Lenvatinib + Pembrolizumab After Platinum in Advanced Endometrial Cancer

- Randomized, multicenter, open-label phase III study



- **Primary endpoints:** PFS by BICR, OS
- **Secondary endpoints:** ORR, health-related quality of life, pharmacokinetics, safety
- **Key exploratory endpoint:** DoR

Makker. SGO 2021. Abstr 11512.

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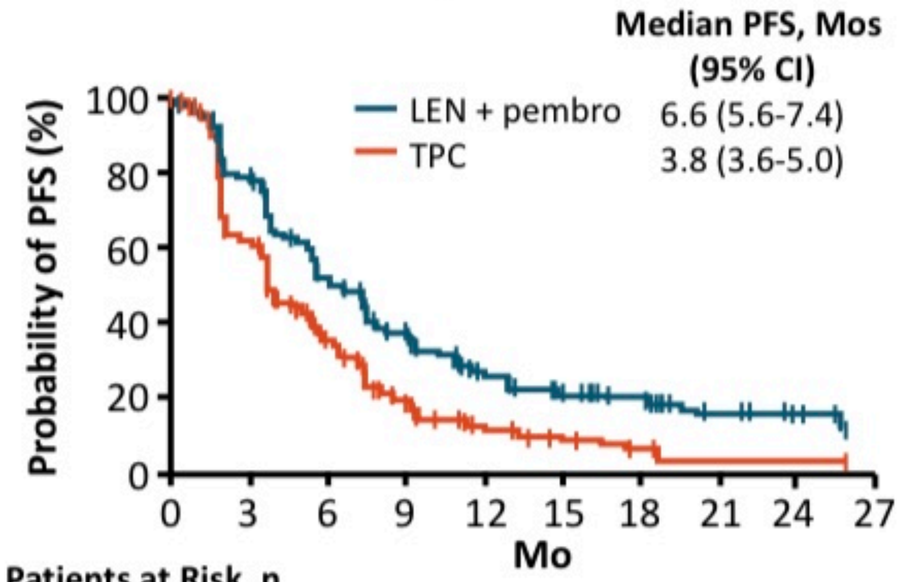
Study 309/KEYNOTE-775: PFS

pMMR

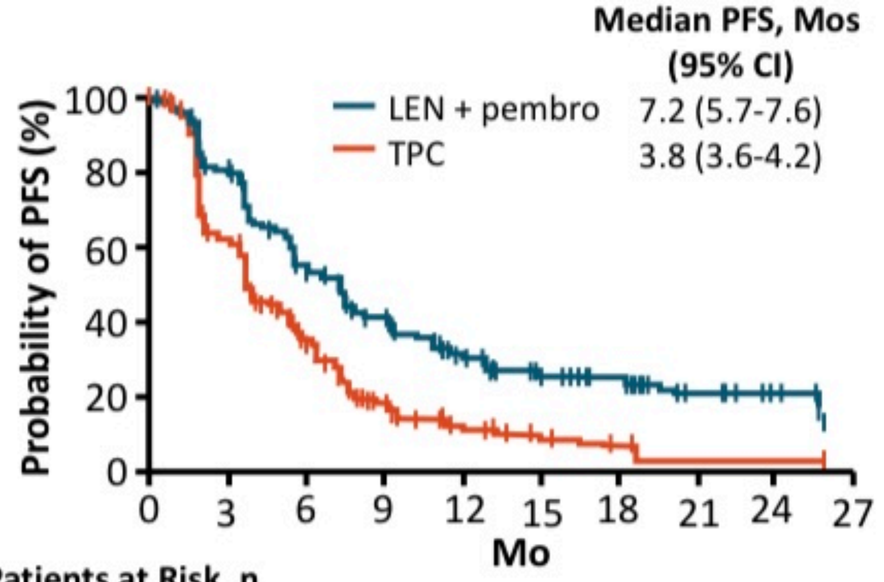


Patients at Risk, n

346	264	165	112	60	39	30	12	5	0
351	177	83	37	15	8	3	1	1	0

	Events	HR (95% CI)	*P* Value
LEN + pembro	247	0.60 (0.50-0.72)	<.0001
TPC	238		

All Comers



Patients at Risk, n

411	316	202	144	86	56	43	17	6	0
416	214	95	42	18	10	4	1	1	0

	Events	HR (95% CI)	*P* Value
LEN + pembro	281	0.56 (0.47-0.66)	<.0001
TPC	286		

- PFS benefit with lenvatinib + pembrolizumab seen across patient subgroups, including histology, MMR status, and previous therapies

