Applications for Community Oncology

ESMO Data Review

October 27, 2022

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2022 ESMO Key Studies

Breast and Gynecological Cancer	Lung Cancer	GU/GI and Other Cancer
• TROPiCS-02 • MONARCH 3 • SOLO1 • PAOLA-1	• CodeBreaK 200* • IPSOS* • DESTINY-Lung02 • CheckMate-816 • NADIM II‡ • IMpower010‡	• NICHE-2* • RADICALS-HD* • COSMIC-313* • EV-103 K • EXPLORER/PATHFINDER

*ESMO Presidential Symposium
‡WCLC 2022

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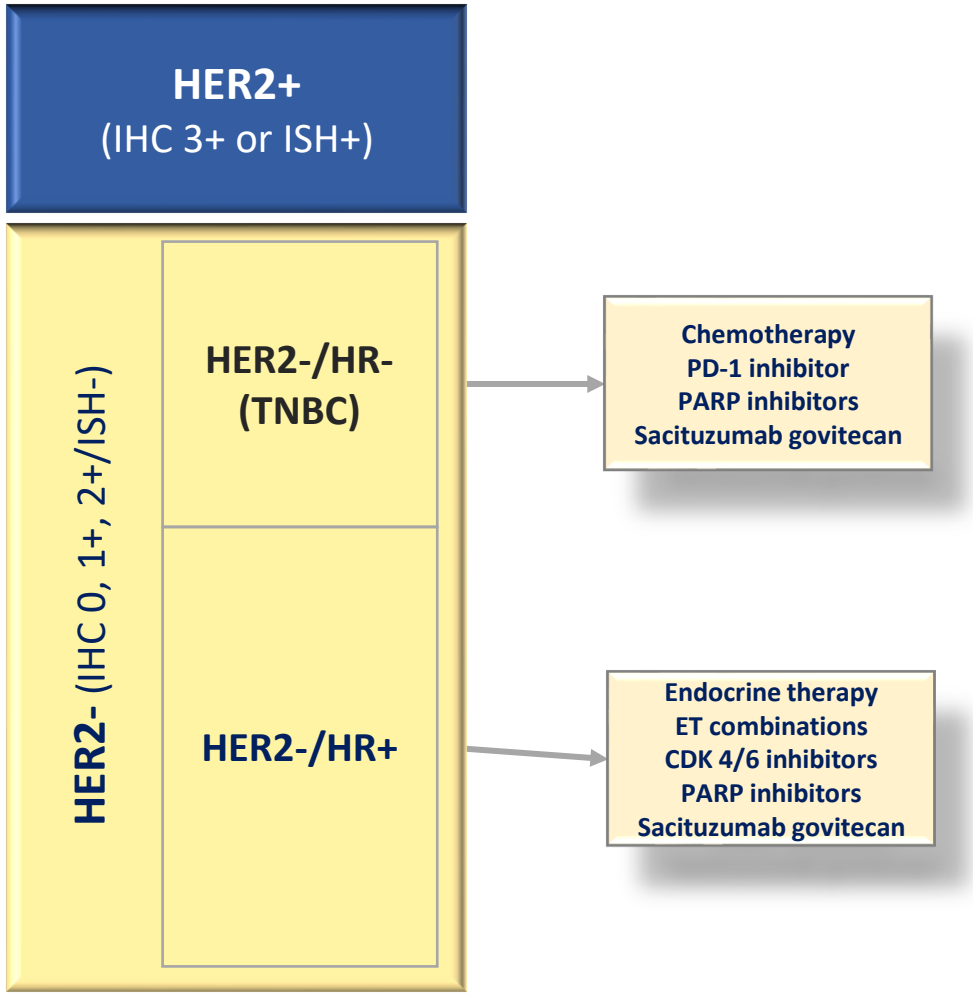
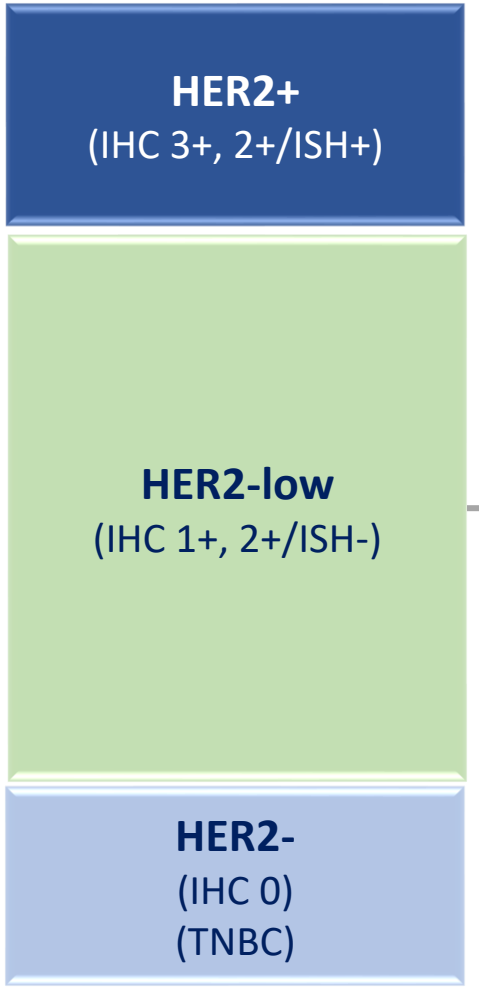
CLINICAL QUESTION

How is HER2-low defined? Therapeutic Impact

Classification and Treatment based on HER2 testing



Updated Classification and Treatment



August 2022: The FDA approved ENHERTU® (fam-trastuzumab-deruxtecan-nxki) for adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

Trastuzumab deruxtecan

October 4, 2022 : The FDA approval of the companion diagnostic PATHWAY anti-HER2 (4B5) test that can be used to identify patients with mBC with low HER2 expression

CLINICAL QUESTION

TROPiCS-02

refractory HR+ breast cancer

Does sacituzumab govitecan provide benefit to patients with previously treated *HR+/HER2-* mBC?

Second interim analysis and post-hoc subgroup analysis in HER2-low and HER2 IHC0

On April 7, 2021, the Food and Drug Administration granted regular approval to sacituzumab govitecan (Trodelvy, Immunomedics Inc.) for patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease

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KEY DATA

TROPiCS-02

Study Design: Randomized, multicenter, open-label phase III study

Stratification by visceral metastases (yes vs no), ET in metastatic setting ≥6 mo (yes vs no), prior lines of chemotherapy (2 vs 3/4)

- Metastatic or locally recurrent, inoperable HR+/HER2- breast cancer with disease progression
- At least 1 ET, taxane, and CDK4/6 inhibitor in any setting
- 2-4 previous lines of chemotherapy for metastatic disease (neo/adjuvant therapy qualified as a prior line if disease recurred within 12 mo)
- Measurable disease by RECIST v1.1

(N = 543)

R 1:1

Sacituzumab Govitecan
10 mg/kg IV d1 and 8, q 21 days
(n = 272)

Physician's Choice of Treatment
(Capecitabine, vinorelbine, gemcitabine, or eribulin)
(n = 271)

Until PD or unacceptable toxicity

Primary endpoint: PFS (BICR)
Secondary endpoints: OS, ORR, DoR, CBR (by LIR and BICR), PRO, safety
Post hoc subgroup analysis: evaluated efficacy in HER2-low and HER2 IHC0 subgroups

At the planned second interim analysis of OS, 390 events have occurred, and median duration of follow-up was 12.5 months

Data cutoff date: July 1, 2022

ESMO 2022. Abstr LBA76. . ESMO 2022. Abstr 214MO.

KEY DATA

TROPiCS-02: Demographics

Sacituzumab govitecan for refractory HER+/HER2 neg breast cancer

Baseline characteristic	Sacituzumab Govitecan (n = 272)	Physician's Choice (n = 271)
Female, n (%)	270 (99)	268 (99)
Median age, yr (range)	57 (29-86)	55 (27-78)
• <65 yr, n (%)	199 (73)	204 (75)
• ≥65 yr, n (%)	73 (27)	67 (25)
Race/ethnicity, n (%)		
• White	184 (68)	178 (66)
• Black	8 (3)	13 (5)
• Asian	11 (4)	5 (2)
• Other or not reported	69 (25)	75 (28)
ECOG PS, n (%)		
• 0	116 (43)	126 (46)
• 1	156 (57)	145 (54)
Visceral mets at baseline, n (%)	259 (95)	258 (95)
Liver mets, n (%)	229 (84)	237 (87)
De novo MBC, n (%)	78 (29)	60 (22)

Baseline characteristic	Sacituzumab Govitecan (n = 272)	Physician's Choice (n = 271)
Median time from MBC diagnosis to randomization, mo (range)	48.5 (1.2-243.8)	46.6 (3.0-248.8)
Prior CT in neo/adjuvant setting, n (%)	173 (64)	184 (68)
Prior ET use in MBC setting ≥6 mo, n (%)	235 (86)	234 (86)
Prior CDK4/6 inhibitor use, n (%)		
• ≤12 mo	161 (59)	166 (61)
• >12 mo	106 (39)	102 (38)
• Unknown	5 (2)	3 (1)
Median prior CT regimens* for mBC, n (range)	3 (0-8)	3 (1-5)

*In total, 9 patients received prior CT regimens in the metastatic setting outside the per protocol inclusion criteria of 2-4

- ***Of 543 patients in ITT population, 92% evaluable by IHC***
- ***Baseline characteristics comparable among HER2-low, HER2 IHC0, and ITT populations***

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KEY DATA

TROPiCS-02: PFS, ORR, Planned second interim analysis of OS

PFS and OS in the ITT Population

PFS by BICR Analysis	Sacituzumab Govitecan (n = 272)	Physician's Choice (n = 271)
Median PFS, mo (95% CI)	**5.5** (4.2-7.0)	**4.0** (3.1-4.4)
• Stratified hazard ratio (95% CI)	**0.66** (0.53-0.83)	
• Stratified log-rank *P* value	**0.0003**	
6-mo PFS, % (95% CI)	46.1 (39.4-52.6)	30.3 (23.6-37.3)
9-mo PFS, % (95% CI)	32.5 (25.9-39.2)	17.3 (11.5-24.2)
12-mo PFS, % (95% CI)	**21.3** (15.2-28.1)	**7.1** (2.8-13.9)

OS at second interim analysis	Sacituzumab Govitecan (n = 272)	Physician's Choice (n = 271)
Number of events	191	199
Median OS, mo (95% CI)	**14.4** (13.0 – 15.7)	**11.2** (10.1 – 12.7)
• Stratified hazard ratio (95% CI)	**0.79** (0.65-0.96)	
• Stratified log-rank *P* value	**0.020**	
12-mo OS, % (95% CI)	**61** (55 – 66)	**47** (41–53)

Response Rates in the ITT Population

BICR Analysis	Sacituzumab Govitecan (n = 272)	Physician's Choice (n = 271)
ORR, n (%)	57 (21)	38 (14)
• Odds ratio (95% CI)	1.63 (1.03 – 2.56), *P* = 0.035	
Best overall response, n (%)		
• CR	2 (1)	0
• PR	55 (20)	38 (14)
• SD	142 (52)	106 (39)
• SD ≥6 mo	35 (13)	21 (8)
• PD	58 (21)	76 (28)
• NE	15 (6)	51 (19)
CBR,* n (%)	92 (34)	60 (22)
• Odds ratio (95% CI)	1.80 (1.23 – 2.63), *P* = 0.003	
Median DoR, mo (95% CI)	**8.1** (6.7-9.1)	**5.6** (3.8-7.9)

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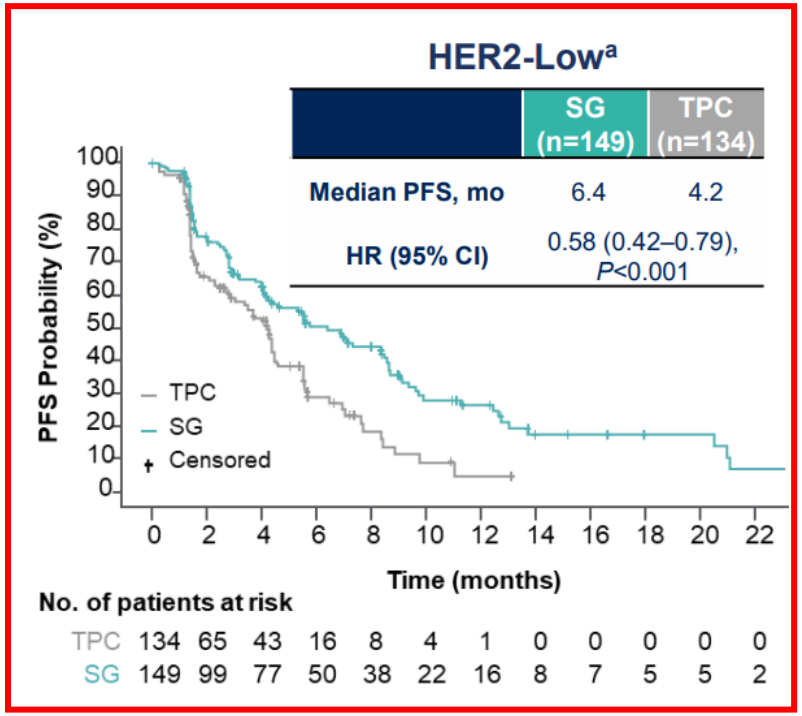
KEY DATA

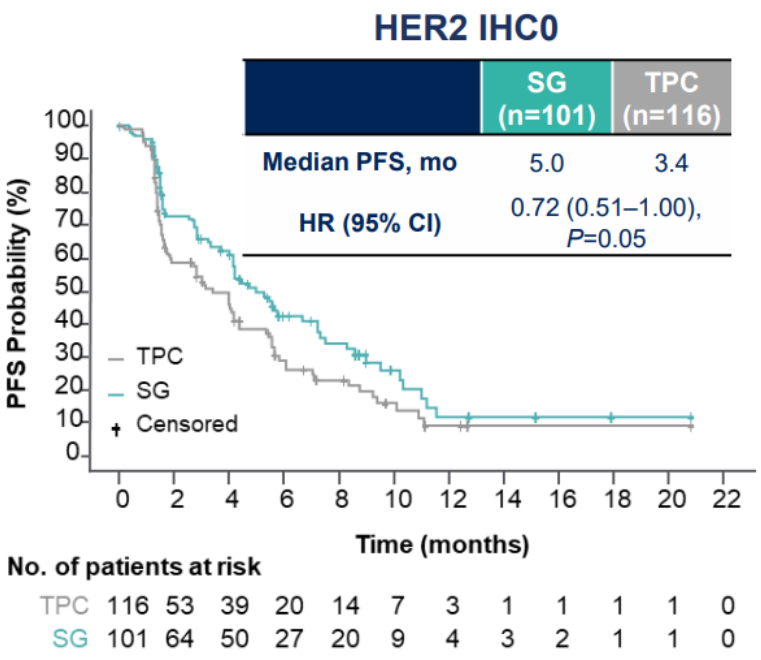
TROPiCS-02: Retrospective Analysis by HER2 Status

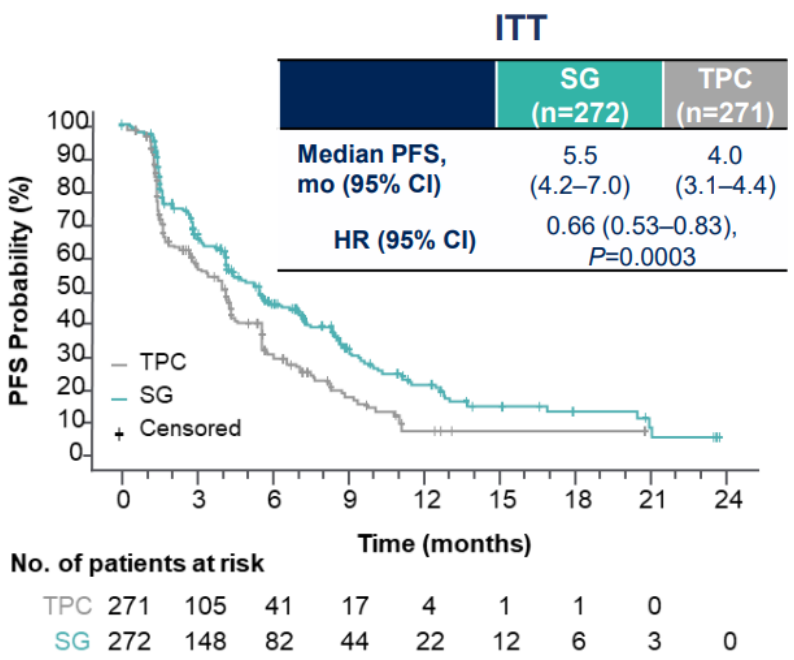
Of the 543 patients from the TROPiCS-02 ITT population, 92% had tumors that were HER2-evaluable by IHC

- **52% HER2-Low** ([a]IHC1+, IHC2+ [ISH-negative/unverified]): N=283
- **40% HER2 IHC0**: N=217
- 8% were excluded from the analysis due to missing HER2 IHC status: N=43 (SG, n=22; TPC, n=21)

Demographics and baseline characteristics between the HER2-Low, HER2 IHC0, and ITT populations were comparable







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KEY DATA

TROPiCS-02: Retrospective Analysis by HER2 Status

Response Rates

	HER2-Low*		HER2 IHC0	
	SG (n = 149)	TPC (n=134)	SG (n = 101)	TPC (n=116)
ORR, n (%)	38 (26)	16 (12)	16 (16)	17 (15)
• Odds ratio (95% CI)	2.52 (1.33-4.78)		1.10 (0.52-2.30)	
Best Overall Response, n (%)				
• CR	2 (1)	0	0	0
• PR	36 (24)	16 (12)	16 (16)	17 (15)
• SD	73 (49)	61 (46)	56 (55)	39 (34)
• SD6mo	18 (12)	10 (7)	15 (15)	8 (7)
• PD	29 (19)	36 (27)	23 (23)	38 (33)
• NE	9 (6)	21 (16)	6 (6)	22 (19)
CBR,* n (%)	56 (38)	26 (19)	31 (31)	25 (22)
• Odds ratio (95% CI)	2.50 (1.46-4.30)		1.61 (0.87-2.97)	
Median DoR, mo (95% CI)	7.4 (5.8 – 8.9)	4.1 (2.8 – 6.1)	8.1 (4.1 – NE)	6.1 (2.8 – 8.3)

* HER2-Low defined as IHC1+, or IHC2+ and ISH-negative/unverified.

SUMMARY

TROPiCS-02: Sacituzumab govitecan

- Sacituzumab govitecan provided a statistically significant PFS and OS benefit over physician choice chemotherapy (TPC) in ITT population with HR+/HER2- mBC previously treated with ET, CDK4/6 inhibitors, and ≥2 CT regimens for mets
  - 3.2-mo OS improvement (median 14.4 vs 11.2 mo; HR: 0.79; 95% CI: 0.65-0.96; *P* = 0.02)
  - ORR, CBR, and DoR also improved with sacituzumab govitecan vs TPC
- Outcomes in HER2-low and HER2 IHC0 HR+/HER2- mBC were consistent with overall population
- No new safety concerns

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TROPiCS-02

Sacituzumab govitecan demonstrated statistically significant and clinical benefit to patients with heavily pre-treated HR+ breast cancer regardless of HER2 IHC status: better for mOS than mPFS

(3 mo median OS improvement; HR 0.79, p=0.02)

COMPARISON

DESTINY-Breast04 vs TROPiCS-02: HER2-low

Cross-study Comparison

HER2-low	DESTINY-Breast04			TROPiCS-02		
FDA approval	*Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer patients who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy*			*Unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) patients who have received two or more prior systemic therapies, at least one of them for metastatic disease*		
Study Design	**T-DXd**	**vs**	**TPC**	**Sacituzumab govitecan**	**vs**	**TPC**
Inclusion Criteria	• HER2-low (IHC 1+ or IHC 2+/ISH-) unresectable or metastatic BC • ≥1 ET if HR+ • **1-2 lines of chemotherapy** in the metastatic setting or recurrence ≤6 mo after adjuvant CT • Treated, stable brain metastases eligible			• Metastatic or locally recurrent, inoperable HR+/HER2- breast cancer • ***Post hoc subgroup analysis*** in HER2-low and HER2 IHC0 subgroups • At least 1 ET, taxane, and CDK4/6 inhibitor in any setting • **2-4 previous lines of CT** for metastatic disease (neo/adjuvant therapy qualified as a prior line of CT if disease recurred within 12 mo)		
N	331	*HR+ve cohort*	163	149		134
Median PFS, mo	**10.1**	HR **0.51** (0.40-0.64) *P* < 0.0001	5.4	**6.4**	HR **0.58** (0.42-0.79) *P* < 0.001	4.2
ORR, %	**52.6**		16.3	**26**		12
Median DoR, mo	**10.7**		6.8	**7.4**		4.1
Safety, Grade 3 TEAE	**195 (53%)**		116 (67%)	**109 (74%)**		73 (59%)
PRO data, time to deterioration				(*In ITT population*)		
• Global health status/QoL	**11.4 months**		7.5 months	**4.3 months**		3.0 months
• Pain symptoms	**16.4 months**		6.1 months	**3.8 months**		3.5 months
• Fatigue	**11.1 months**		4.5 months	**2.2 months**		1.4 months

ASCO 2022. Abstr LBA03; ESMO 2022. Abstr 2170

ESMO 2022. Abstr 214MO.

2022 ESMO Key Studies

Breast and Gynecological Cancer

- TROPiCS-02
- MONARCH 3
- SOLO1
- PAOLA-1

Lung Cancer

- CodeBreaK 200*
- IPSOS*
- DESTINY-Lung02
- CheckMate-816
- NADIM II‡
- IMpower010‡

GU/GI and Other Cancer

- NICHE-2*
- RADICALS-HD*
- COSMIC-313*
- EV-103 K
- EXPLORER/PATHFINDER

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CLINICAL QUESTION

MONARCH 3

1st-line HR+ HER2 neg

Does front-line abemaciclib in combination with a non-steroidal aromatase inhibitor provide benefit for postmenopausal patients with HR+/HER2- advanced breast cancer?