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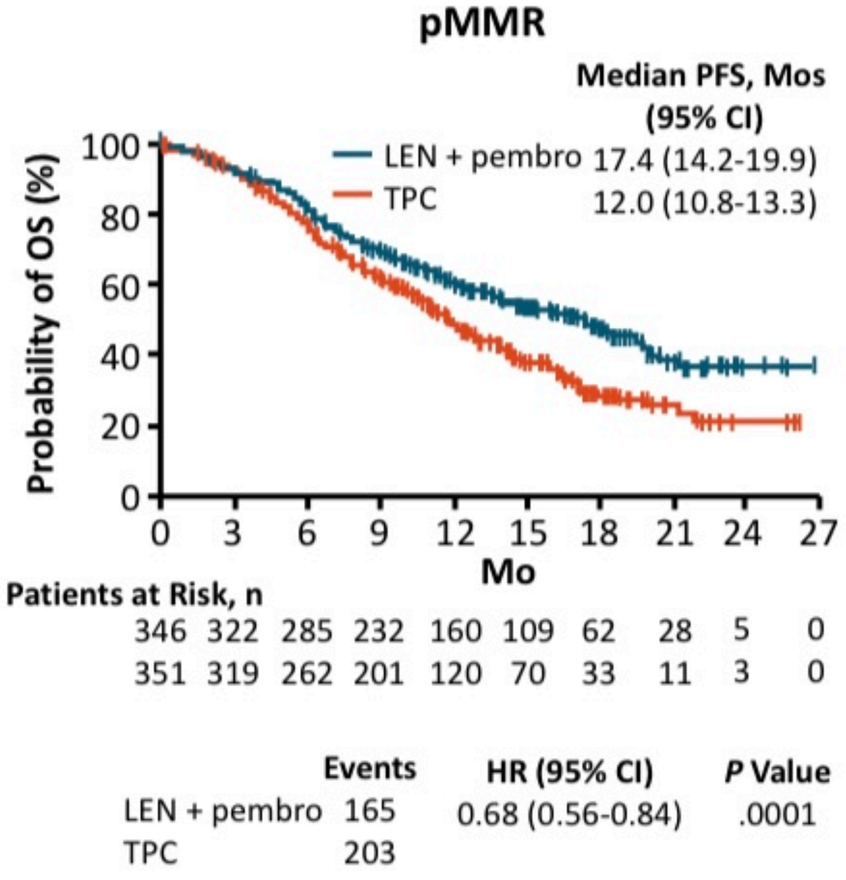
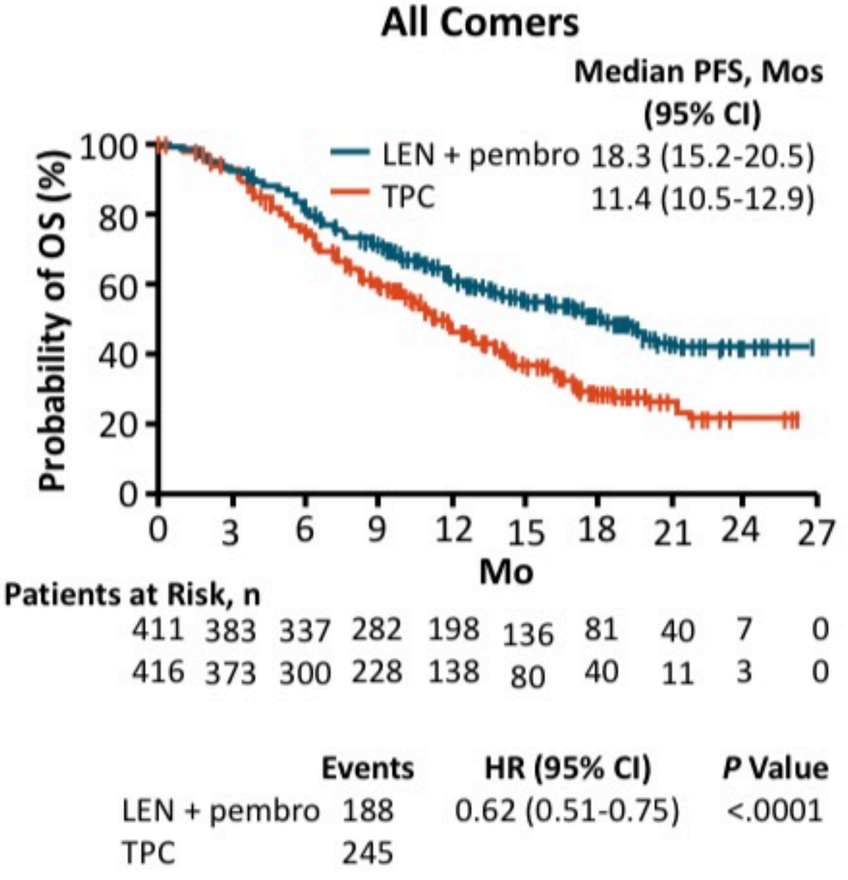
Study 309/KEYNOTE-775: Overall Survival



	Events	HR (95% CI)	*P* Value
LEN + pembro	165	0.68 (0.56-0.84)	.0001
TPC	203		



	Events	HR (95% CI)	*P* Value
LEN + pembro	188	0.62 (0.51-0.75)	<.0001
TPC	245		

- OS benefit with lenvatinib + pembrolizumab seen in all analyzed subgroups, including histology, MMR status, and prior number of therapies

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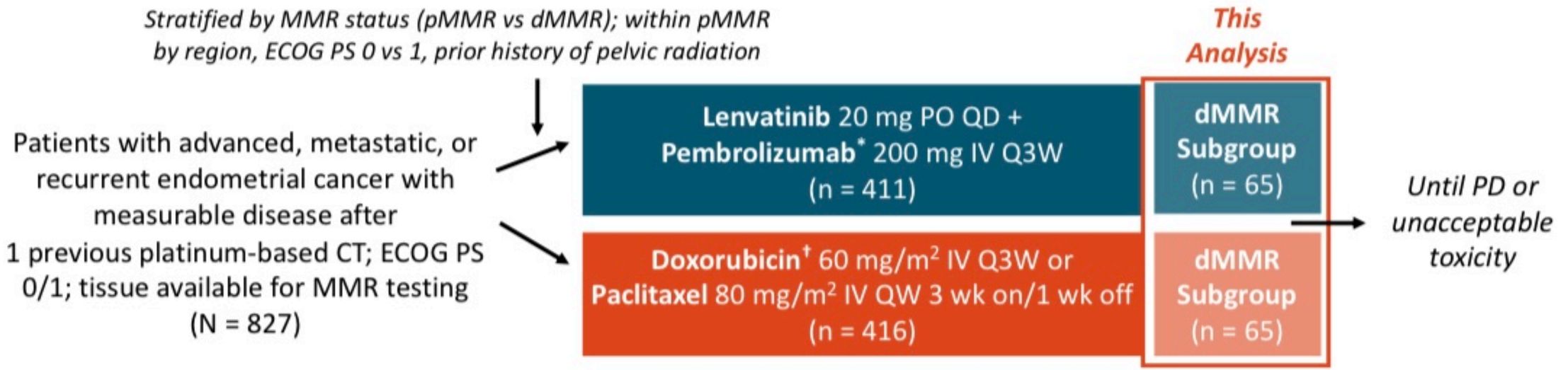
Study 309/KEYNOTE-775 dMMR Subgroup: Lenvatinib + Pembrolizumab in Advanced Endometrial Cancer

- Randomized, multicenter, open-label phase III study



- **Primary endpoints:** PFS by BICR, OS
  - In primary analysis, lenvatinib + pembrolizumab significantly improved PFS, OS, and ORR regardless of MMR status[1]
- **Secondary endpoints:** ORR, health-related quality of life, PK, safety[1]
- **Exploratory endpoints for dMMR subgroup:** PFS, OS, ORR, DoR, safety[2]