Interim analysis

Abemaciclib is the first and only CDK4/6 inhibitor approved as a monotherapy in advanced breast cancer (ABC) and in combination with endocrine therapy (ET) for the adjuvant treatment of high-risk, HR+, HER2- early breast cancer

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KEY DATA

MONARCH 3: Abemaciclib for 1st-line HR+ HER2 neg

Study Design: Randomized, multicenter, phase III study

Stratification by metastatic site (visceral, bone only, or other) and prior ET (AI, no ET, or other)

- Patients with HR+/HER2- metastatic or locoregionally recurrent disease with no prior systemic therapy
- postmenopausal
- >12 mo disease-free interval since (neo)adjuvant ET, if applicable
- ECOG PS ≤1

(N = 493)

R 2:1

Abemaciclib 150 mg po BID
+ Anastrozole* 1 mg po QD
or **Letrozole*** 2.5 m
(n=328)

Placebo PO BID
+ Anastrozole* 1 mg po QD
or **Letrozole*** 2.5 mg po QD
(n = 165)

*per physician's choice: 79.1% received letrozole
19.9% received anastrozole

Primary endpoint: Investigator-assessed PFS
Key secondary endpoints: Overall survival, response rates, safety

ESMO 2022. Abstr LBA15.

KEY DATA

MONARCH 3: Abemaciclib

Preplanned Final PFS Analysis

Data cutoff: 03 Nov 2017

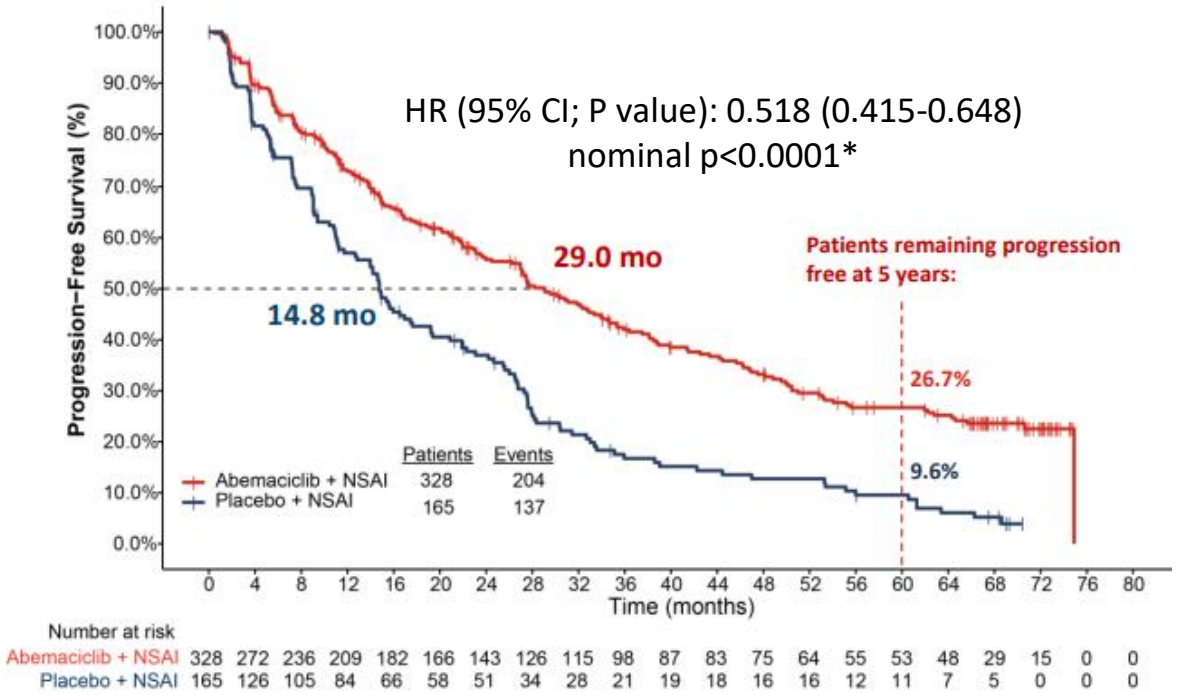
	Abemaciclib + NSAI (n = 328)	Placebo + NSAI (n = 165)
Median PFS, mo	**28.2**	**14.8**
• HR (95% CI)	0.540 (0.418-0.698)	
• *P* value	0.000021	
Events, n	138	108

NSAI, nonsteroidal aromatase inhibitor

- Statistical significance reached at interim PFS analysis led to FDA approval
  - PFS prolonged by 13.4 months
- OS data were immature at final PFS data cutoff; 29.5% events observed across both arms

Updated PFS in ITT Population

Data cut: 02 Jul 2021



- With a median follow-up of 5.8 yrs (additional 3.6 yrs from final PFS analysis), efficacy is maintained

ESMO 2022. Abstr LBA15.

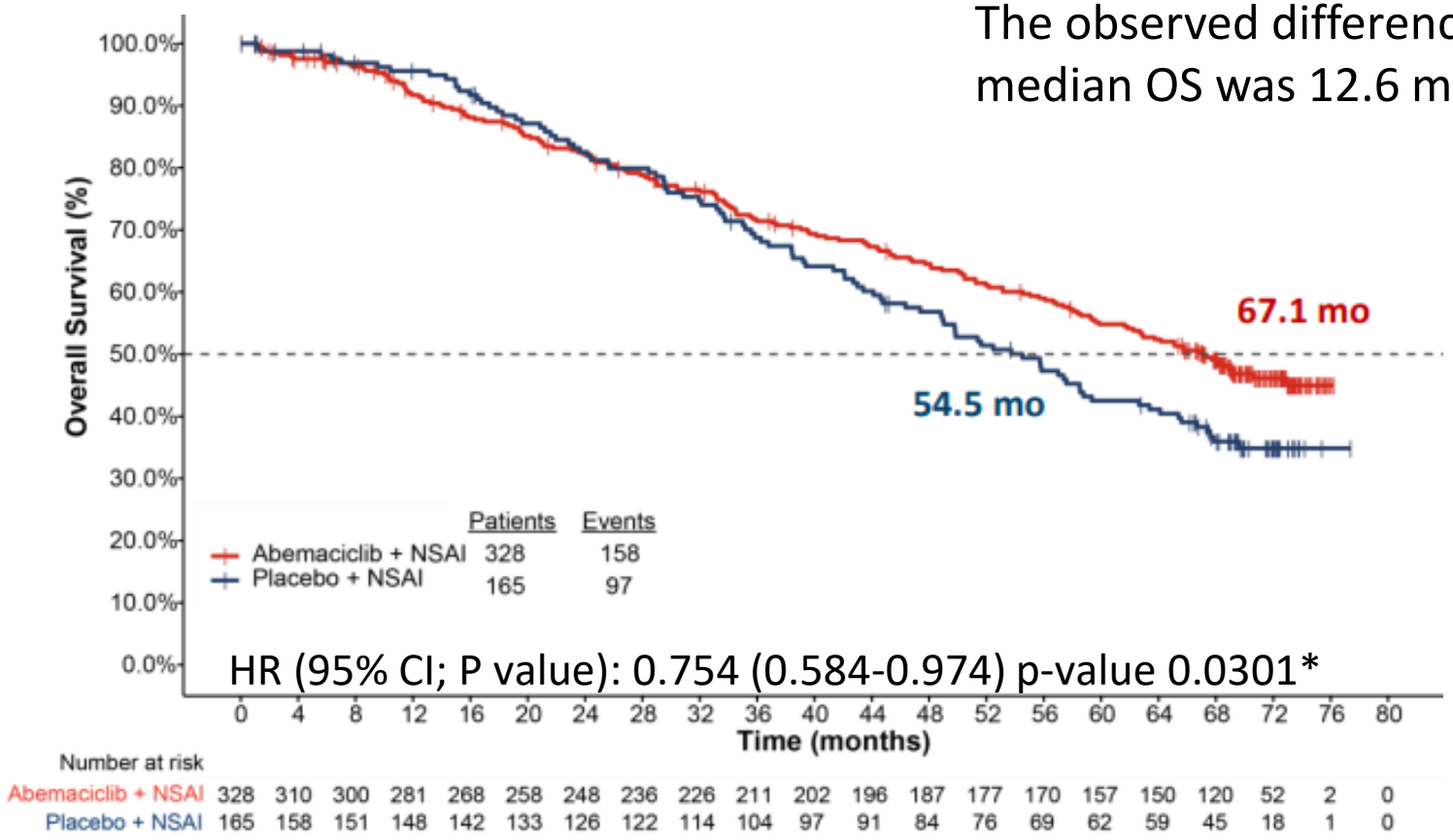
KEY DATA

MONARCH 3: Abemaciclib

Pre-planned OS Interim Analysis 2

Data cut: 02 Jul 2021

The observed difference in median OS was 12.6 months



*p-value did not reach threshold for statistical significance at this interim

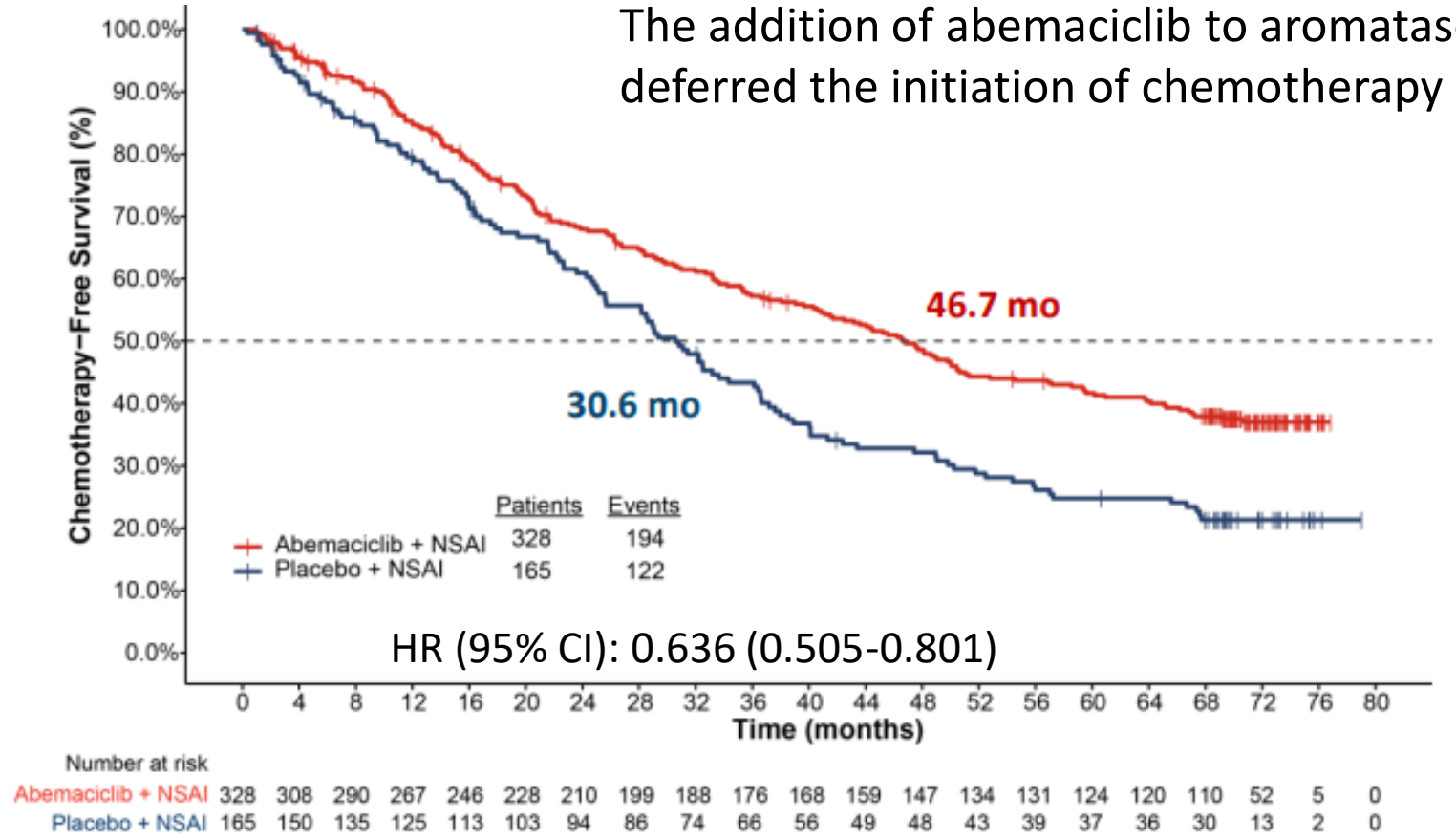
ESMO 2022. Abstr LBA15.

KEY DATA

MONARCH 3

Chemotherapy-Free Survival in the ITT Population

The addition of abemaciclib to aromatase inhibitor(NSAI) deferred the initiation of chemotherapy by 16.1 months



Chemotherapy-Free Survival defined as the time to the initiation of subsequent chemotherapy or death from any cause, whichever was earlier

ESMO 2022. Abstr LBA15.

SUMMARY

MONARCH 3: Abemaciclib

- With an additional follow-up of 3.6 years from final PFS analysis, efficacy is maintained and provides a significant benefit for patients
  - HR (95% CI; P value): 0.518 (0.415-0.648) nominal p<0.0001*
- Abemaciclib plus a nonsteroidal aromatase inhibitor in patients with hormone receptor–positive/HER2-negative advanced breast cancer showed a non-significant overall survival trend when compared to placebo with a NSAI at the second interim analysis
  - HR (95% CI; P value): 0.754 (0.584-0.974) p-value 0.0301
  - Median 12.6 month difference between treatment arms favoring abemaciclib
- No new safety concerns with prolonged exposure to abemaciclib

ESMO 2022. Abstr LBA15.

MONARCH 3

The addition of abemaciclib to a nonsteroidal aromatase inhibitor in the front line setting for patients with hormone receptor-positive/HER2-negative advanced breast cancer provides benefit and delays the use of chemotherapy

Final OS data to come…

2022 ESMO Key Studies

Breast and Gynecological Cancer	Lung Cancer	GU/GI and Other Cancer
• TROPiCS-02 • MONARCH 3 • SOLO1 • PAOLA-1	• CodeBreaK 200* • IPSOS* • DESTINY-Lung02 • CheckMate-816 • NADIM II‡ • IMpower010‡	• NICHE-2* • RADICALS-HD* • COSMIC-313* • EV-103 K • EXPLORER/PATHFINDER

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FDA NEWS

PARP Inhibitors in Ovarian Cancer

- ***On June 10, 2022**, Clovis Oncology, Inc. voluntarily withdrew Rubraca (rucaparib) as a treatment of BRCA-mutated ovarian cancer after two or more chemotherapies based on OS data from the Phase III ARIEL4 study showing disappointing results (31.3% greater risk for death) for rucaparib compared with chemotherapy, and particularly in patients with platinum-resistant tumors.*

- ***On August 11, 2022**, AstraZeneca voluntarily withdrew Lynparza (olaparib) indication for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy based on the randomized Phase III SOLO3 study stating there is a "potential detrimental effect on the overall survival" (33% greater risk of death) for olaparib compared to the chemotherapy control arm.*

- ***On September 14, 2022**, GSK voluntarily withdrew ZEJULA (niraparib) indication for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status "based on a totality of information from PARP inhibitors in the late line treatment setting" and on the single arm, uncontrolled QUADRA trial with no comparative overall survival information.*

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CLINICAL QUESTION

SOLO1: 7-year follow-up

Does maintenance olaparib continue to provide benefit to patients with newly diagnosed advanced ovarian cancer and a BRCA mutation?

7-year follow-up

***Olaparib is FDA approved**:*

- ***for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza***
- *in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either: a deleterious or suspected deleterious BRCA mutation, and/or genomic instability. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza*
- *and for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.*

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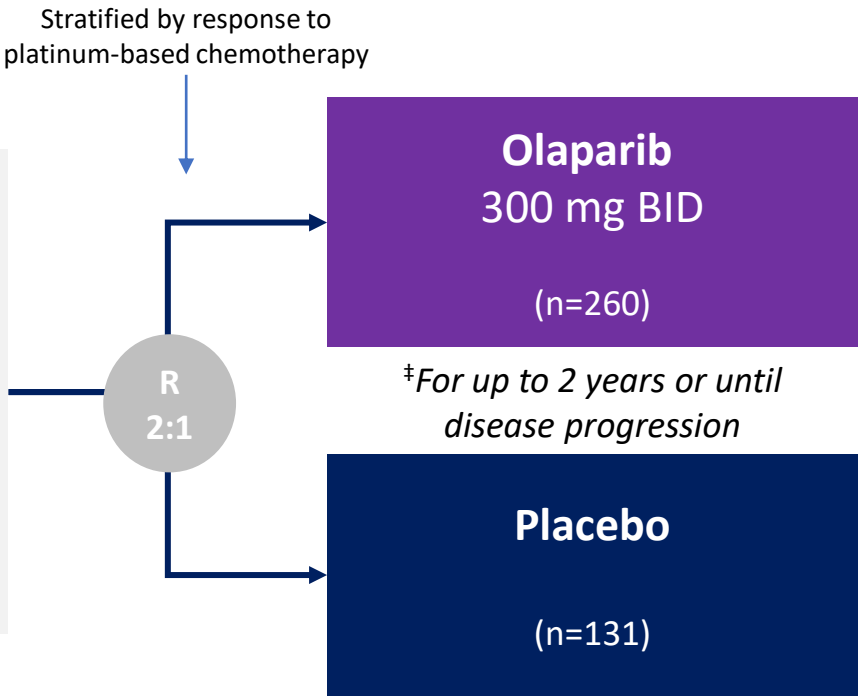
KEY DATA

SOLO1: 7-year follow-up

Study Design: Randomized, double-blind, phase III study

- Patients with newly diagnosed, FIGO stage III/IV, high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer
- *BRCA* mutation
- ECOG PS 0/1
- Cytoreductive surgery*
- In CR† or PR after platinum-based therapy

(N = 391)



Prespecified descriptive OS conducted 7 years after the last patient was randomized

Data cutoff: 7 March 2022

Primary endpoint: PFS (investigator assessed)

Key secondary endpoints: OS, TFST (time to first subsequent therapy or death), TSST (time to second subsequent therapy or death), Safety

*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease

† Including patients with no evidence of disease

‡ Patients with evidence of disease at 2 years could continue to receive study treatment if, in the investigator's opinion, this was in the patient's best interest

ESMO 2022. Abstr 5170.

KEY DATA

SOLO1: 7-year follow-up

Baseline Characteristics

Characteristic, n (%)	Olaparib (n = 260)	Placebo (n = 131)
FIGO stage		
• III	220 (84.6)	105 (80.2)
• IV	40 (15.4)	26 (19.8)
BRCA mutation		
• BRCA1	191 (73.5)	91 (69.5)
• BRCA2	66 (25.4)	40 (30.5)
• BRCA1 + BRCA2	3 (1.2)	0
Upfront cytoreductive surgery	161 (61.9)	85 (64.9)
• Residual macroscopic disease	37 (23.0)	22 (25.9)
• No residual macroscopic disease	123 (76.4)	62 (72.9)
• Unknown	1 (0.6)	1 (1.2)
Interval cytoreductive surgery	94 (36.2)	43 (32.8)
• Residual macroscopic disease	18 (19.1)	7 (16.3)
• No residual macroscopic disease	76 (80.9)	36 (83.7)
No surgery	4 (1.5)	3 (2.3)
Response after surgery/platinum-based chemotherapy		
• Clinical CR (includes pts with no evidence of disease)	213 (81.9)	107 (81.7)
• Clinical PR	47 (18.1)	24 (18.3)

ESMO 2022. Abstr 5170.