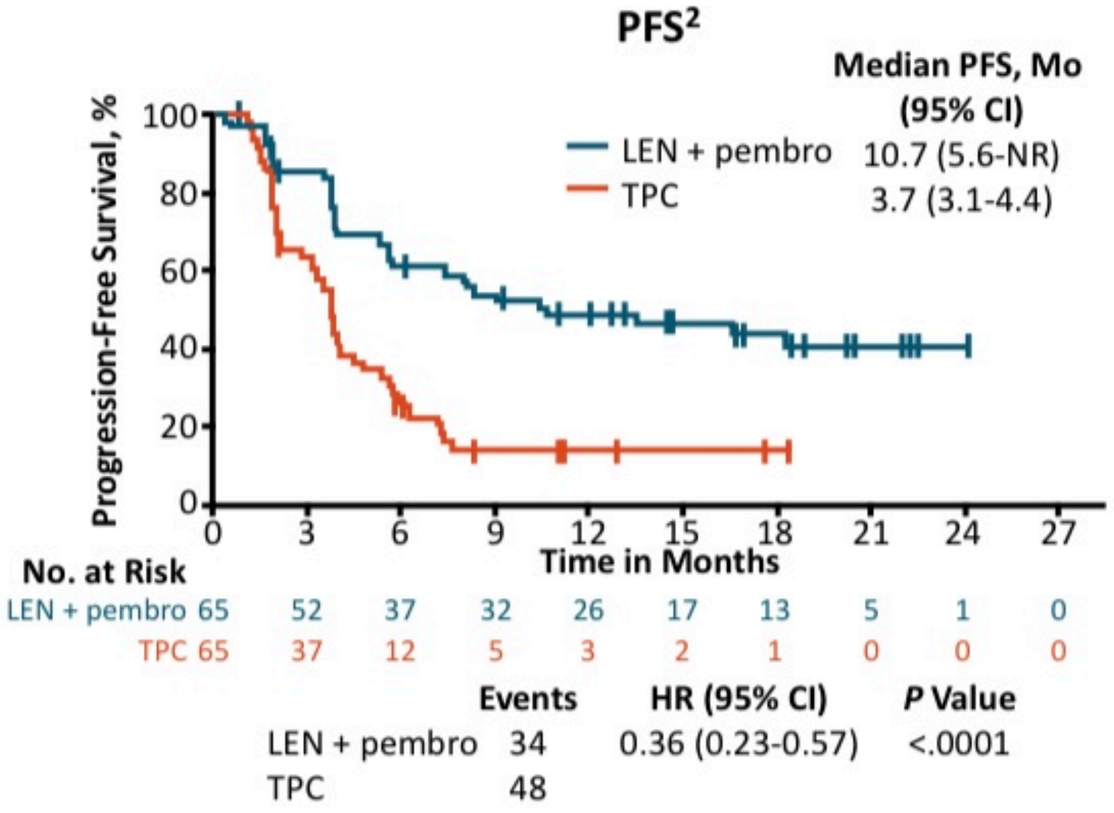
*Up to 35 doses. †Up to cumulative dose of 500 mg/m².