KEY DATA

SOLO1: 7-year follow-up

PFS Analysis

Primary PFS Analysis (data cutoff: 17 May 2018)	**Olaparib (n-=260)**	**Placebo (n=131)**
Events, n (%)	102 (39.2)	96 (73.3)
Median PFS, months	**NR**	**13.8**
3-year PFS rate, %	60.4	26.9
HR (95% CI), *P*-value	**0.30** (0.23 – 0.41), *P < 0.001*	

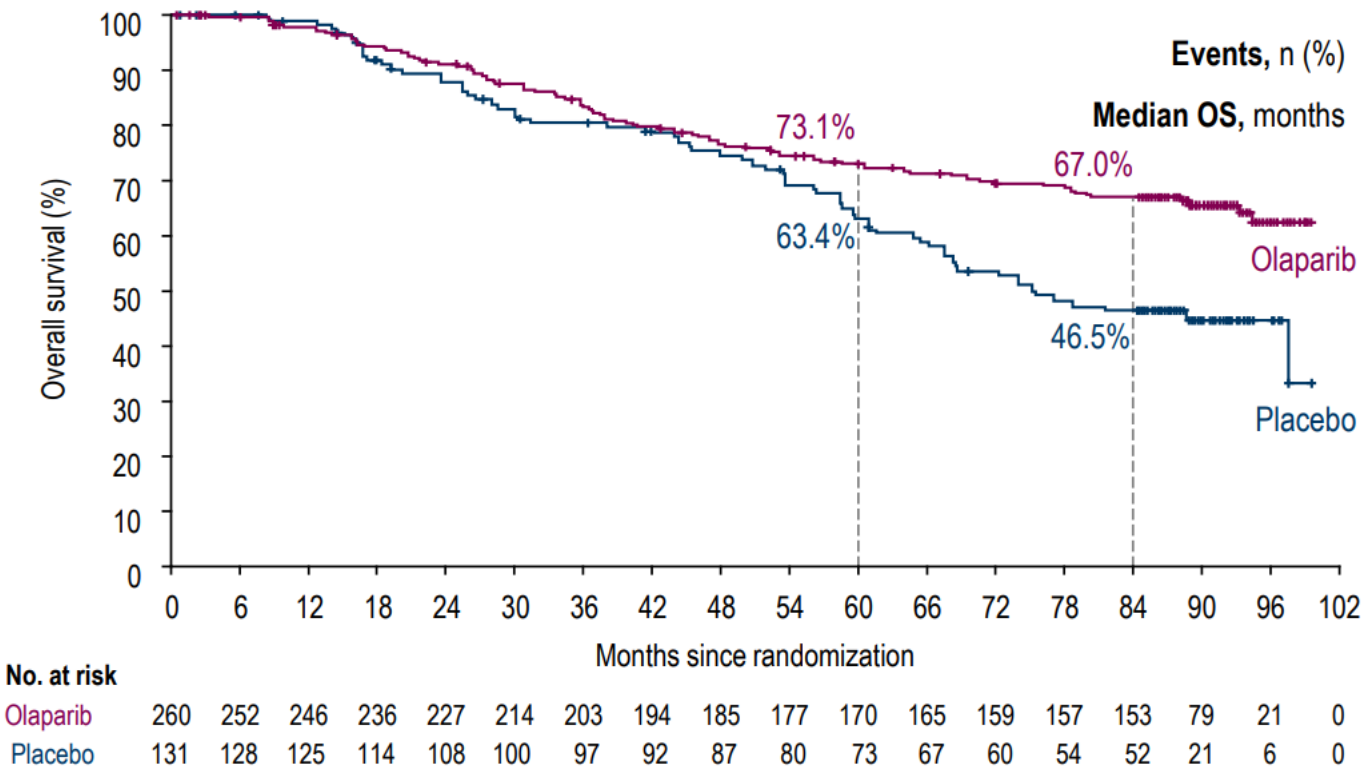
Updated PFS Analysis (data cutoff: 5 March 2020)	**Olaparib (n-=260)**	**Placebo (n=131)**
Events, n (%)	118 (45.4)	100 (76.3)
Median PFS, months	**56.0**	**13.8**
5-year PFS rate, %	48.3	20.5
HR (95% CI), *P*-value	**0.33** (0.25 – 0.43), *P < 0.001*	

ESMO 2022. Abstr 5170.

KEY DATA

SOLO1: 7-year follow-up

Overall Survival



OS	Olaparib (n-=260)	Placebo (n=131)
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	**NR**	**75.2**
HR (95% CI) *P*-value	**0.55** (0.40 – 0.76) *P* = 0.0004*	

* P<0.0001 required to declare statistical significance

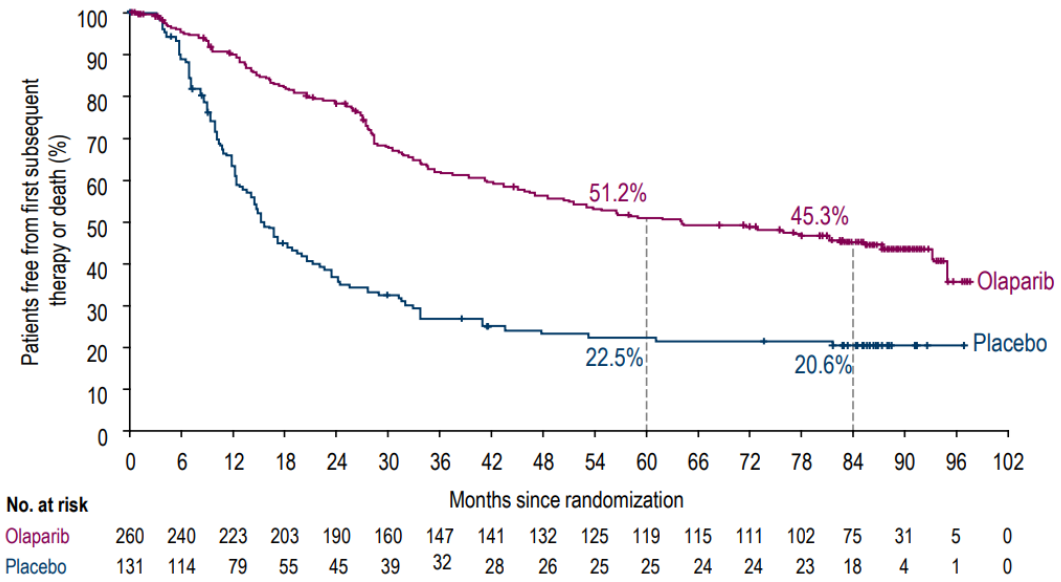
- 44.3% of patients in the placebo group received subsequent PARP inhibitor therapy, compared with 14.6% of patients in the olaparib group

ESMO 2022. Abstr 5170.

KEY DATA

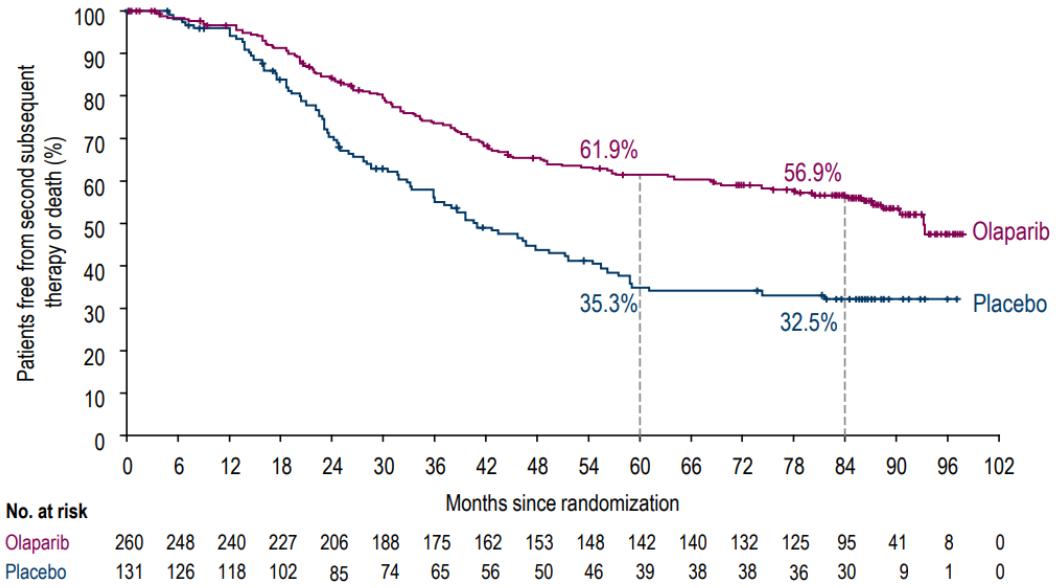
SOLO1: 7-year follow-up

TFST (time to first subsequent therapy or death)



TFST	Olaparib (n-=260)	Placebo (n=131)
Events, n (%)	135 (51.9)	98 (74.8)
Median PFS, months	**64.0**	**15.1**
HR (95% CI)	**0.37** (0.28 – 0.48)	

TSST (time to second subsequent therapy or death)



TSST	Olaparib (n-=260)	Placebo (n=131)
Events, n (%)	110 (42.3)	80 (61.1)
Median PFS, months	**93.2**	**40.7**
HR (95% CI)	**0.50** (0.37 – 0.67)	

ESMO 2022. Abstr 5170.

SUMMARY

SOLO1: 7-year follow-up

- Clinically meaningful signal, although not significant improvement in OS with maintenance olaparib in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation
  - Median OS not yet reached
  - HR 0.55 (95% CI, 0.40 to 0.76; *P* = .0004 [*P* < .0001 required to declare statistical significance])

- At 7 yrs after diagnosis, 67.0% of olaparib pts versus 46.5% of placebo pts were alive, and 45.3% versus 20.6%, respectively, were alive and had not received a first subsequent treatment

- No new safety signals observed during long-term follow-up

ESMO 2022. Abstr 5170.

SOLO1: 7-year follow-up

For newly diagnosed advanced ovarian cancer and a BRCA mutation, olaparib continues to provide long term benefit far beyond the 2-year treatment cap and should be considered for eligible patients

BRCA testing is important to identify patients

2022 ESMO Key Studies

Breast and Gynecological Cancer

- TROPiCS-02
- MONARCH 3
- SOLO1
- PAOLA-1

Lung Cancer

- CodeBreaK 200*
- IPSOS*
- DESTINY-Lung02
- CheckMate-816
- NADIM II‡
- IMpower010‡

GU/GI and Other Cancer

- NICHE-2*
- RADICALS-HD*
- COSMIC-313*
- EV-103 K
- EXPLORER/PATHFINDER

*ESMO Presidential Symposium
‡WCLC 2022

CLINICAL QUESTION

PAOLA-1

Does maintenance olaparib plus bevacizumab benefit previously treated patients with newly diagnosed advanced ovarian cancer?

Final Overall Survival Analysis

***Olaparib is FDA approved**:*

- *for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza*
- ***in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either: a deleterious or suspected deleterious BRCA mutation, and/or genomic instability. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza***
- *and for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.*

cornerstone specialty network™

KEY DATA

PAOLA-1

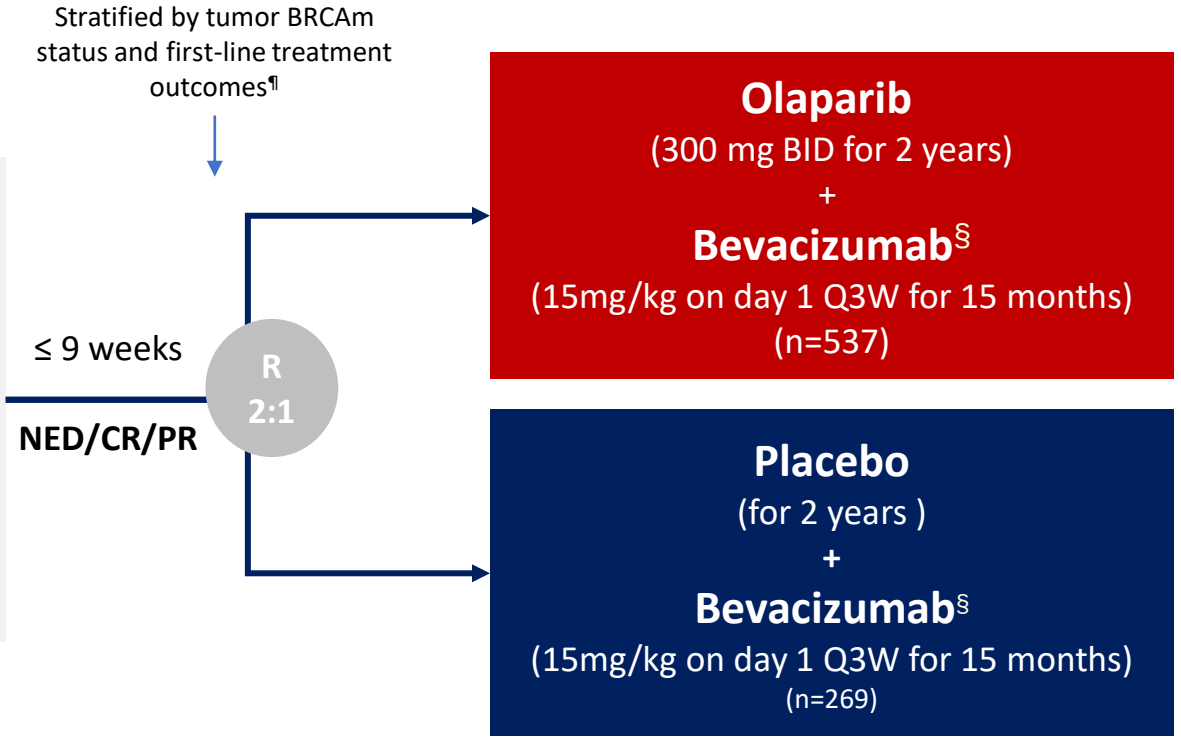
Study Design: Randomized, placebo-controlled, phase III study

- Patients with newly diagnosed, FIGO stage III/IV, high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer*

First line-treatment:

- Upfront or interval surgery
- Platinum-taxane based chemotherapy, and ≥2 cycles of bevacizumab†‡

(N = 806)



Primary endpoint: PFS (investigator assessed, RECIST v1.1)

Key secondary endpoints: PFS2, OS (planned for 3 years after the primart PFS analysis or 60% data maturity

Final OS Date Cutoff: 22 March 2022

*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a gBRCAm; †Patients must have received ≥4 and ≤9 cycles of platinum-based chemotherapy; ‡Patients must have received ≥3 cycles of bevacizumab with the last 3 cycles of chemotherapy, apart from patients undergoing interval surgery who were permitted to receive only 2 cycles of bevacizumab with the last 3 cycles of chemotherapy; §Bevacizumab 15 mg/kg every 3 weeks for a total of 15 months, including when administered with chemotherapy; ¶According to timing of surgery and NED/CR/PR.

PAOLA-1

Baseline Characteristics

Characteristic	Olaparib + Bev (n = 537)	Placebo + Bev (n = 269)
Median age, yr (range)	61 (32-87)	60 (26-85)
FIGO stage, n (%)		
• III	378 (70)	186 (69)
• IV	159 (30)	83 (31)
HRD status,* n (%)		
• HRD positive	255 (47)	132 (49)
• tBRCAm	157 (29)	80 (30)
• HRD positive excluding tBRCAm	97 (18)	55 (20)
• HRD negative/HRD unknown	282 (53)	137 (51)
• HRD negative	192 (36)	85 (32)

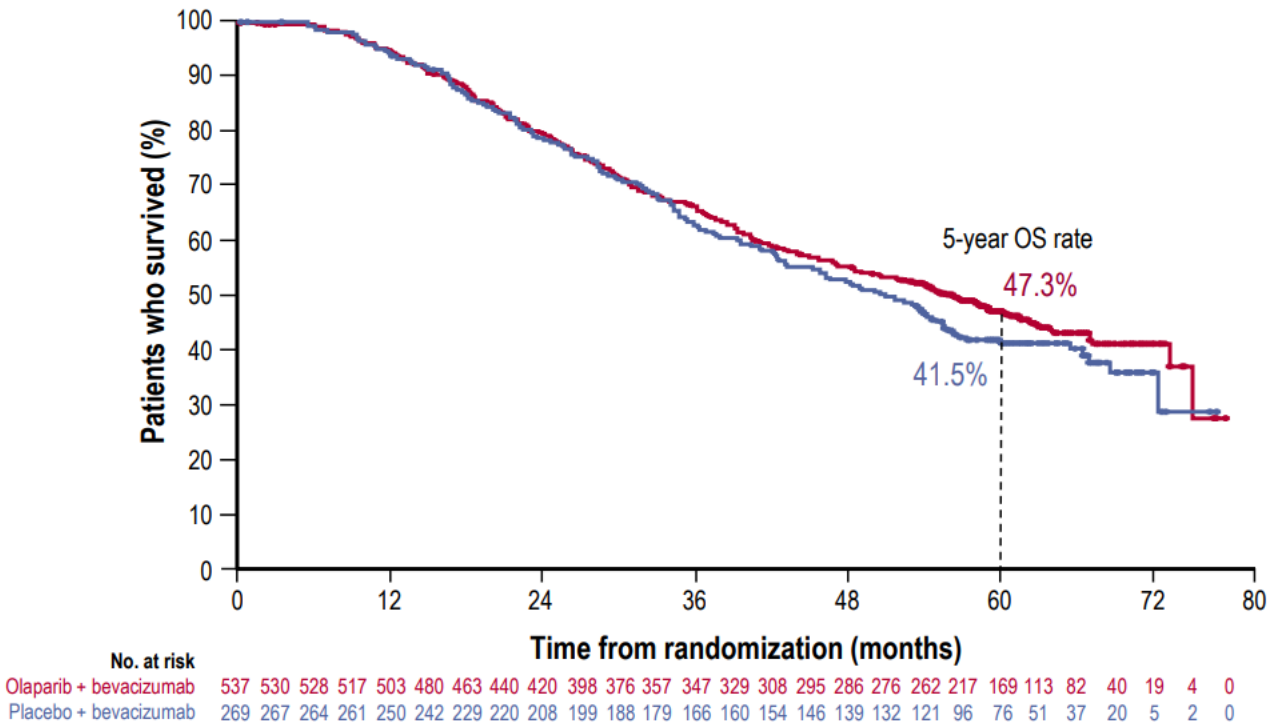
*BRCAm status by central labs and HRD status by Myriad myChoice HRD Plus; patients in tBRCAm and HRD positive excluding tBRCAm subgroups do not equal the total number of patients in the HRD-positive subgroup because of different testing methods.
tBRCAm, tumour BRCAm.

Characteristic, n (%)	Olaparib + Bev (n = 535)	Placebo + Bev (n = 269)
History of cytoreductive surgery		
Upfront surgery	271 (50)	138 (51)
• No residual macroscopic disease	160 (59)	85 (62)
• Residual macroscopic disease	111 (41)	53 (38)
Interval cytoreductive surgery	228 (42)	110 (41)
• No residual macroscopic disease	163 (71)	75 (68)
• Residual macroscopic disease	65 (29)	35 (32)
No surgery	38 (7)	21 (8)
Response after surgery/PBC		
• NED	290 (54)	141 (52)
• CR	106 (20)	53 (20)
• PR	141 (26)	75 (28)

KEY DATA

PAOLA-1: Bev +/- Olaparib

Overall Survival: ITT population



OS (ITT population)	Olaparib + bevacizumab (n-=537)	Placebo + bevacizumab (n=269)
Events, n (%)	288 (53.6)	158 (58.7)
Median OS, months	56.5	51.6
5-year OS rate, %	47.3	41.5
HR (95% CI)	0.92 (0.76 – 0.76)	
P-value	*P* = 0.4118	

Patients receiving a PARP inhibitor during any subsequent treatment:

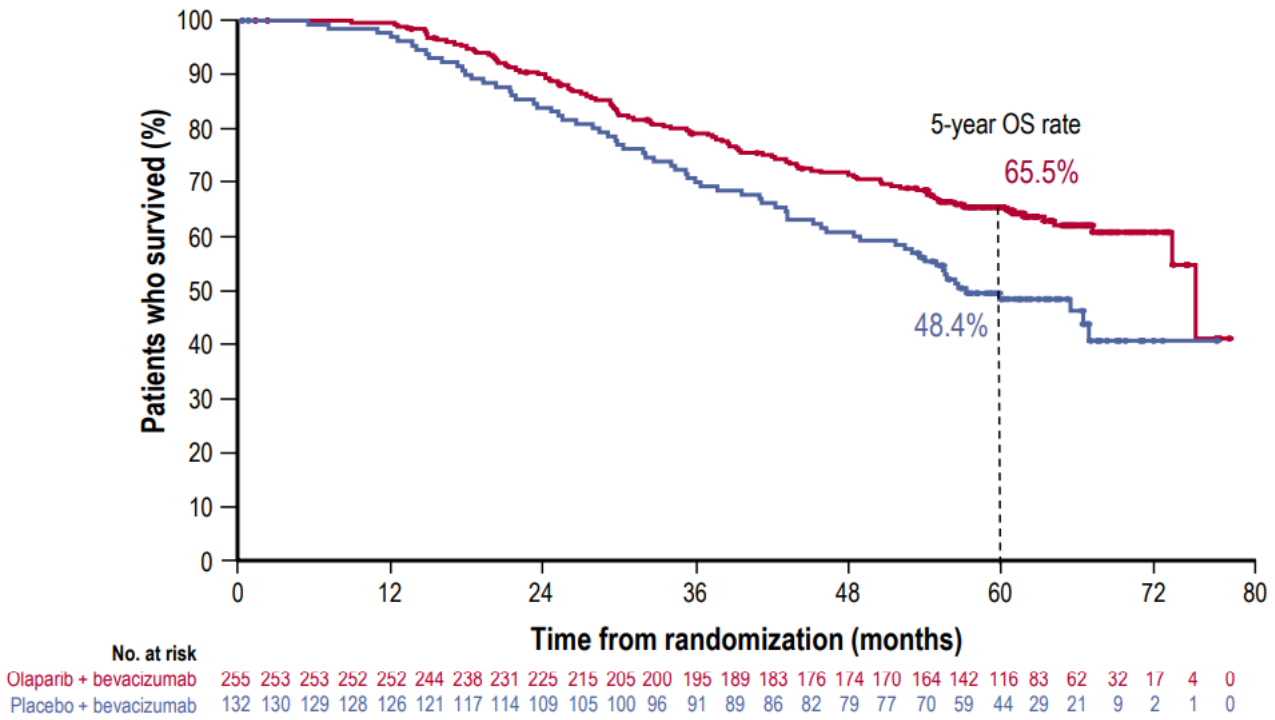
- Olaparib + bevacizumab: 19.6% (105/537)
- Placebo + bevacizumab: 45.7% (123/269)

ESMO 2022. Abstr LBA29.

KEY DATA

PAOLA-1: Bev +/- Olaparib

Overall Survival: HRD-positive subgroup



OS (HRD-positive)	Olaparib + bevacizumab (n=255)	Placebo + bevacizumab (n=132)
Events, n (%)	93 (36.5)	69 (52.3)
Median OS, months	**75.2**	**57.3**
5-year OS rate, %	**65.5**	**48.4**
HR (95% CI)	**0.62** (0.45 – 0.85)	

Patients receiving a PARP inhibitor during any subsequent treatment:

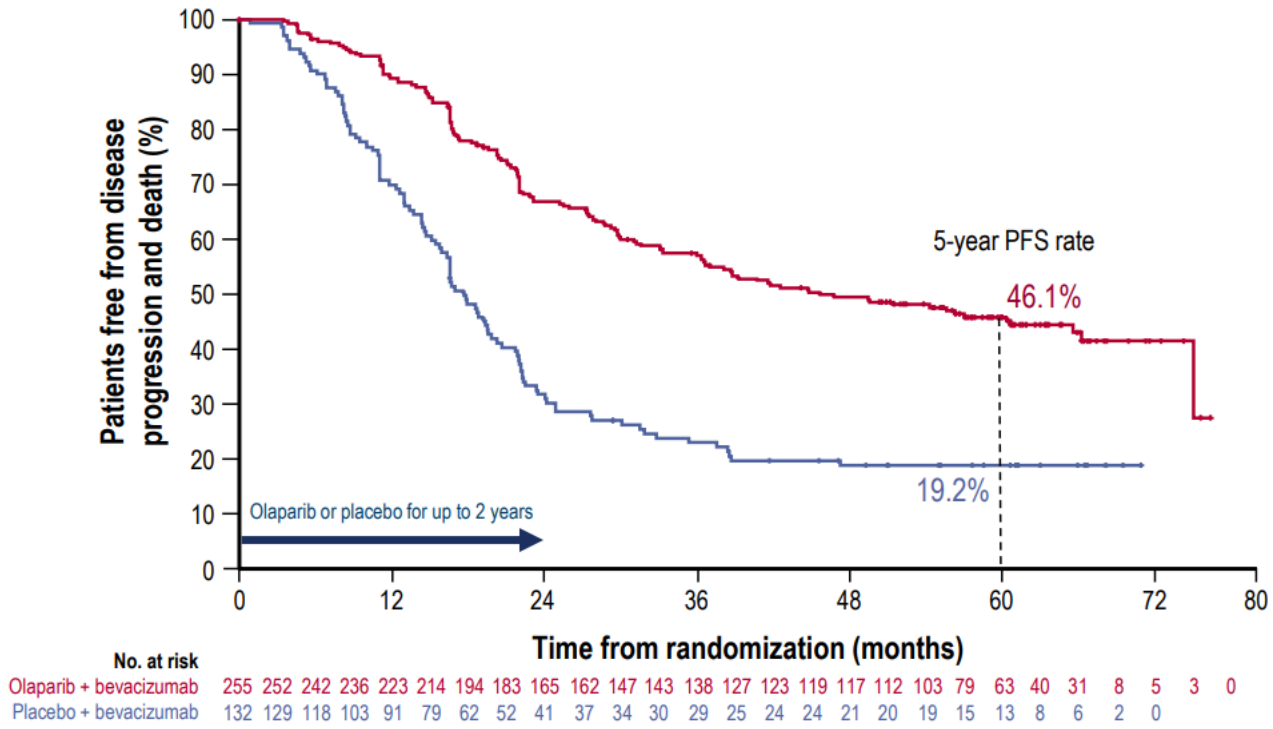
- Olaparib + bevacizumab: 17.3% (44/255)
- Placebo + bevacizumab: 50.8% (67/132)

ESMO 2022. Abstr LBA29.

KEY DATA

PAOLA-1: Bev +/- Olaparib

Updated PFS: HRD-positive subgroup



Updated PFS (HRD-positive)	Olaparib + bevacizumab (n=255)	Placebo + bevacizumab (n=132)
Events, n (%)	136 (53.3)	104 (78.8)
Median OS, months	**46.8**	**17.6**
5-year OS rate, %	**46.1**	**19.2**
HR (95% CI)	**0.41** (0.32 – 0.54)	

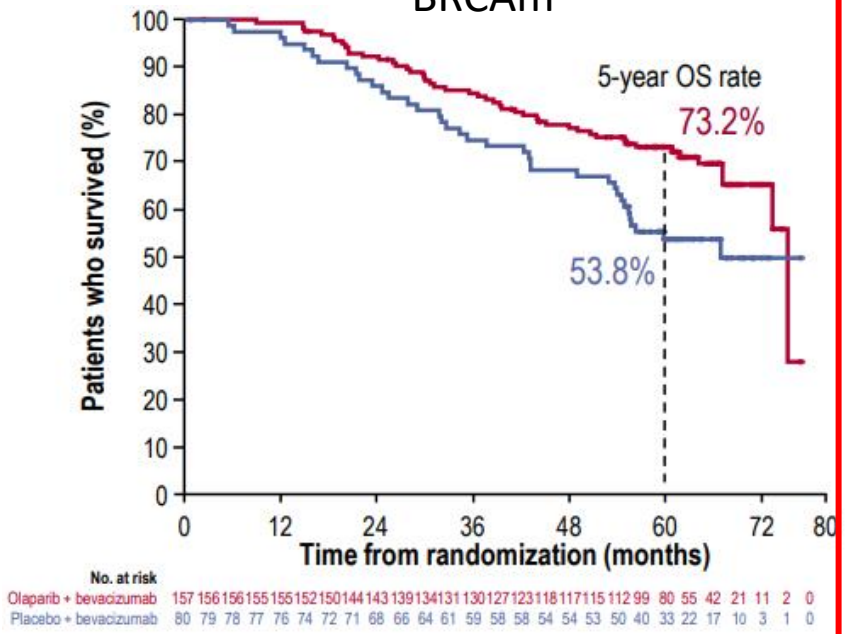
ESMO 2022. Abstr LBA29.

KEY DATA

PAOLA-1: Bev +/- Olaparib

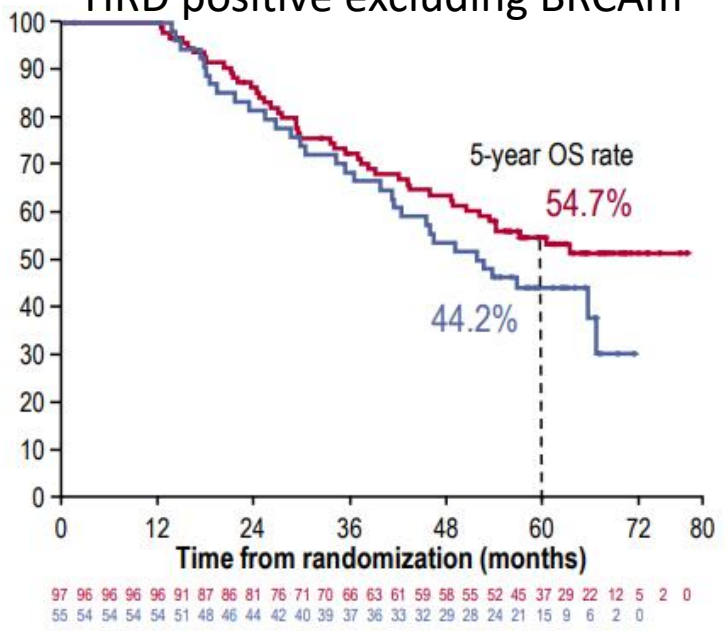
OS subgroup analysis: by BRCAm and HRD status

BRCAm



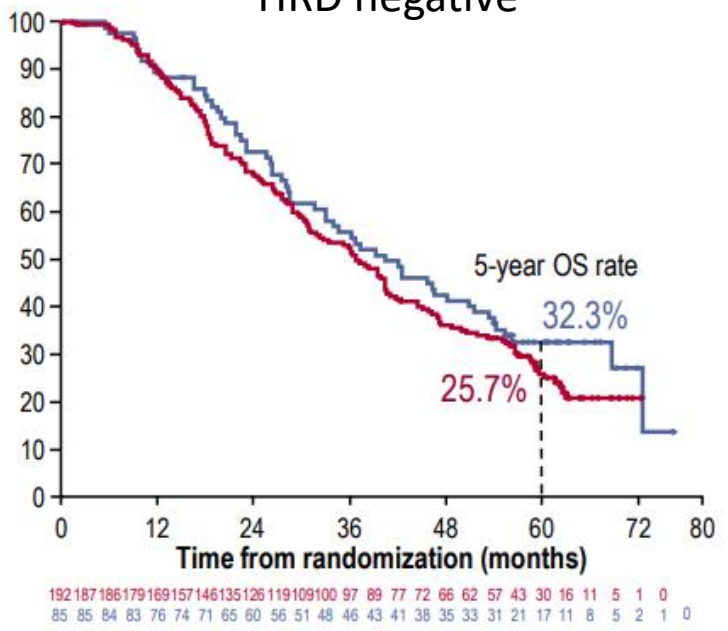
BRCAm	Olaparib + bevacizumab (n=157)	Placebo + bevacizumab (n=80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, months	**75.2**	**66.9**
5-year OS rate, %	**73.2**	**53.8**
Subsequent PARPi	**38 (24.2)**	**44 (55.0)**
HR (95% CI)	**0.60** (0.39-0.93)	

HRD positive excluding BRCAm



HRD positive (excluding BRCAm)	Olaparib + bevacizumab (n=255)	Placebo + bevacizumab (n=132)
Events, n (%)	44 (45.4)	32 (58.2)
Median OS, months	**NR**	**52.0**
5-year OS rate, %	**54.7**	**44.2**
Subsequent PARPi	**9 (9.3)**	**23 (41.8)**
HR (95% CI)	**0.71** (0.45-1.13)	

HRD negative



HRD negative	Olaparib + bevacizumab (n=255)	Placebo + bevacizumab (n=132)
Events, n (%)	140 (72.9)	58 (68.2)
Median OS, months	**36.8**	**40.4**
5-year OS rate, %	**25.7**	**32.2**
Subsequent PARPi	**46 (24.0)**	**34 (40.0)**
HR (95% CI)	**1.19** (0.88-1.63)	

ESMO 2022. Abstr LBA29.

PAOLA-1: Bev +/- Olaparib

AEs of Special Interest in Final OS Analysis

AEs, n (%)	Primary PFS Analysis 22 March 2019		Final PFS2 Analysis 22 March 2020		Final OS Analysis 22 March 2022	
	Olaparib + Bev (n = 535)	Placebo + Bev (n = 267)	Olaparib + Bev (n = 535)	Placebo + Bev (n = 267)	Olaparib + Bev (n = 535)	Placebo + Bev (n = 267)
MDS/AML/AA	6 (1.1)	1 (0.4)	7 (1.3)	4 (1.5)	9 (1.7)	6 (2.2)
New primary malignancies*	7 (1.3)	3 (1.1)	13 (2.4)	5 (1.9)	22 (4.1)	8 (3.0)
Pneumonitis/ILD/bronchiolitis†	6 (1.1)	0 (0.0)	6 (1.1)	0 (0.0)	7 (1.3)	2 (0.7)

All patients had discontinued treatment at PFS2 DCO

*New primary malignancies were: 1 plasma cell myeloma, 2 basal cell carcinoma, 11 breast cancer, 1 bronchial carcinoma, 1 colon cancer, 1 glioblastoma, 1 malignant neoplasm, 1 pancreatic carcinoma, 2 squamous cell carcinoma, and 1 ureteric cancer in the olaparib arm; and 1 papillary thyroid cancer, 4 breast cancer, 1 diffuse large B-cell lymphoma, 1 malignant lung neoplasm, and 1 malignant neoplasm in the placebo arm

†Pneumonitis/ILD/bronchiolitis events were: 1 bronchiolitis, 1 pneumonia, 1 acute respiratory distress syndrome, 2 interstitial lung disease, and 2 pneumonitis in the olaparib arm; and 1 corona virus infection and 1 pneumonitis case in the placebo arm.

SUMMARY

PAOLA-1: Bev +/- Olaparib

- At 5-yr follow-up, for patients with newly diagnosed advanced ovarian cancer who had received first-line standard-of-care treatment including bevacizumab, the addition of maintenance olaparib to bevacizumab provided a clinically meaningful OS benefit in the HRD positive population regardless of BRCAm status
  - *HRD-positive*: 65.5% vs 48.4%; HR 0.62, 95% CI 0.45 – 0.85
  - *HRD-positive excluding BRCAm*: 54.7% vs 44.2%; HR 0.71, 95% CI 0.45 – 1.13
- No OS difference in the ITT population or HRD-negative group
- No new safety signals with follow-up

ESMO 2022. Abstr LBA29.

PAOLA-1

The addition of olaparib to bevacizumab should be considered as a standard of care for HRD-positive patients with newly diagnosed advanced ovarian cancer who had received first-line standard-of-care treatment including bevacizumab

Highlights the importance of precision medicine and biomarker testing to guide treatment decisions, and HRD testing is evolving

2022 ESMO Key Studies

Breast and Gynecological Cancer	Lung Cancer	GU/GI and Other Cancer
• TROPiCS-02 • MONARCH 3 • SOLO1 • PAOLA-1	• CodeBreaK 200* • IPSOS* • DESTINY-Lung02 • CheckMate-816 • NADIM II‡ • IMpower010‡	• NICHE-2* • RADICALS-HD* • COSMIC-313* • EV-103 K • EXPLORER/PATHFINDER

*ESMO Presidential Symposium
‡ WCLC 2022

CodeBreaK 200

Does sotorasib provide benefit for patients previously treated for advanced NSCLC with *KRAS* G12C mutation?

On May 28, 2021, the Food and Drug Administration granted accelerated approval to sotorasib (Lumakras™), a RAS GTPase family inhibitor based on CodeBreaK 100, for adult patients with KRAS G12C -mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.

cornerstone specialty network™

KEY DATA

CodeBreaK 200

CodeBreaK 100: phase I/II trial

- *ORR of 41%*
- *mPFS of 6.3 mo*
- *mOS of 12.5 mo*

Study Design: Randomized, double-blind phase III study

Stratified by prior lines of therapy, Asian vs non-Asian race, and history of CNS involvement

- Patients with locally advanced/unresectable or metastatic *KRAS* G12C-mutated NSCLC
- ≥1 prior treatment including platinum-based chemotherapy and checkpoint inhibitor*
- no active brain metastases
- ECOG PS 0/1

(N = 345)

R
1:1

Sotorasib 960 mg oral QD
(n = 171)

Docetaxel 75 mg/m² IV Q3W
(n = 174)

Primary endpoint: PFS by BICR

Secondary endpoints: OS†, ORR, DOR, TTR, DCR, safety/tolerability, PRO

Protocol amendment: February 15, 2021
Per regulatory guidance, protocol was amended to reduce planned enrolment from 650 to ~330 patients, and crossover from docetaxel to sotorasib was permitted.

Enrollment period: June 4, 2020 to April 26, 2021
Data cutoff: August 2, 2022

*Treatment with chemotherapy and checkpoint inhibitor could be concurrent or sequential; patients with medical contraindication to these therapies could be included with approval.
†Analysis of OS planned if PFS was found to be statistically significant and when at least 198 OS events have been reached.

CodeBreaK 200

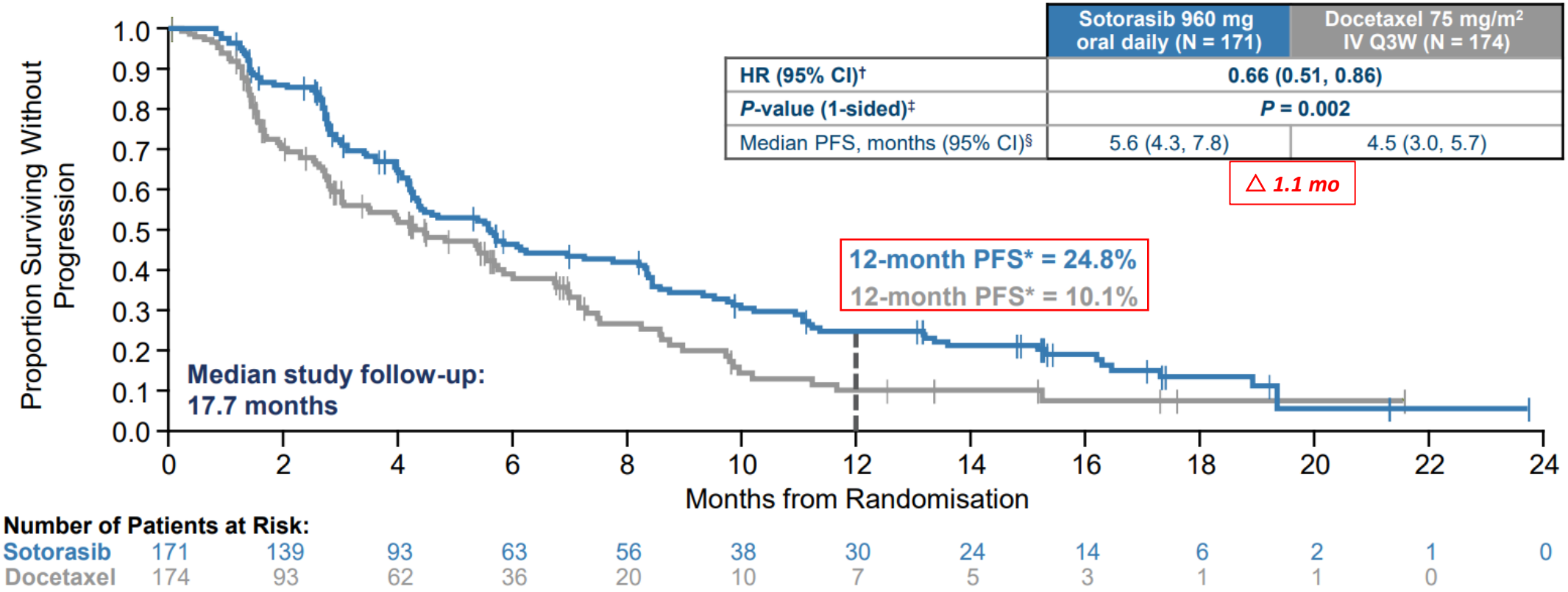
Baseline Characteristics

Characteristic	Sotorasib (n = 171)	Docetaxel (n = 174)
Median age, yr (range)	64.0 (32-88)	64.0 (35-87)
Female, n (%)	62 (36.3)	79 (45.4)
North America/Europe/Other,* %	11.7/73.7/14.6	12.6/72.4/14.9
Current or former smoker, n (%)	166 (97.1)	166 (95.4)
ECOG PS 1, n (%)	112 (65.5)	115 (66.1)
History of CNS involvement, n (%)	58 (33.9)	60 (34.5)
Liver metastasis, n (%)	30 (17.5)	35 (20.1)
Prior lines of therapy for advanced disease, n (%)		
• 1	77 (45.0)	78 (44.8)
• 2	65 (38.0)	69 (39.7)
• >2	29 (17.0)	27 (15.5)
PD-L1 expression, n (%)		
• <1%	57 (33.3)	55 (31.6)
• ≥1 to <50%	46 (26.9)	70 (40.2)
• ≥50%	60 (35.1)	40 (23.0)

*Other includes Asia, Australia, South America.

CodeBreaK 200

Primary Endpoint: PFS by BICR



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)‡	*P* = 0.002	
Median PFS, months (95% CI)§	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

△ *1.1 mo*

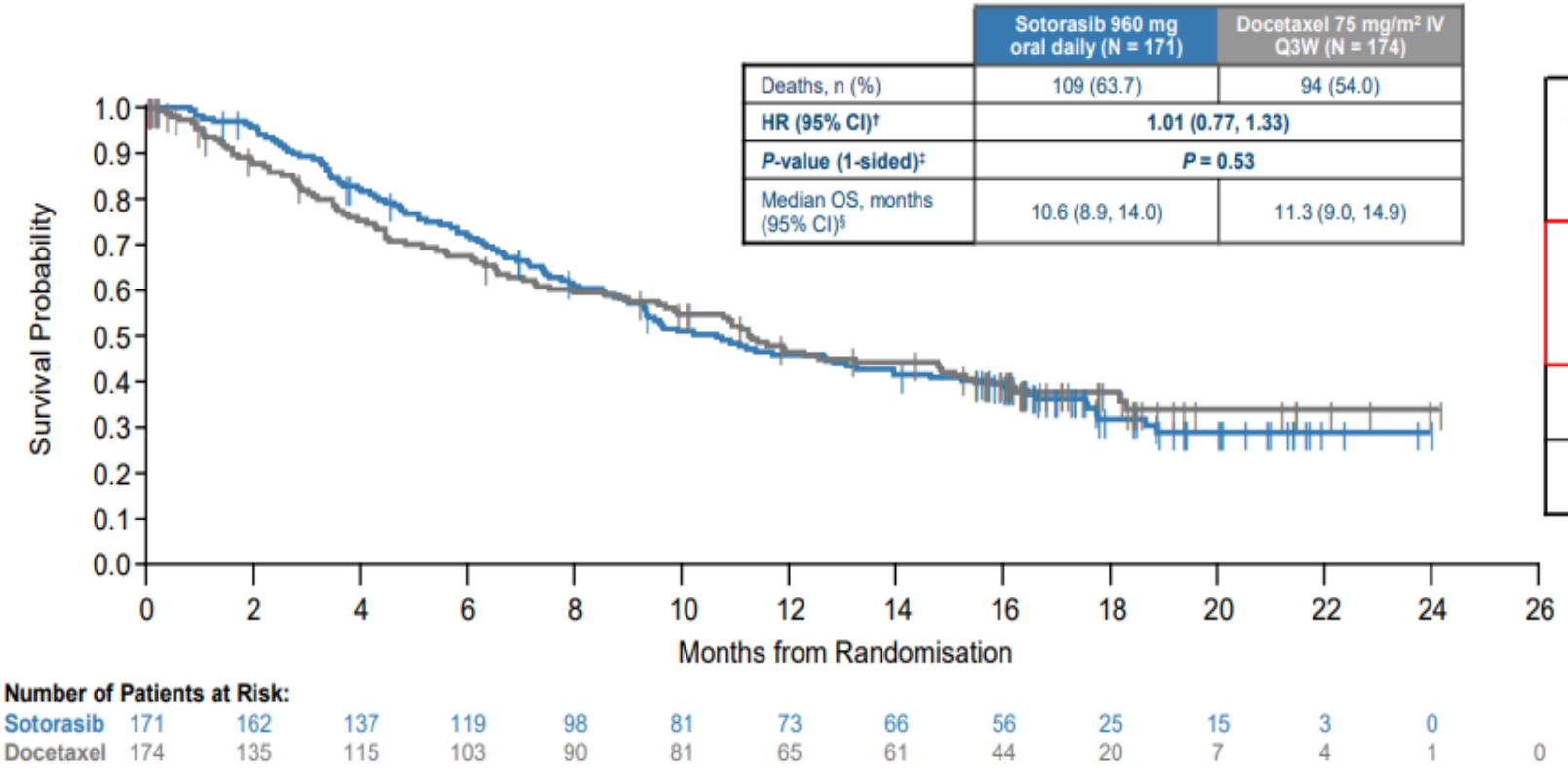
*PFS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model.
‡P-value calculated using a stratified log-rank test. §Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation

ESMO 2022. Abstr LBA10.