1. Makker. SGO 2021. Abstr 11512. 2. Makker. IGCS 2021. Abstr 43.

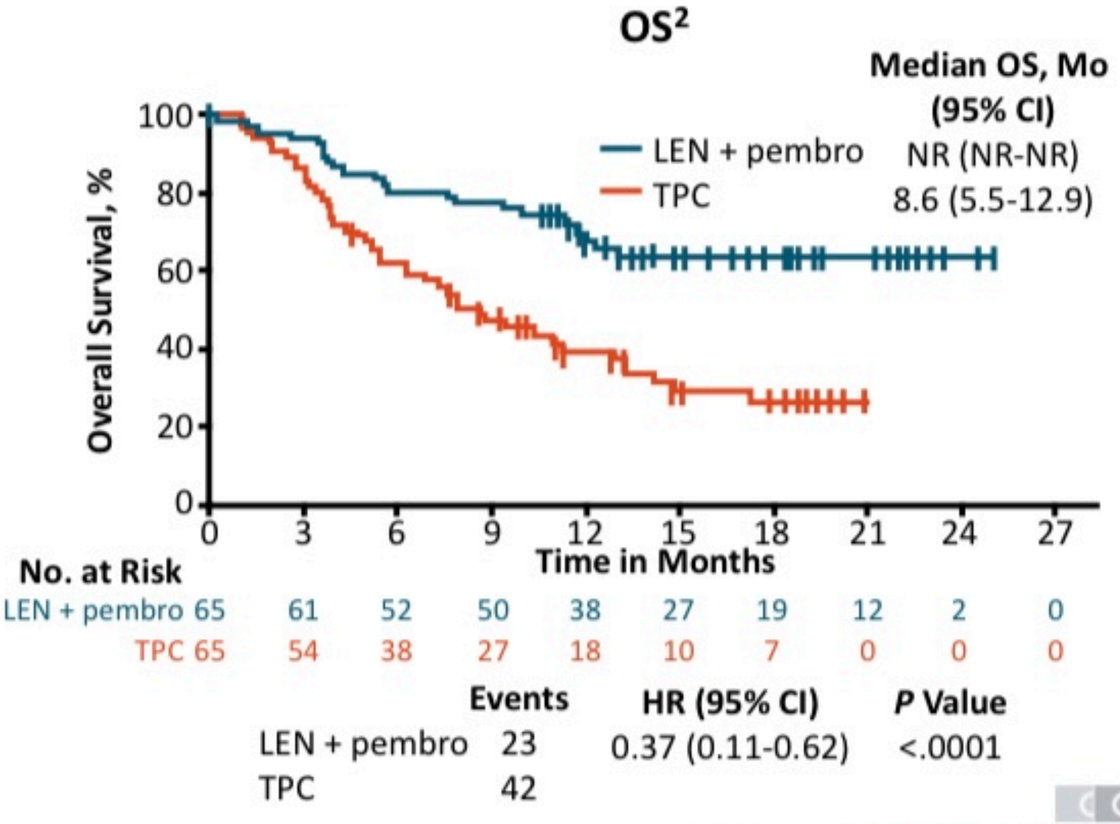
Slide credit: clinicaloptions.com

Study 309/KEYNOTE-775 dMMR Subgroup: Survival

- PFS, OS benefit with lenvatinib + pembrolizumab in dMMR subgroup consistent with that in pMMR, full study populations previously reported[1]