KEY DATA

CodeBreaK 200

Overall Survival



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	109 (63.7)	94 (54.0)
HR (95% CI)†	1.01 (0.77, 1.33)	
P-value (1-sided)‡	*P* = 0.53	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)

	Sotorasib	Docetaxel
Any subsequent treatment, including crossover**	36%	42%
Subsequent $KRAS^{G12C}$ inhibitor, including crossover	4%	34%
Subsequent chemo	21%	12%
Subsequent IO	9%	6%

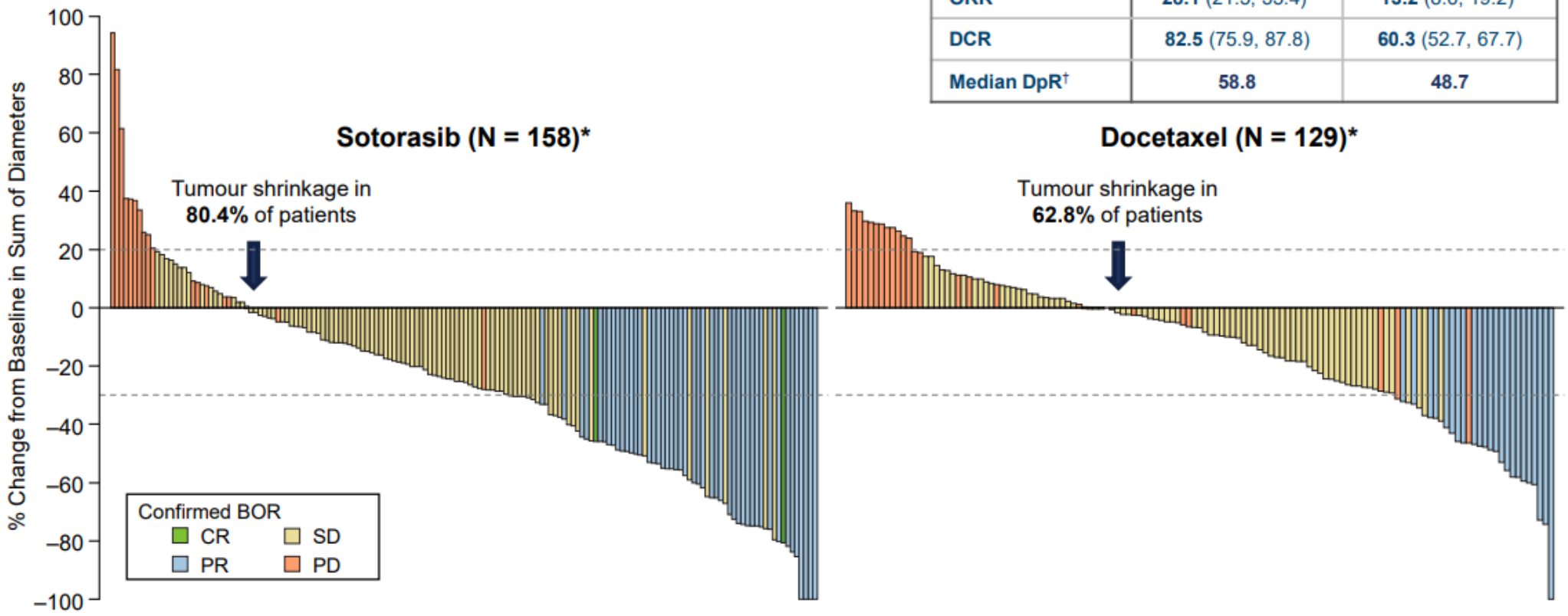
OS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model
‡ P-value calculated using a stratified log-rank test.
§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.
**Patients (16.4% in sotorasib arm, 5.2% in docetaxel arm) were treated beyond progression

ESMO 2022. Abstr LBA10.

CodeBreaK 200

Tumor Response by BICR

% (95% CI)	Sotorasib	Docetaxel
ORR	**28.1** (21.5, 35.4)	**13.2** (8.6, 19.2)
DCR	**82.5** (75.9, 87.8)	**60.3** (52.7, 67.7)
Median DpR†	**58.8**	**48.7**

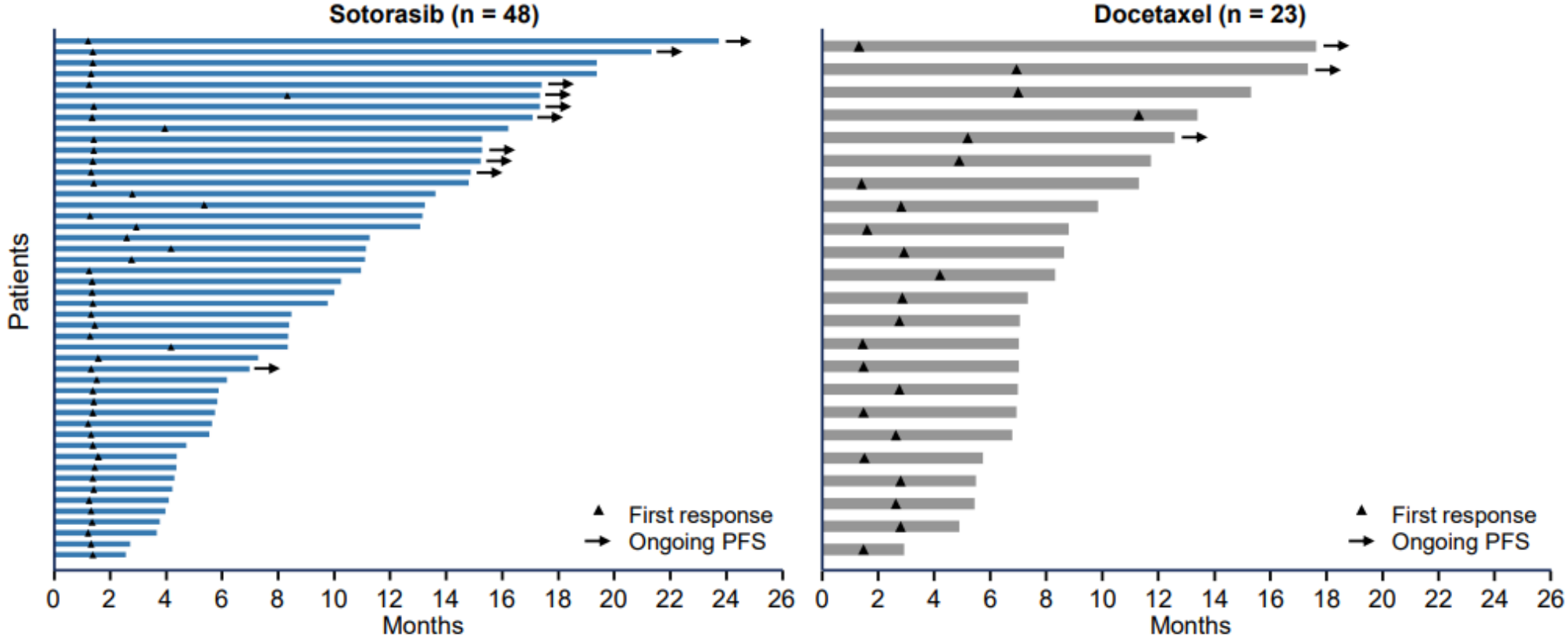


ORR: Overall response rate; DCR: Disease control rate; DpR: Depth of response

ESMO 2022. Abstr LBA10.

CodeBreaK 200

Duration of Response



	Sotorasib 960 mg oral daily (n = 48)†	Docetaxel 75 mg/m² IV Q3W (n = 23)†
Median TTR, months (range)‡	1.4 (1.2, 8.3)	2.8 (1.3, 11.3)
Median DOR, months (95% CI)‡	8.6 (7.1, 18.0)	6.8 (4.3, 8.3)

*DOR and TTR calculated only for patients who achieved a confirmed best overall response of PR or CR; ITT population. †Number of responders. ‡Medians and 95% CIs estimated using Kaplan-Meier method
DoR, duration of response; PFS, progression-free survival; TTR, time to response.

CodeBreaK 200

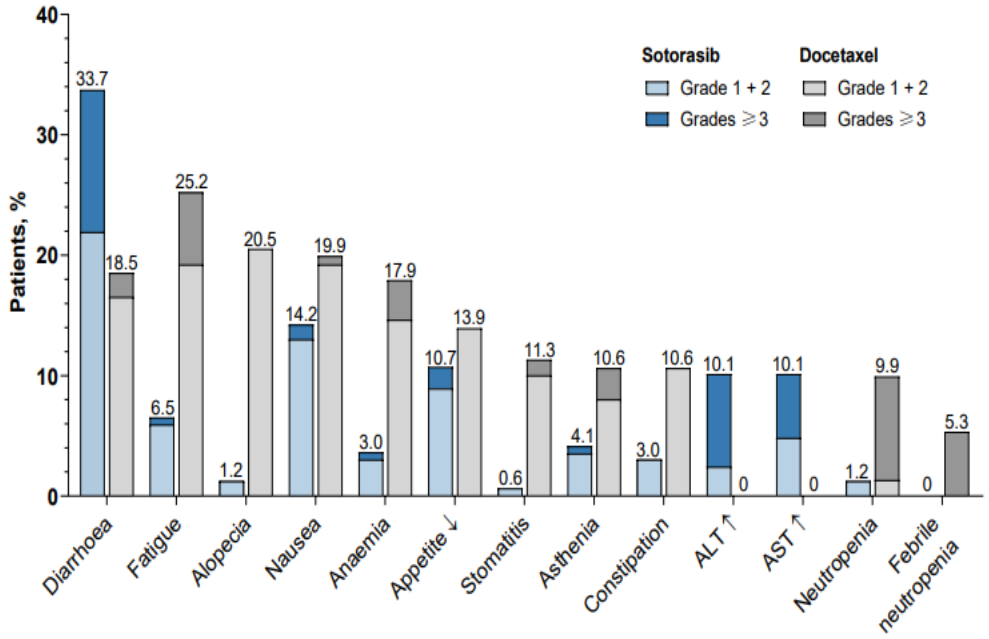
Safety Summary

Parameter	Sotorasib (n = 169)	Docetaxel (n = 151)
TEAEs, n (%)	**166 (98.2)**	**148 (98.0)**
• Grade ≥3	121 (71.6)	91 (60.3)
TRAEs, n (%)	**119 (70.4)**	**130 (86.1)**
• Grade ≥3	56 (33.1)	61 (40.4)
• Serious	18 (10.7)	34 (22.5)
• Leading to dose interruption*	60 (35.5)	23 (15.2)
• Lading to dose reduction†	26 (15.4)	40 (26.5)
• Leading to dose discontinuation‡	16 (9.5)	17 (11.3)
Fatal TRAEs, n (%)§	**1 (0.6)**	**2 (1.3)**
Median duration of treatment, weeks (range)	**20 (0.4-101)**	**12 (3-101)**

*For sotorasib, diarrhoea (n=22), increased ALT (n=9), and AST (n=7), and for docetaxel, fatigue and pneumonia (both n=3), hypersensitivity and myalgia (both n=2) were the most common.
†For sotorasib, diarrhoea (n=14), increased ALT (n=6), and AST (n=3), and for docetaxel, neutropenia (n=7), fatigue (n=6), febrile neutropenia, peripheral neuropathy, and asthenia (n=4 each) were the most common.
‡For sotorasib, increased ALT (n=6), blood bilirubin (n=4), AST and blood alkaline phosphatase (both n=2), and drug-induced liver injury (n=2), and for docetaxel, fatigue (n=3) and febrile neutropenia (n=2) were most common.
§Fatal TRAEs were observed in 1 patient in the sotorasib group (interstitial lung disease) and 2 patients in the docetaxel group (ileus and multiorgan failure)

Most Common TRAEs

Any Grade TRAEs (≥ 10%) or Grade ≥ 3 (≥ 5%)



SUMMARY

CodeBreaK 200

- Modest but significant PFS improvement with sotorasib vs docetaxel in previously treated patients with *KRAS* G12C-mutated advanced NSCLC
  - Median PFS: 5.6 vs 4.5 mo (HR: 0.66; *P = 0*.002)
  - 12-mo PFS: 24.8% vs 10.1%
  - Benefit similar across most subgroups
- ORR, DCR, TTR, and DoR improved for sotorasib vs docetaxel but no difference in OS (not powered)
- Acceptable safety profile; fewer grade ≥3 TRAEs with sotorasib vs docetaxel
- Patient-reported outcomes more favorable for sotorasib vs docetaxel

ESMO 2022. Abstr LBA10

CodeBreaK 200

Sotorasib continues to show benefit in pre-treated patients with KRAS G12C mutated NSCLC and provides an important targeted treatment option

Highlights importance of biomarker testing for all patients with advanced disease

2022 ESMO Key Studies

Breast and Gynecological Cancer	Lung Cancer	GU/GI and Other Cancer
• TROPiCS-02 • MONARCH 3 • SOLO1 • PAOLA-1	• CodeBreaK 200* • IPSOS* • DESTINY-Lung02 • CheckMate 816 • NADIM II‡ • IMPower010‡	• NICHE-2* • RADICALS-HD* • COSMIC-313* • EV-103 K • EXPLORER/PATHFINDER

* ESMO Presidential Symposium
‡ WCLC 2022

IPSOS

Does atezolizumab in the 1L setting improve outcomes for patients with NSCLC with poor performance status and are ineligible for a platinum-containing regimen?

IPSOS

Study Design: global, multicenter, open-label, randomized, controlled phase III study

Stratified by histology (squamous or non-squamous); PD-L1 expression level by SP142 IHC assay (TC3 or IC3 vs TC0/1/2 or IC0/1/2b vs unknown); Brain metastases (yes/no)

- Patients with treatment-naïve stage IIIB/IV NSCLC
- Squamous or non-squamous
- *ECOG PS 2 or 3*
- *ECOG PS 0 or 1 if ≥70 yrs of age with substantial comorbidities or other contraindications for platinum chemotherapy*
- Treated asymptomatic brain metastases allowed
- *EGFR*+ or *ALK*+ excluded

(N = 453)

R
2:1

Atezolizumab
1200 mg IV q3w

Vinorelbine or Gemcitabine
(investigators choice)

PD
or
loss of
clinical
benefit

Primary endpoint: OS
Secondary endpoints: OS rates at 6, 12, 18 and 24 months, PFS, ORR, DOR, OS and PFS in PD-L1 positive subgroups
Other endpoints: PROs, safety, exploratory biomarker analyses

Baseline Characteristics

Characteristic	Atezolizumab (n=301)	Chemotherapy (n=151)
Median age, yr (range)	75.0 (33, 94)	75.0 (37, 89)
<70 yrs, n (%)	80 (26.5)	43 (28.5)
70-79 yrs, n (%)	125 (41.4)	65 (43.0)
≤80 yrs, n (%)	97 (32.1)	43 (28.5)
ECOG PS, n (%)		
0/1	56 (18.5)	19 (12.6)
2	228 (75.5)	116 (76.8)
3	18 (6.0)	16 (10.6)
Sex, male, n (%)	220 (72.8)	108 (71.5)
Race, n (%)*		
White	203 (67.2)	95 (62.9)
Asian	75 (24.8)	38 (25.2)
Histology, n (%)**		
Non-squamous	173 (57.3)	87 (57.6)
Squamous	129 (42.7)	64 (42.4)

Characteristic	Atezolizumab (n=301)	Chemotherapy (n=151)
Brain metastases, n (%)		
Yes	27 (8.9)	13 (8.6)
No	273 (90.4)	137 (90.7)
Missing	2 (0.7)	1 (0.7)
Smoking status, n (%)		
Previous	209 (69.2)	103 (68.2)
Current	58 (19.2)	28 (18.5)
Never	35 (11.6)	20 (13.2)
PD-L1 expression level, n (%)***		
TC <1%	151 (50.0)	61 (40.4)
TC ≥1%	127 (42.1)	78 (51.7)
TC 1-49%	77 (25.5)	53 (35.1)
TC ≥50%	50 (16.6)	25 (16.6)
Unknown	24 (7.9)	12 (7.9)

Clinical cutoff: 30 Apr 2022.

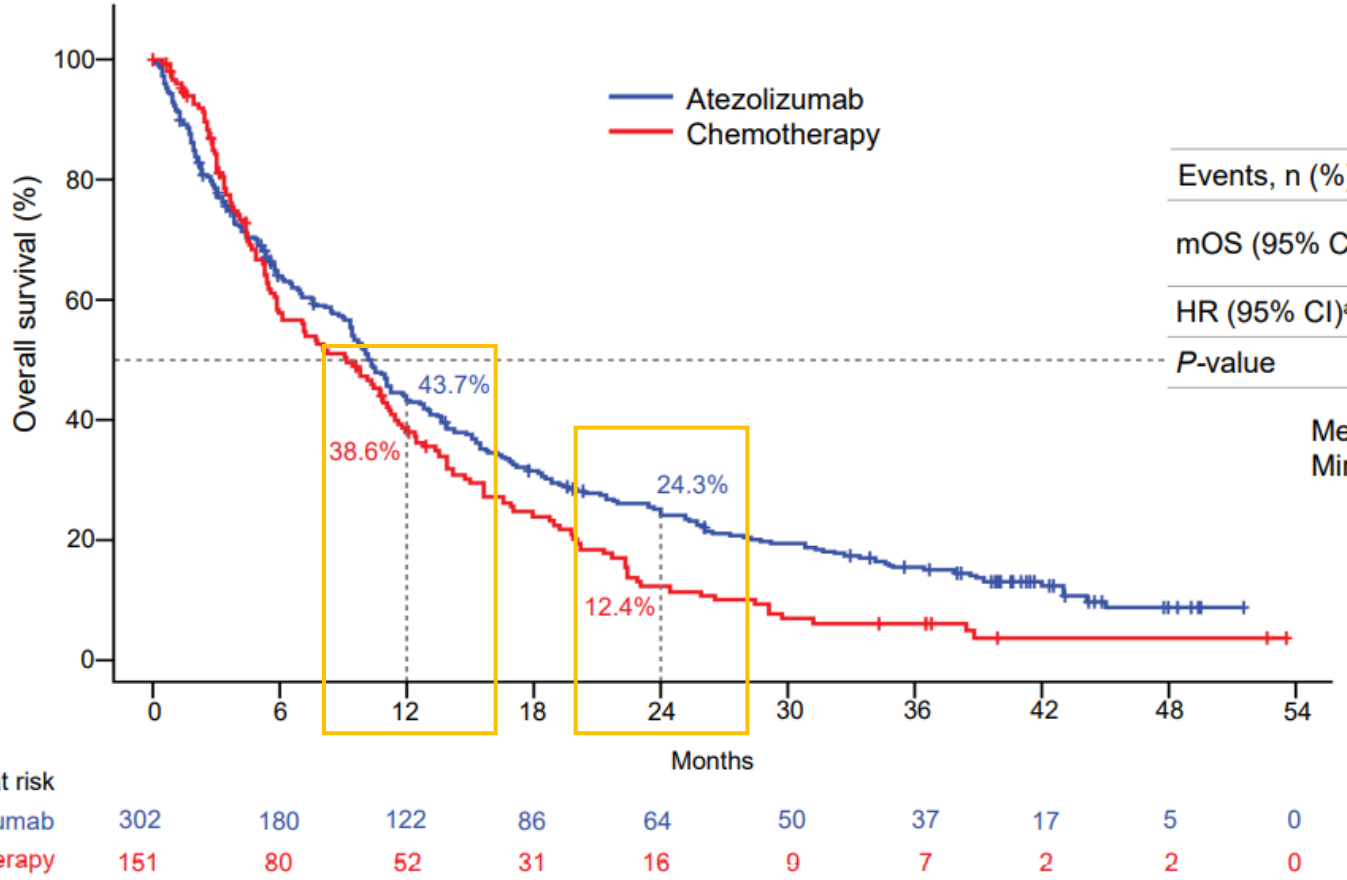
*In the atezolizumab arm, 12 patients were American Indian or Alaska Native, 2 Black or African American, 6 multiple races, and 4 unknown. In the chemotherapy arm, 9 patients were American Indian or Alaska Native, 1 Black or African American, 6 multiple races, and 2 unknown.

**Per electronic case report form.

***By SP263 IHC assay.

IPSOS

Primary Endpoint: OS



	Atezo (n=302)	Chemo (n=151)
Events, n (%)	249 (82.5)	130 (86.1)
mOS (95% CI), mo	10.3 (9.4, 11.9)	9.2 (5.9, 11.2)
HR (95% CI)[a]	**0.78 (0.63, 0.97)**	
P-value	0.028[b]	

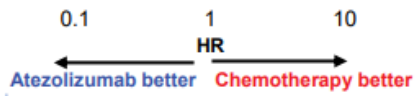
Median follow-up: 41.0 months
Minimum follow-up: 32.0 months

ESMO 2022. Abstr LBA11.

IPSOS

OS by Subgroup

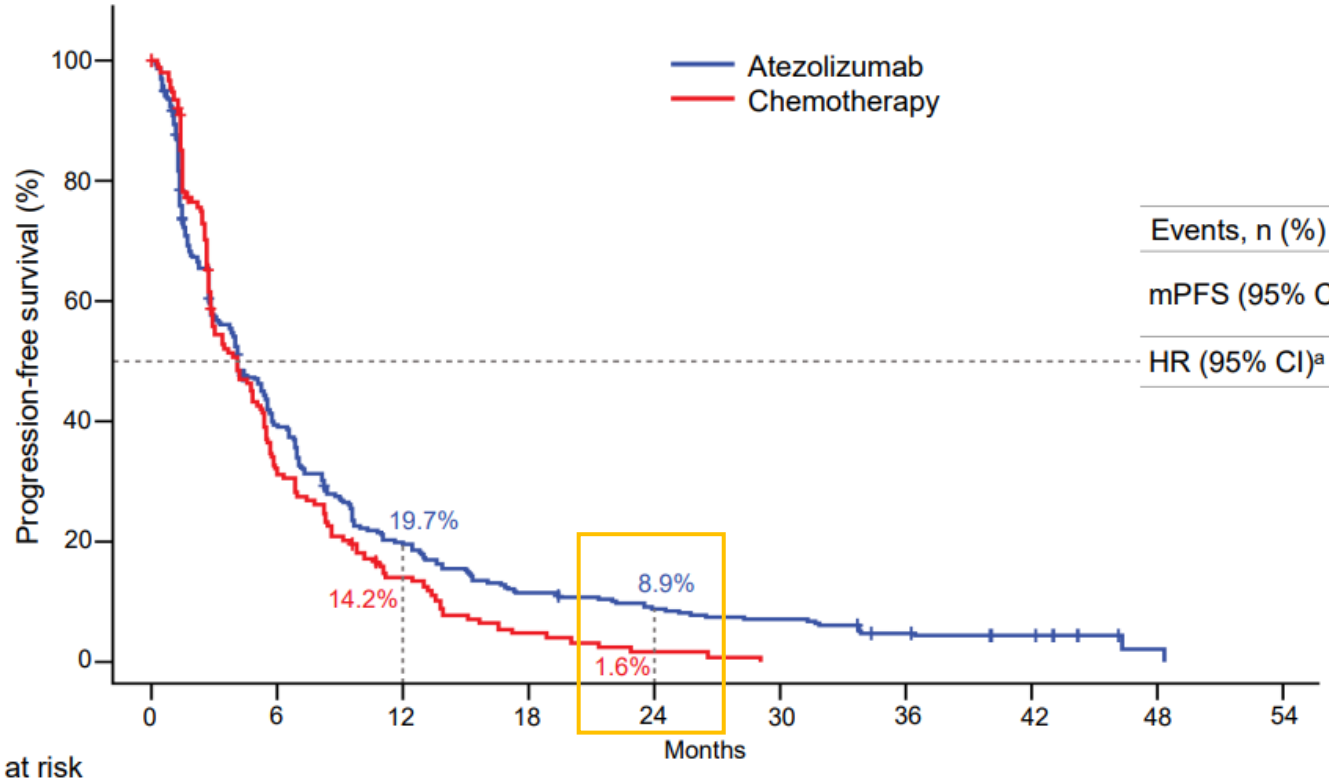
Subgroup	Atezo n	Chemo n	HR (95% CI)
All patients	302	151	0.78 (0.63, 0.97)[a]
Age			
<70 y	80	43	0.75 (0.49, 1.14)
70-79 y	125	65	0.68 (0.49, 0.94)
≥80 y	97	43	0.97 (0.66, 1.44)
Sex			
Male	220	108	0.76 (0.59, 0.98)
Female	82	43	0.86 (0.58, 1.27)
Race			
White	203	95	0.86 (0.67, 1.11)
Asian	75	38	0.74 (0.46, 1.20)
ECOG PS			
0/1	56	19	0.64 (0.36, 1.13)
2	228	116	0.86 (0.67, 1.10)
3	18	16	0.74 (0.35, 1.57)
Tobacco use history			
Previous	209	103	0.83 (0.64, 1.08)
Current	58	28	0.65 (0.40, 1.07)
Never	35	20	0.70 (0.37, 1.35)
Histology			
Non-squamous	173	87	0.77 (0.58, 1.03)
Squamous	129	64	0.80 (0.58, 1.12)
Stage			
IIIB	41	21	0.69 (0.39, 1.24)
IV	261	130	0.81 (0.64, 1.02)
Brain metastases			
Yes	27	13	0.85 (0.40, 1.80)
No	273	137	0.78 (0.62, 0.98)
Liver metastases			
Yes	44	26	0.94 (0.55, 1.59)
No	258	125	0.77 (0.61, 0.98)
Number of metastatic sites			
<3	124	73	0.74 (0.53, 1.03)
≥3	141	59	0.78 (0.56, 1.07)
PD-L1 expression level[b]			
TC <1%	151	61	0.81 (0.58, 1.11)
TC ≥1%	127	78	0.84 (0.62, 1.15)
TC 1-49%	77	53	0.84 (0.57, 1.22)
TC ≥50%	50	25	0.87 (0.50, 1.52)
Unknown	24	12	0.49 (0.21, 1.14)



[a] Stratified for all patients; unstratified for all other subgroups. [b] Per SP263 IHC assay

IPSOS

PFS



	Atezo (n=302)	Chemo (n=151)
Events, n (%)	276 (91.4)	138 (91.4)
mPFS (95% CI), mo	4.2 (3.7, 5.5)	4.0 (2.9, 5.4)
HR (95% CI)[a]	0.87 (0.70, 1.07)	

ESMO 2022. Abstr LBA11.

IPSOS

ORR and DOR

	Atezolizumab (n=302)	Chemotherapy (n=151)
ORR, n (%), (95% CI)	**51 (16.9)** (12.8, 21.6)	**12 (7.9)** (4.2, 13.5)
CR, n (%)	**4 (1.3)**	**0 (0)**
PR, n (%)	**47 (15.6)**	**12 (7.9)**
Stable disease, n (%)	122 (40.4)	73 (48.3)
Disease control rate, n (%)	173 (57.3)	85 (56.3)
Progressive disease, n (%)	67 (22.2)	36 (23.8)
Non-evaluable, n (%)	14 (4.6)	12 (7.9)
Missing, n (%)	48 (15.9)	18 (11.9)
Median DOR, months (95% CI)	**14.0** (8.1, 20.3)	**7.8** (4.8, 9.7)

ESMO 2022. Abstr LBA11.

IPSOS

Safety Summary

	Atezolizumab (n=300)	Gemcitabine (n=63)	Vinorelbine (n=84)
Median treatment duration, months (range)	3.5 (0-51)	2.3 (0-13)	1.8 (0.21)
Median number of cycles initiated (range)	6.0 (1-73)	4.0 (1-19)	3.0 (1-31)

	Atezolizumab (n=300)	Chemotherapy (n=147)
All-grade AE, n (%)	275 (91.7)	143 (97.3)
Treatment-related AE	**171 (57.0)**	**118 (80.3)**
Grade 3-4 AE, n (%)	136 (45.3)	71 (48.3)
Treatment-related Grade 3-4 AE	**49 (16.3)**	**49 (33.3)**
Serious AE, n (%)	146 (48.2)	53 (36.1)
Treatment-related SAE	**35 (11.7)**	**23 (15.6)**
Grade 5 AE, n (%)	35 (11.7)	13 (8.8)
Treatment-related Grade 5 AE	3 (1.0)	4 (2.7)
AE leading to discontinuation of study drug, n (%)	39 (13.0)	20 (13.6)
AE leading to modification/interruption of study drug, n (%)	96 (32.0)	71 (48.3)

ESMO 2022. Abstr LBA11.

SUMMARY

IPSOS

- In this poor-prognosis difficult to treat population, atezolizumab in the 1L setting improved OS compared to single agent chemotherapy
  - 2-year OS rate nearly doubled with atezolizumab (24.3% vs 12.4%)
- ORR was better with atezolizumab with durable responses (14 vs 7.8 months)
- No new safety signals with fewer treatment related Grade 3/4 AEs in the atezolizumab arm compared to the chemotherapy arm (16.3% vs 33.3%, respectively)
  - Atezolizumab stabilized health-related QOL functions and significantly improved time to deterioration of chest pain (HR: 0.51) vs chemotherapy

ESMO 2022. Abstr LBA11.

IPSOS

Atezolizumab in the IL setting improves outcomes for patients with poor prognosis NSCLC and provides an alternative treatment option for those ineligible to receive platinum-doublet chemotherapy

2022 ESMO Key Studies

Breast and Gynecological Cancer

- TROPiCS-02
- MONARCH 3
- SOLO1
- PAOLA-1

Lung Cancer

- CodeBreaK 200*
- IPSOS*
- DESTINY-Lung02
- CheckMate 816
- NADIM II‡
- IMPower010‡

GU/GI and Other Cancer

- NICHE-2*
- RADICALS-HD*
- COSMIC-313*
- EV-103 K
- EXPLORER/PATHFINDER

* ESMO Presidential Symposium

‡ WCLC 2022

cornerstone specialty network™

CLINICAL QUESTION

DESTINY-Lung02

Does trastuzumab deruxtecan provide benefit for patients with HER2 mutant metastatic non-small cell lung cancer?

Interim Analysis

On August 11, 2022, the FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu) for adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating human epidermal growth factor receptor 2 HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy. This is the first drug approved for HER2-mutant NSCLC.

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KEY DATA

DESTINY-Lung02

Study Design: randomized, multicenter, International, 2-arm, noncomparative phase II trial

- Patients with metastatic HER2m NSCLC
- Activating HER2 mutation
- ≥1 prior anti-cancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease by BICR based on RECIST v1.1
- ECOG PS of 0 or 1

(N = 152)

Stratified by previous use of anti–PD-1/PD-L1 therapy

R 2:1

Full analysis

T-DXd 5.4 mg/kg Q3W (n = 102)

T-DXd 6.4 mg/kg Q3W (n = 50)

The prespecified early cohort included patients randomized ≥ 4.5 months before the interim analysis data cutoff to have a more robust efficacy assessment

T-DXd 5.4 mg/kg Q3W (n = 52)

Interim analysis

T-DXd 6.4 mg/kg Q3W (n = 28)

The prespecified early cohort was defined in the protocol to assess those patients with ≥3 post-baseline assessments at data cutoff (assessments performed every 6 weeks)

Primary endpoint: confirmed ORR by BICR

Secondary endpoints: ORR by investigator, DoR,* DCR,* PFS,* OS,* PK, PROs, safety and tolerability

Data cutoff: Mar 24, 2022

Median follow-up: 5.54 months

Patients, investigators, and site staff are blinded to the dose level

DESTINY-Lung02

Response by BCIR

Response	T-DXd 5.4 mg/kg (n = 52)	T-DXd 6.4 mg/kg (n = 28)
Confirmed ORR,* n (%; 95% CI)	**28** (**53.8**; 39.5-67.8)	**12** (**42.9**; 24.5-62.8)
Best overall response, n (%)		
CR	1 (1.9)	1 (3.6)
PR	27 (51.9)	11 (39.3)
SD	19 (36.5)	14 (50.0)
PD	2 (3.8)	1 (3.6)
NE[†]	3 (5.8)	1 (3.6)
DCR[‡], n (%; 95% CI)	47 (90.4; 79.0-96.8)	26 (92.9; 76.5-99.1)
Median DoR, mo (95% CI)	NE (4.2-NE)	5.9 (2.8-NE)
Median TTIR, mo (range)	1.4 (1.2-5.8)	1.4 (1.2-3.0)
Median follow-up, mo (range)	5.6 (1.1-11.7)	5.4 (0.6-12.1)

Data cutoff: Mar 24, 2022.

*Proportion of patients with confirmed CR or PR assessed by BICR per RECIST v1.1.

[†]3 patients were not evaluable at 5.4 mg/kg (1 patient never received treatment due to Covid; 2 patients discontinued before first tumor assessment); 1 not evaluable at 6.4 mg/kg (discontinued due to adverse event before first tumor assessment).

[‡]Proportion of patients with confirmed CR, PR, or SD assessed by BICR.

CR, complete response; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease; TTIR, time to initial response.

DESTINY-Lung02

Response by BCIR

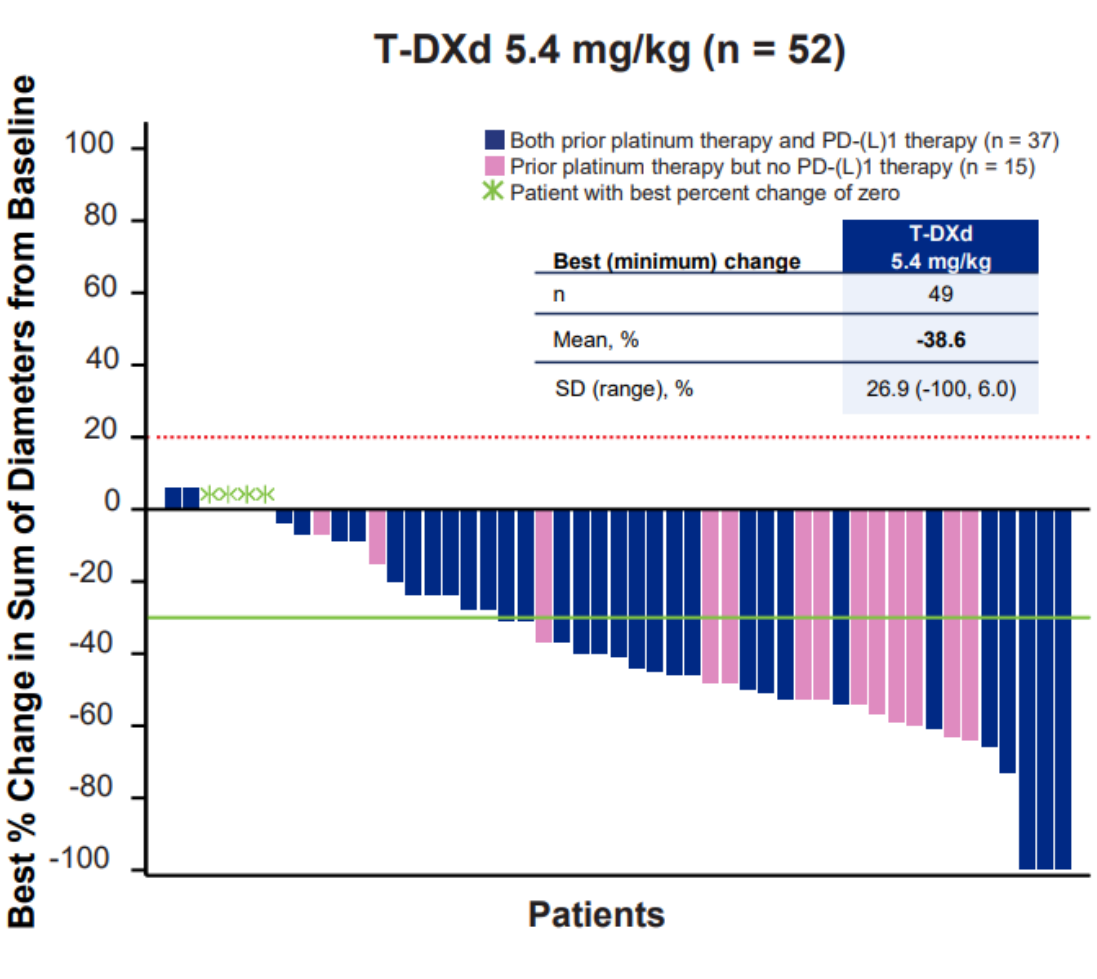
90-Day Follow Up for T-DXd 5.4 mg/kg

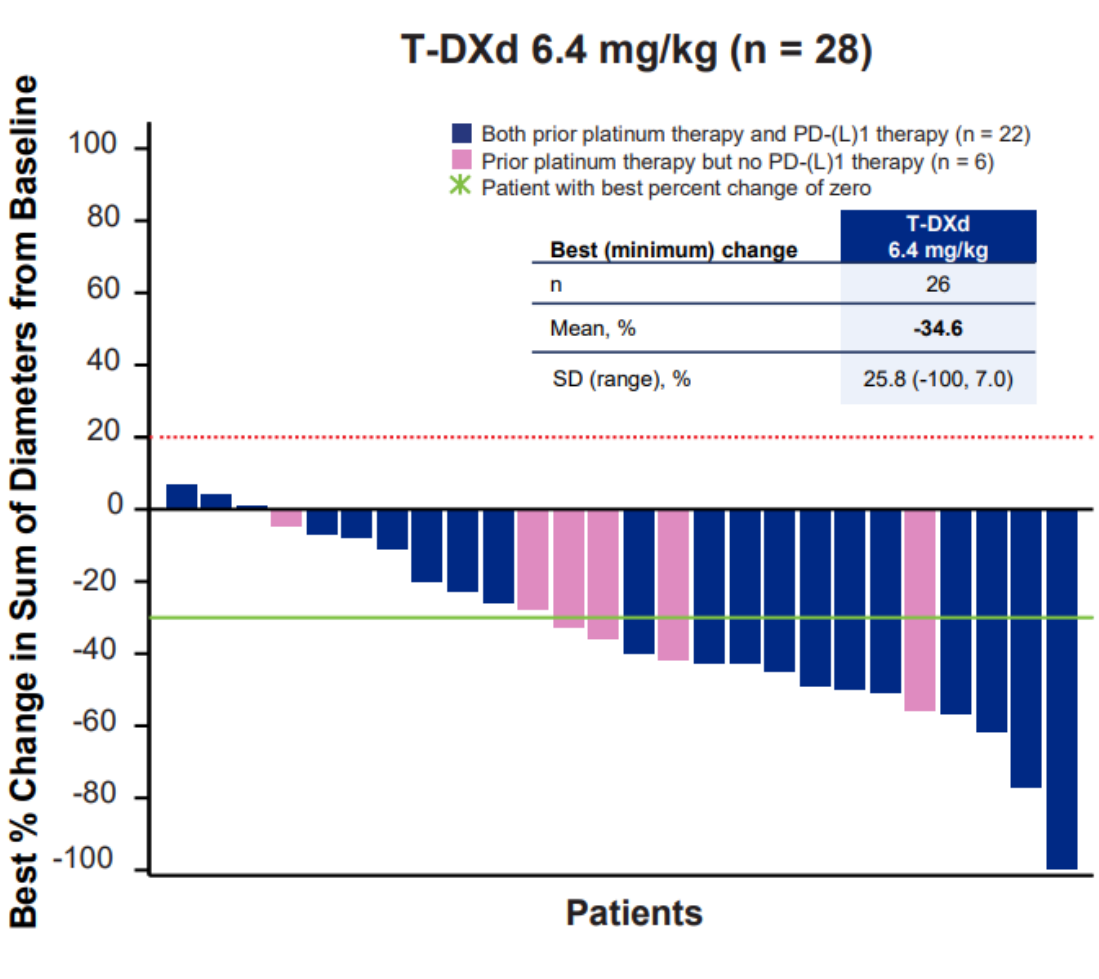
Response	Prespecified Early Cohort T-DXd 5.4 mg/kg (n = 52)	
	Data cutoff: March 24, 2022	**Data cutoff: June 22, 2022**
Confirmed ORR,* % (95% CI)	**53.8** (39.5-67.8)	**57.7** (43.2-71.3)
CR, %	1.9	1.9
PR, %	51.9	55.8
Median DoR,† mo (95% CI)	NE (4.2-NE)	**8.7** (7.1-NE)

- Median DoR was reached with the additional follow-up response analysis
- Confirmed ORR by BICR continued to demonstrate strong and clinically meaningful antitumor activity

DESTINY-Lung02

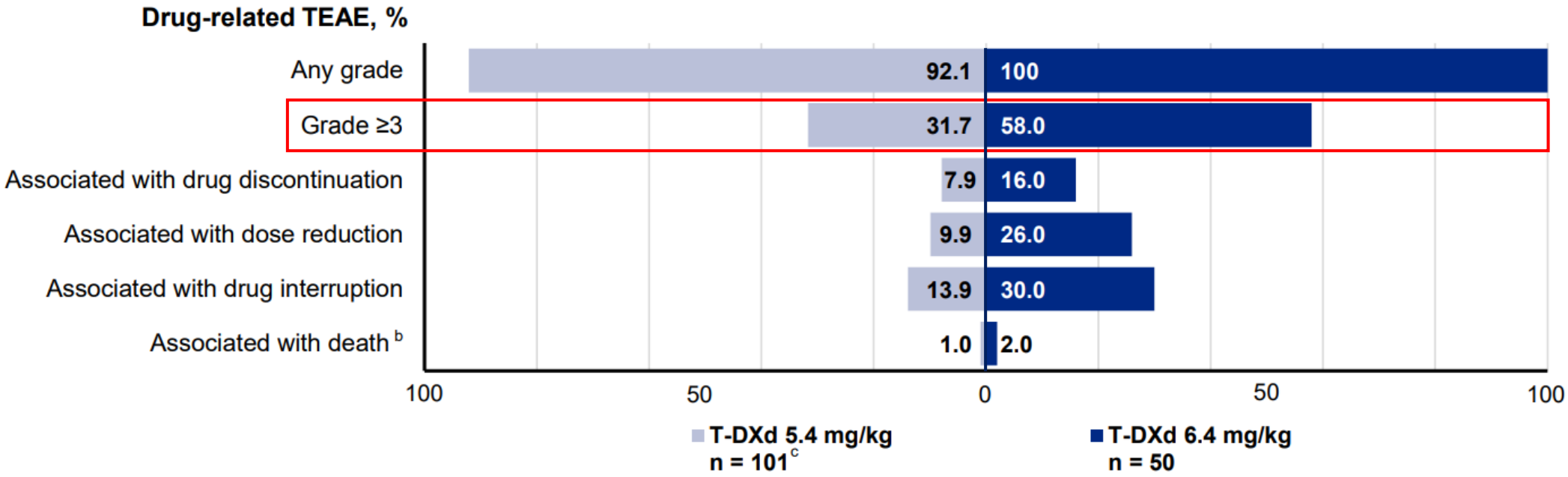
Best Percent Change in Tumor Size by BICR





DESTINY-Lung02

Safety



Median treatment duration, months (range)	3.7 (0.7-11.8)	3.3 (0.7-12.6)
Median follow-up, months (range)	3.8 (0-11.7)	3.9 (0.5-12.1)

DESTINY-Lung02

Adjudicated Drug-Related ILD in Safety Analysis Set

Adjudicated Drug-Related ILDs*	T-DXd 5.4 mg/kg (n = 101)	T-DXd 6.4 mg/kg (n = 50)
Any grade, n (%)	**6 (5.9)**	**7 (14.0)**
Grade 1	3 (3.0)	1 (2.0)
Grade 2	2 (2.0)	6 (12.0)
Grade 3†	1 (1.0)	0
Grade 4	0	0
Grade 5†	0	0
Cases resolved, n (%)	3 (50.0)	1 (14.3)
Median time to onset of first adjudicated ILD, days (range)	67.5 (40-207)	41.0 (36-208)

*Cases of potential ILD or pneumonitis were evaluated via independent adjudication committee. Data reported are for cases that were deemed drug related by ILD adjudication committee. †In safety analysis set, 1 investigator reported grade 3 for 5.4-mg/kg dose, and 1 investigator reported grade 5 ILD with 6.4-mg/kg dose were pending adjudication at data cutoff and were later adjudicated as grade 2 and grade 5 ILD, respectively.