	Events	HR (95% CI)	*P* Value
LEN + pembro	34	0.36 (0.23-0.57)	<.0001
TPC	48		

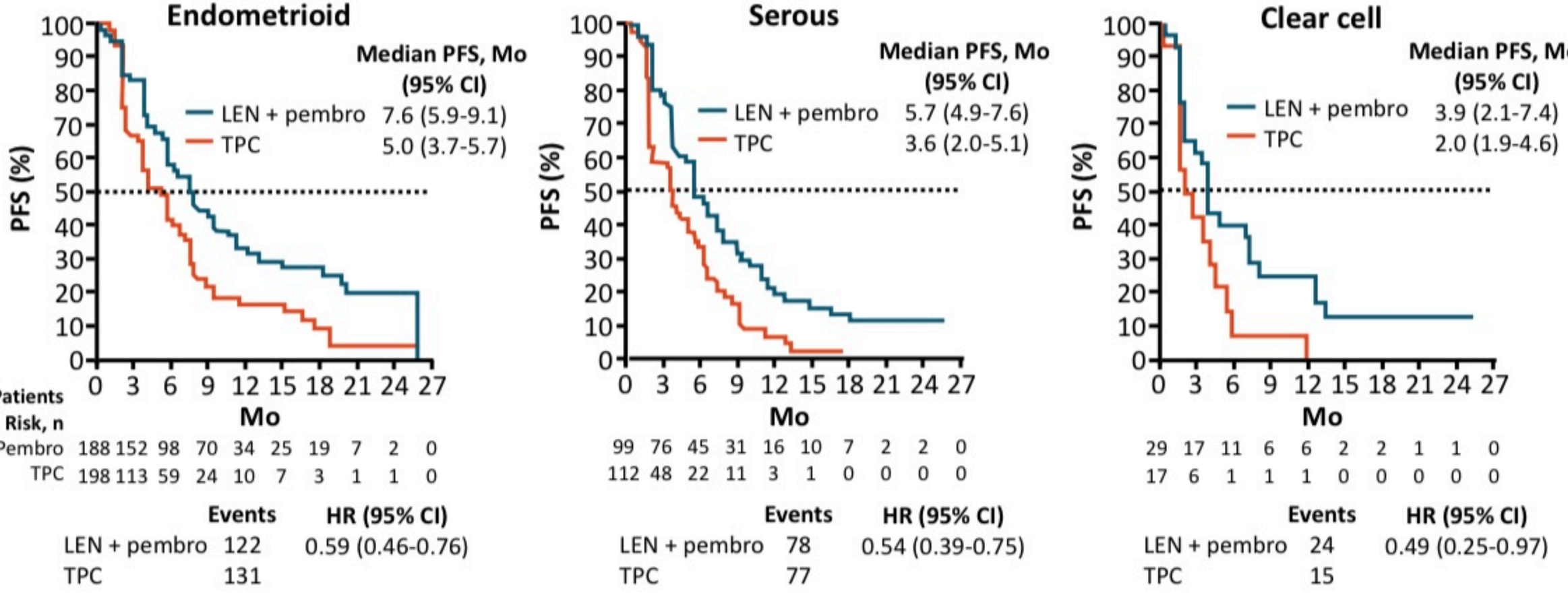


	Events	HR (95% CI)	*P* Value
LEN + pembro	23	0.37 (0.11-0.62)	<.0001
TPC	42		

1. Makker. SGO 2021. Abstr 11512. 2. Makker. IGCS 2021. Abstr 43.

Slide credit: clinicaloptions.com

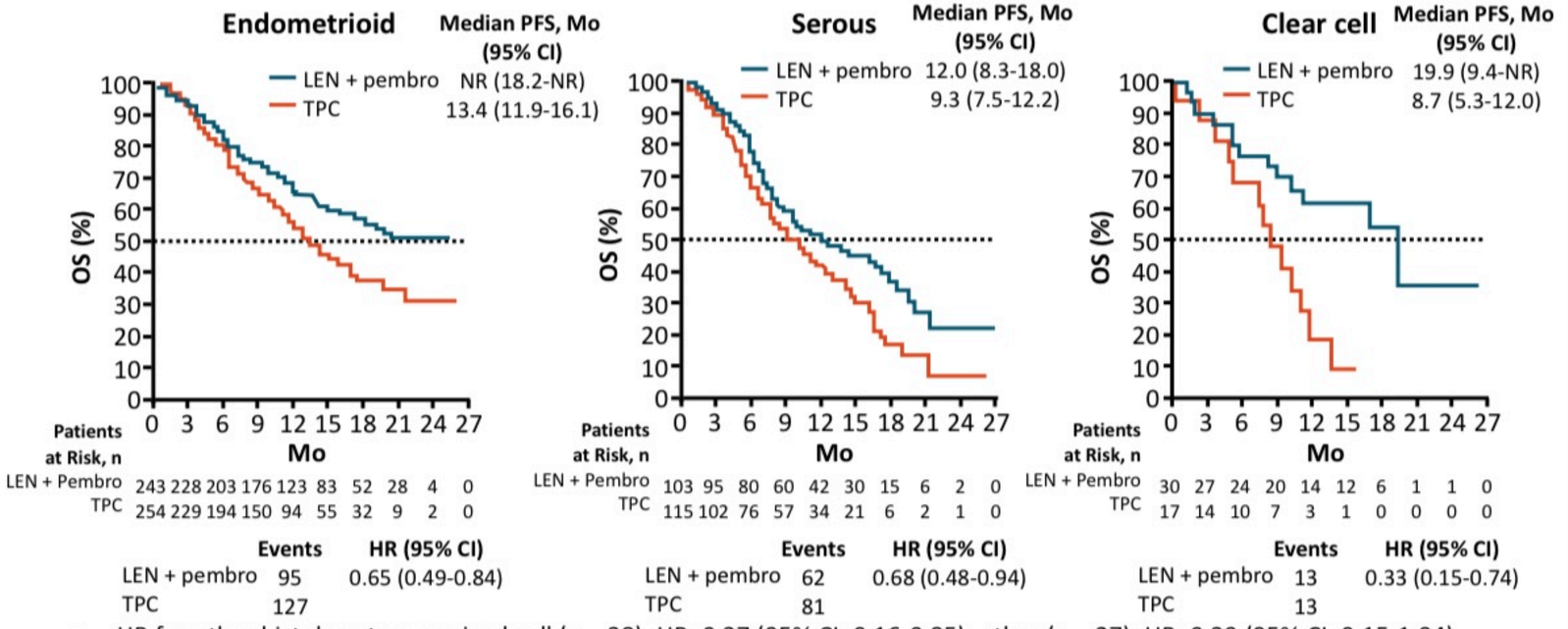
Study 309/KEYNOTE-775 Post Hoc Analysis: PFS* by Tumor Histology (pMMR Subgroup)



- HR for other histology types: mixed cell (n = 31); HR: 0.90 (95% CI: 0.35-2.29); other (n = 23); HR: 0.38 (95% CI: 0.12-1.19)

*Per RECIST v1.1 by BICR; randomization by MMR status.

Study 309/KEYNOTE-775 Post Hoc Analysis: OS by Tumor Histology (All-Comers)



- HR for other histology types: mixed cell (n = 38); HR: 0.37 (95% CI: 0.16-0.85); other (n = 27); HR: 0.39 (95% CI: 0.15-1.94)

Colombo. ESMO 2021. Abstr 726MO. Reproduced with permission.

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