The rate of adjudicated drug-related ILD was lower in the 5.4 mg/kg arm compared with the 6.4 mg/kg arm

Most cases of adjudicated drug-related ILD were low grade (grade 1/2); there were no Grade 4 or Grade 5 events

SUMMARY

DESTINY-Lung02

- At interim analysis, trastuzumab deruxtecan at 5.4 mg/kg provided clinically meaningful responses for HER2m NSCLC patients in the 2L+ setting
  - 57.7% confirmed ORR by BICR (n=30/52; 95% CI: 43.2, 71.3) 1.9% CR (n=1) + 55.8% PR (n=29)
  - 8.7 months median DOR (n=30; 95% CI: 7.1, NE)

- No new safety concerns; consistent with established safety profile of T-DXd
  - More favorable safety profile and lower incidence of ILD in the 5.4 mg/kg arm compared to 6.4 mg/kg arm
  - Early detection of and monitoring for ILD remains important for management

ESMO 2022. Abstr LBA55

DESTINY-Lung02

Trastuzumab deruxtecan (at 5.4 mg/kg) should be considered as a new standard of care for patients previously treated for HER2-mutant NSCLC

More to come…

2022 ESMO Key Studies

Breast and Gynecological Cancer

- TROPiCS-02
- MONARCH 3
- SOLO1
- PAOLA-1

Lung Cancer

- CodeBreaK 200*
- IPSOS*
- DESTINY-Lung02
- CheckMate-816
- NADIM II‡
- IMpower010‡

GU/GI and Other Cancer

- NICHE-2*
- RADICALS-HD*
- COSMIC-313*
- EV-103 K
- EXPLORER/PATHFINDER

* ESMO Presidential Symposium

‡ WCLC 2022

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CLINICAL QUESTION

CheckMate-816

Does neoadjuvant nivo plus platinum-doublet chemotherapy provide benefit for patients with resectable NSCLC regardless of lymph node involvement?

Post hoc analysis

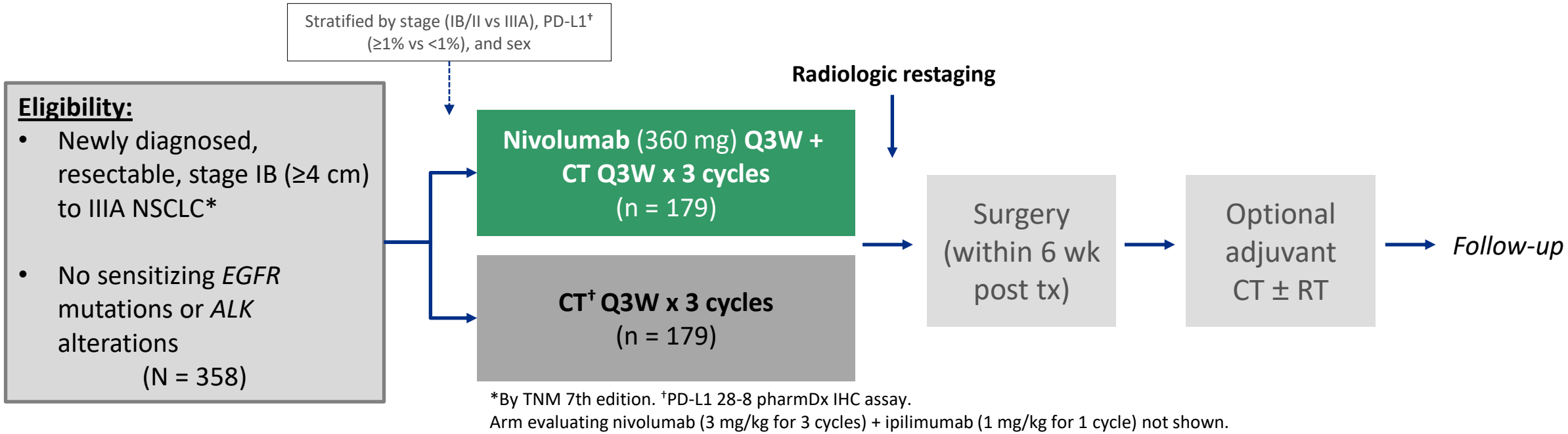
On March 4 2022, the Food and Drug Administration approved nivolumab (Opdivo, Bristol-Myers Squibb Company) with platinum-doublet chemotherapy for adult patients with resectable non-small cell lung cancer (NSCLC) in the neoadjuvant setting. This represents the first FDA approval for neoadjuvant therapy for early-stage NSCLC.

cornerstone specialty network™

KEY DATA

CheckMate-816

Study Design: Randomized, open-label phase III trial neoadjuvant nivolumab + platinum chemotherapy for resectable Stage IB-IIIA NSCLC



*By TNM 7th edition. †PD-L1 28-8 pharmDx IHC assay.
Arm evaluating nivolumab (3 mg/kg for 3 cycles) + ipilimumab (1 mg/kg for 1 cycle) not shown.

Primary endpoints: pCR (by BIPR), EFS (by BICR)
Key secondary endpoints: OS, MPR (by BIPR), time to death or distant metastasis
Key exploratory endpoints: ORR (by BICR), surgery feasibility, peri/postoperative surgery-related AEs

†Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin, pemetrexed + cisplatin, or paclitaxel + carboplatin

Data cutoff: October 20, 2021; median follow up: 29.5 months

KEY DATA

CheckMate-816

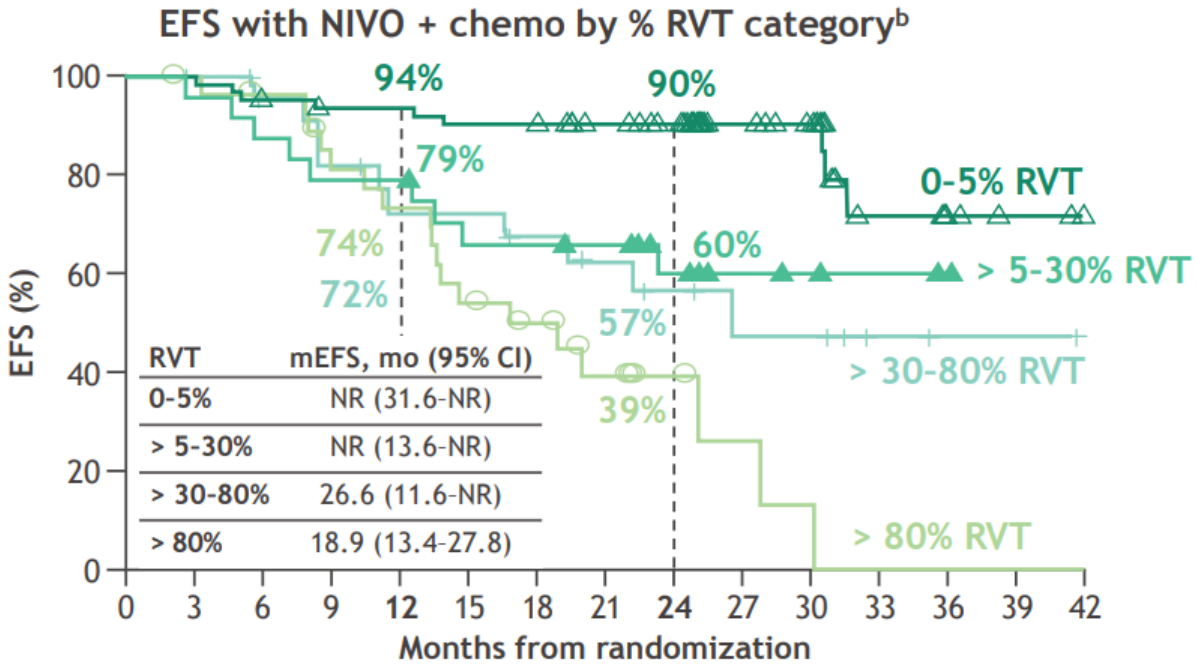
Primary Endpoints

Neoadjuvant nivo plus platinum-doublet chemotherapy results in significant improvements compared with chemotherapy alone

- Statistically significant improvement in EFS over chemotherapy alone with a **37**% reduction in the risk of progression, recurrence or death (HR 0.63; 95% CI: 0.45 to 0.87; P=0.0052)

- pCR rate **24**% vs 2.2%

- Depth of pathological response (low % residual viable tumor [RVT]) was associated with improved EFS outcomes with neoadjuvant NIVO + chemo



Key Secondary Endpoint

- Overall survival (OS): HR=0.57 (95% CI: 0.38–0.87); OS data were immature at the pre-specified interim analysis, and did not cross the boundary for statistical significance

[b]ASCO 2022 LBA8511; AACR 2022 CT012,; NEJM 386(21):1973

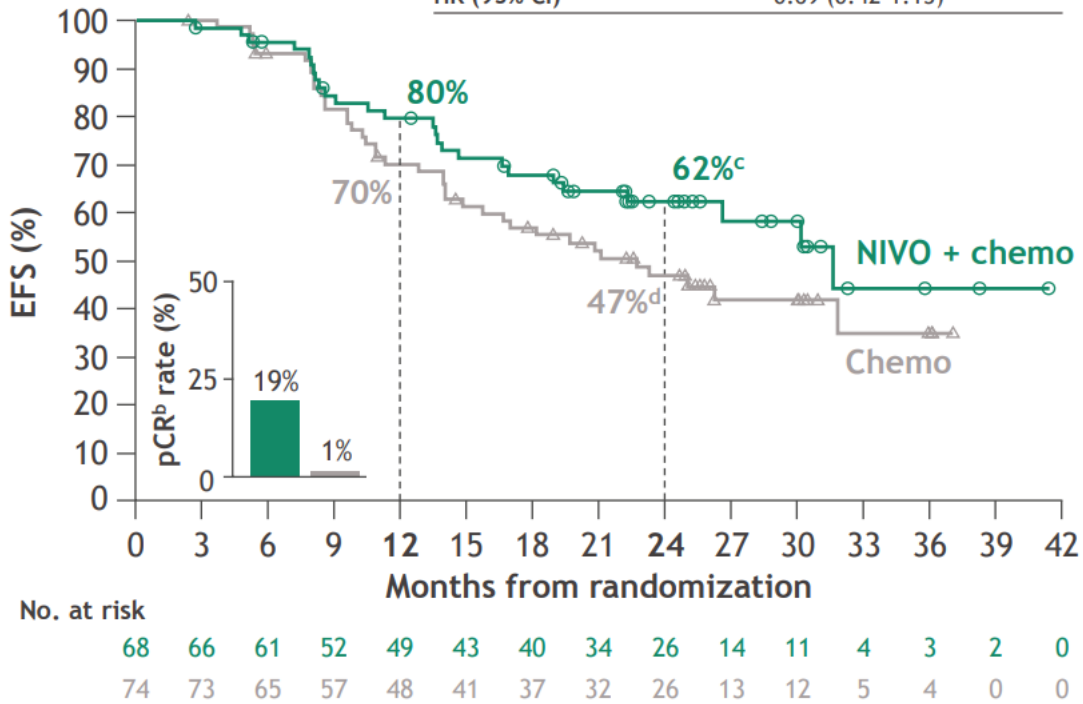
KEY DATA

CheckMate-816

EFS in patients with or without pathologic evidence of LN involvement

With LN involvement

	NIVO + chemo (n = 68)	Chemo (n = 74)
Median EFS, mo (95% CI)	31.6 (22.2-NR)	22.7 (14.8-NR)
HR (95% CI)	0.69 (0.42-1.13)	

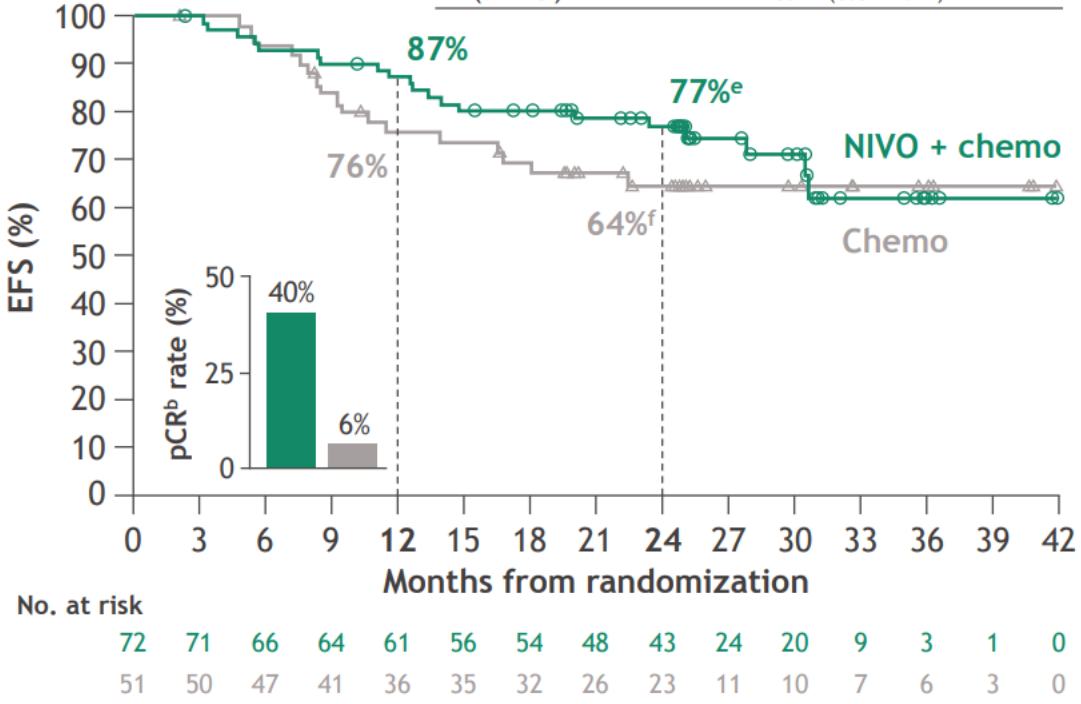


No. at risk

68	66	61	52	49	43	40	34	26	14	11	4	3	2	0
74	73	65	57	48	41	37	32	26	13	12	5	4	0	0

Without LN involvement

	NIVO + chemo (n = 72)	Chemo (n = 51)
Median EFS, mo (95% CI)	NR (30.7-NR)	NR (22.4-NR)
HR (95% CI)	0.74 (0.39-1.41)	



No. at risk

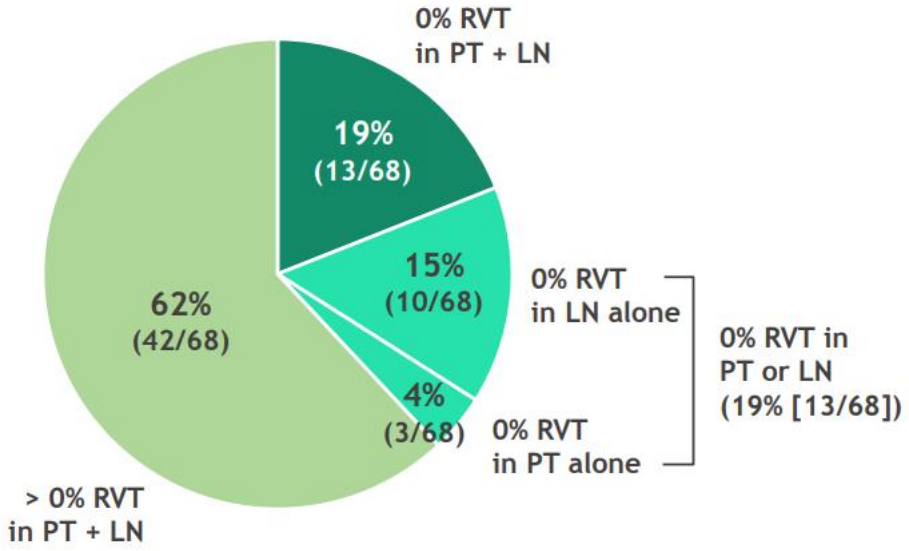
72	71	66	64	61	56	54	48	43	24	20	9	3	1	0
51	50	47	41	36	35	32	26	23	11	10	7	6	3	0

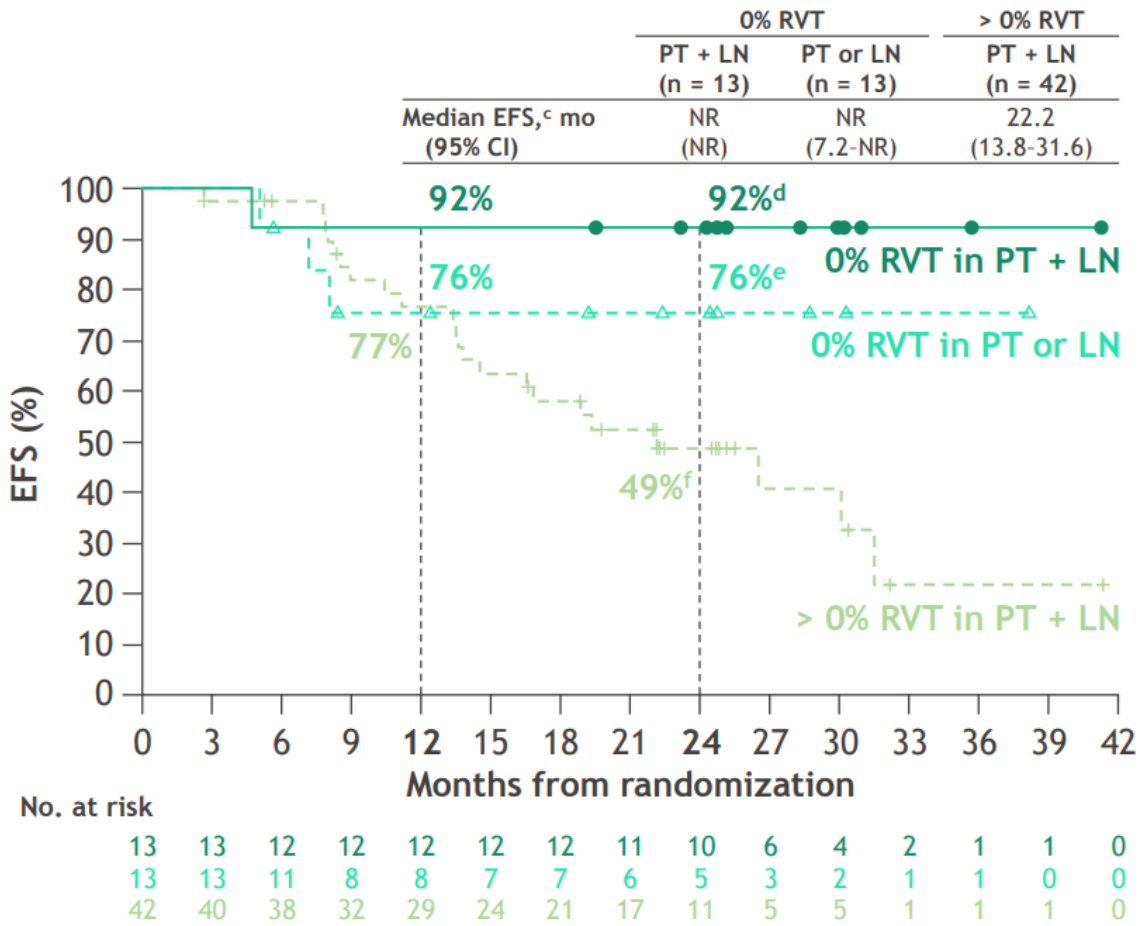
ESMO 2022. Abstr LBA50.

CheckMate-816

EFS by %RVT in patients with LN involvement[a]: Nivo + CT

% RVT: primary tumor (PT) and lymph node (LN)[b]





Minimum / median follow-up: 21 months / 29.5 months.

[a]LN involvement refers to pathologic evidence of LN disease at resection that had or had not fully regressed after neoadjuvant treatment (0% or > 0% RVT in the resected LN).
[b]Patients in the chemo arm with 0% RVT in both PT + LN, 1% (1/74); PT alone, 1% (1/74); LN alone, 4% (3/74); either PT or LN, 5% (4/74); > 0% RVT in PT + LN, 93% (69/74).
[c]HRs were not computed because of the low number of events in the 0% RVT subgroups. 95% CI: d57–99, e42–91,f32–64

SUMMARY

CheckMate-816

- Post hoc analysis revealed that patients with resectable NSCLC had improved EFS and pCR with neoadjuvant nivo + CT compared to CT alone regardless of pathologic evidence of LN involvement

- Greatest EFS achieved in patients treated with neoadjuvant nivolumab + CT with 0% RVT in both primary tumor and LN (vs those with 0% RVT in either LN or primary tumor, or those with >0% RVT)

- The % regression (area of immune-mediated tumor clearance) and % RVT for nivo + CT were inversely correlated and was predictive of EFS at 2 yr regardless of LN involvement

CheckMate-816

Neoadjuvant nivolumab in combination with platinum-doublet chemotherapy benefits patients with early stage NSCLC regardless of LN involvement and should be considered as a standard of care

Improves the chance of successful surgical treatment and reduces the risk of recurrence

2022 ESMO Key Studies

Breast and Gynecological Cancer

- TROPiCS-02
- MONARCH 3
- SOLO1
- PAOLA-1

Lung Cancer

- CodeBreaK 200*
- IPSOS*
- DESTINY-Lung02
- CheckMate-816
- NADIM II‡
- IMpower010‡

GU/GI and Other Cancer

- NICHE-2*
- RADICALS-HD*
- COSMIC-313*
- EV-103 K
- EXPLORER/PATHFINDER

* ESMO Presidential Symposium

‡ WCLC 2022

cornerstone specialty network™

NADIM II

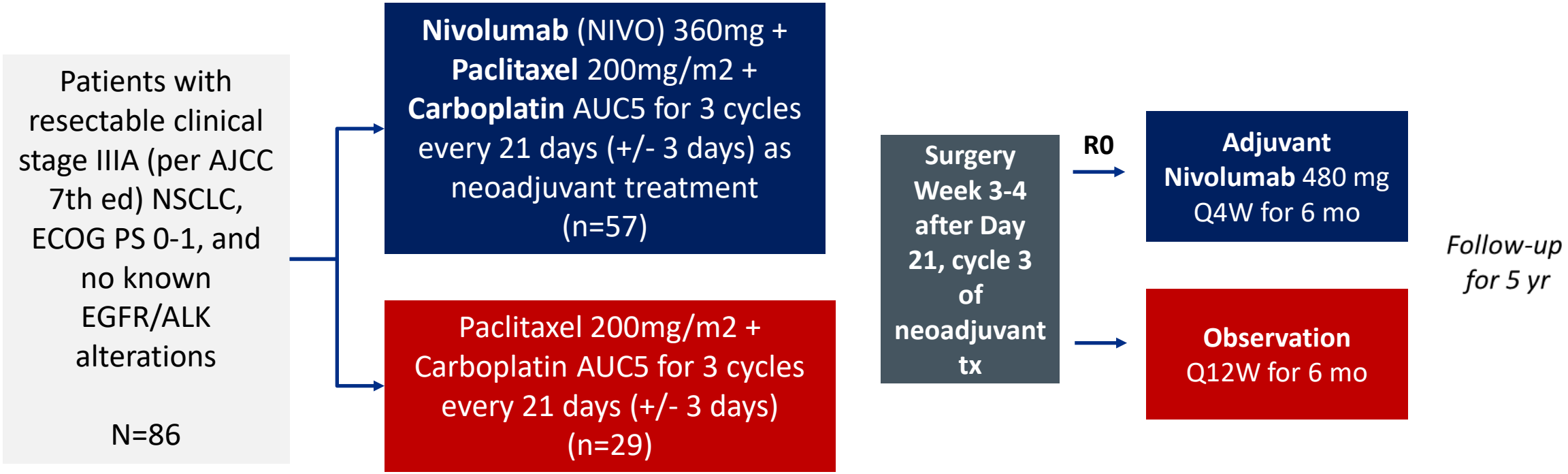
Interim analysis: PFS and OS results

Update from the IASLC 2022 World Conference on Lung Cancer

KEY DATA

NADIM II

Study Design: open-label, randomized, two-arm, phase II, multi-center clinical trial



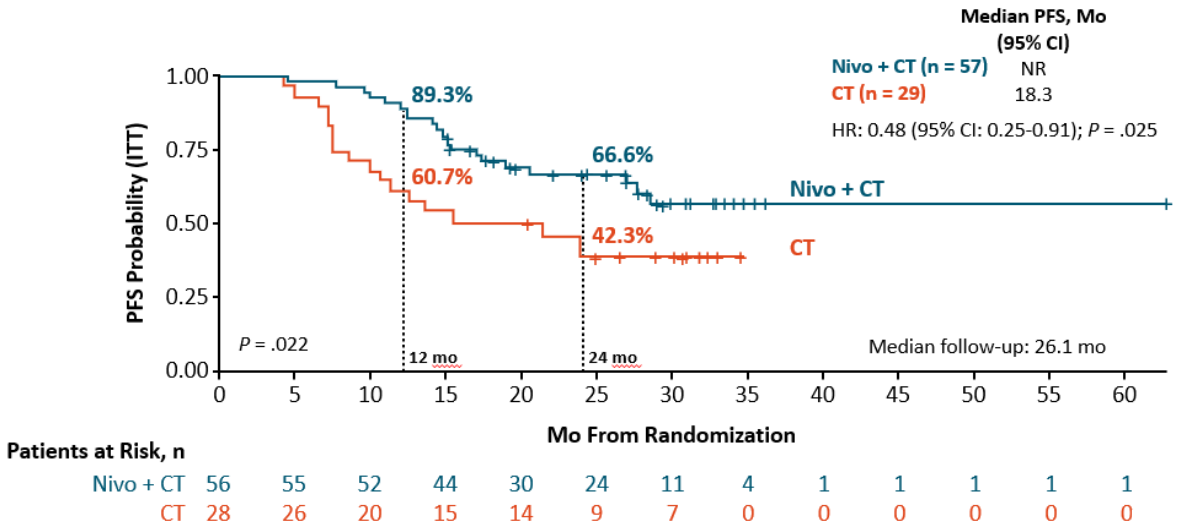
Primary endpoint: pCR
Secondary endpoints: PFS, OS, and biomarker analysis

Median follow-up time: 21.9 months
Data cutoff: March 2021

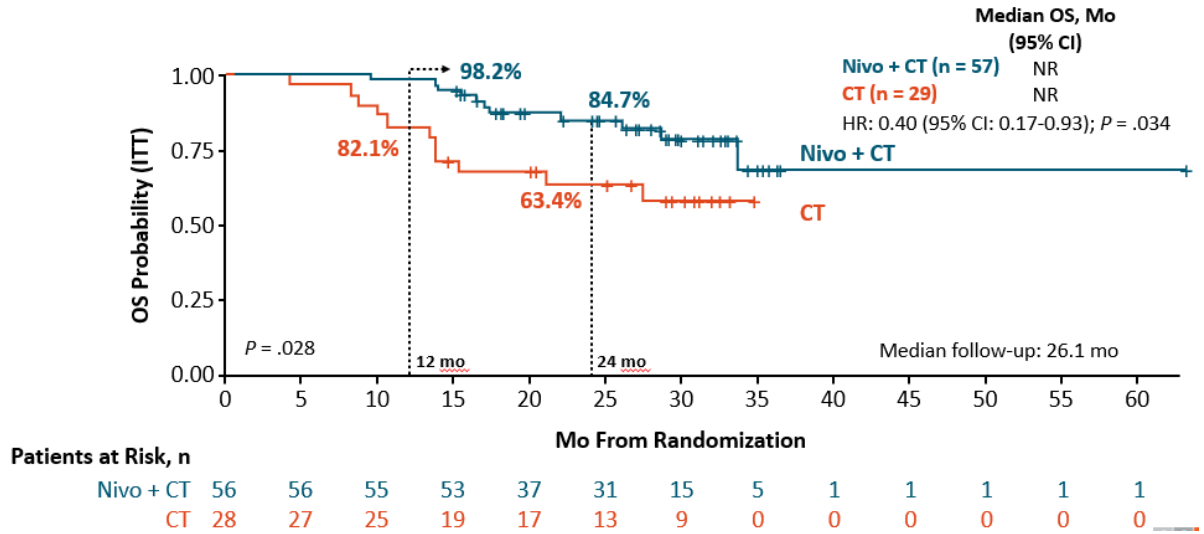
NADIM II

Secondary Endpoints

- PFS at 24 months was 66.6% for patients treated with nivolumab plus chemotherapy versus 42.3% for patients treated with chemotherapy
- Median PFS not reached in nivo + CT arm
- HR 0.48



- OS at 24 months was 84.7% for patients treated with nivolumab plus chemotherapy versus 63.4% for patients treated with chemotherapy
- Median OS not reached in either arm
- HR 0.40



SUMMARY

NADIM II

- The first trial to show improved OS with a neoadjuvant immunotherapy-based combination for patients with resectable stage IIIA–B NSCLC
- PFS and OS improved and sustained with nivo + CT compared to chemo alone
  - PFS rate: 12 mo, 89.3% vs 60.7%; 24 mo, 66.6% vs 42.3%
  - OS rate: 12 mo, 98.2% vs 82.1%; 24 mo, 84.7% vs 63.4%

NADIM II supports the results of CheckMate-816

CheckMate-816

- Overall survival (OS): HR=0.57 (95% CI: 0.38–0.87); OS data were immature at the pre-specified interim analysis, and did not cross the boundary for statistical significance
- 24 mo OS rate, 83% with nivo + chemo vs 71% with chemo alone

IMpower010

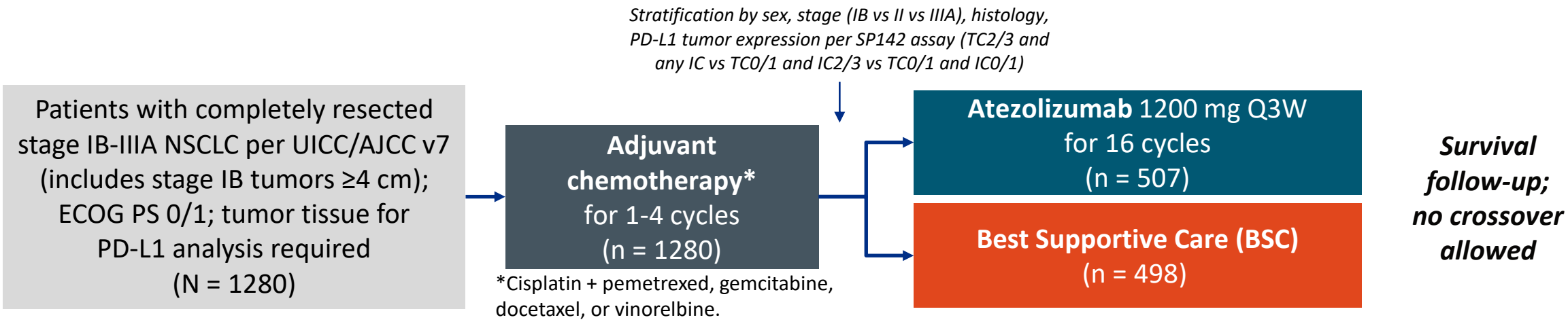
Interim analysis: OS results

Update from the IASLC 2022 World Conference on Lung Cancer

KEY DATA

IMpower010

Study Design: randomized, open-label Phase III



Primary endpoint: hierarchical evaluation of investigator-assessed DFS in 3 populations: stage II-IIIA with PD-L1 TC ≥1%[†] → all randomized stage II-IIIA → ITT population (stage IB-IIIA)

Secondary endpoints: OS (in ITT if primary endpoints are positive); DFS in stage II-IIIA with PD-L1 TC ≥50%[†]; 3-yr, 5-yr DFS in all 3 populations; safety

Exploratory endpoints: OS biomarker analyses

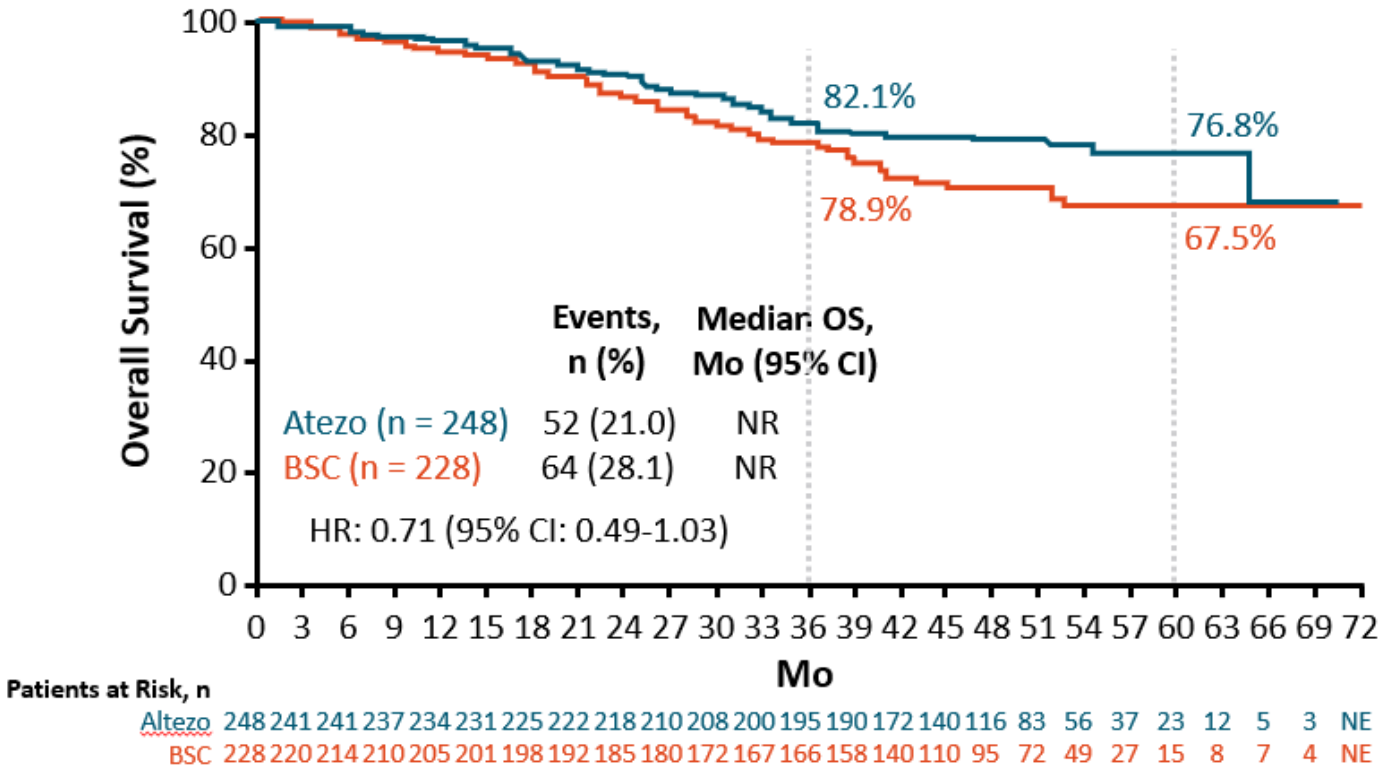
Data cutoff for interim analysis: April 18, 2022
Median 46-mo follow-up

[†]PD-L1 SP264 IHC assay.

KEY DATA

IMpower010

OS in Patients With Stage II-IIIA NSCLC and PD-L1 TC ≥1%

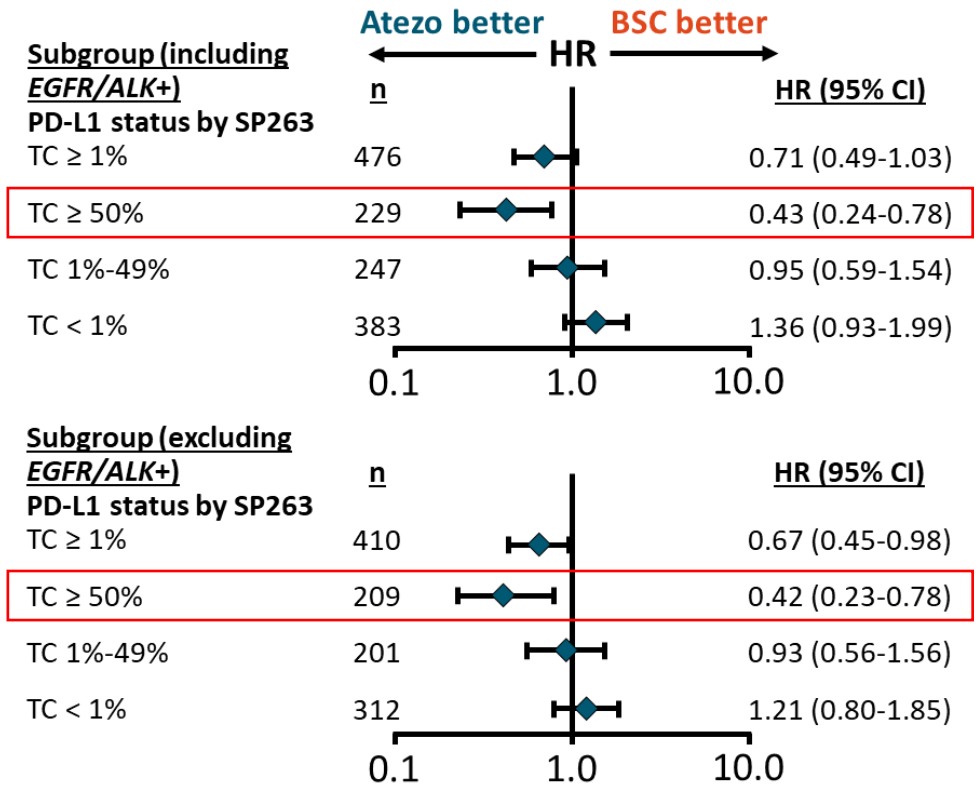


No OS benefit observed in all-randomized stage II-IIIA or ITT (stage IA-III) patient populations

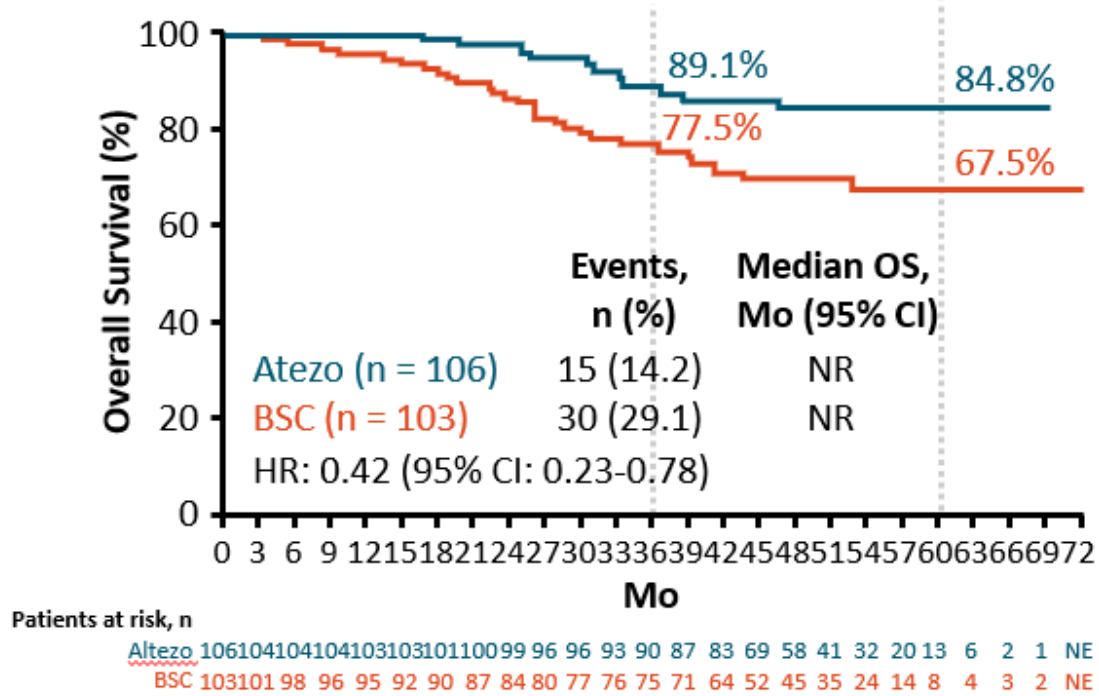
	All randomized stage II-IIIA		ITT (stage I-IIIA)	
	Atezo (n=442)	BSC (n=440)	Atezo (n=507)	BSC (n=498)
Events, n (%)	115 (26.0%)	116 (26.4%)	127 (25.0%)	124 (24.9%)
Median OS, mos	NR	NR	NR	NR
Stratified HR (95% CI)	**0.95** (0.74 – 1.24)		**0.995** (0.78 – 1.28)	
Stratified log-rank p value	NA		0.9661	

IMpower010

OS by biomarker status



OS in Patients With Stage II-IIIA NSCLC and PD-L1 TC ≥50% excluding *EGFR*/*ALK*+



SUMMARY

IMpower010

- In prespecified interim analysis of OS from phase III IMpower010 trial, adjuvant atezolizumab following complete resection and adjuvant chemotherapy suggests trend toward OS benefit (HR: 0.71 [95% CI: 0.49-1.03]) in patients with stage II-IIIA NSCLC with PD-L1 TC ≥1% vs BSC
  - Trend toward OS benefit also seen in patients with stage II-IIIA NSCLC with PD-L1 TC ≥50%;
    - OS HR: 0.43 (95% CI: 0.24-0.78)

- OS data are not mature

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*ESMO Presidential Symposium
‡WCLC 2022

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CLINICAL QUESTION

NICHE-2

Does neoadjuvant immune checkpoint inhibition with nivo + ipi provide benefit for patients with locally advanced MMR-deficient colon cancer?

Previous data from NICHE-1 (n=32) showed that immune checkpoint blockade is highly effective in non-metastatic dMMR colon cancers

- *100% pathologic responses and 60% pathologic complete responses*

Chalabi et. al, Nat Med 2020; Verschoor et. al, ASCO 2022

KEY DATA

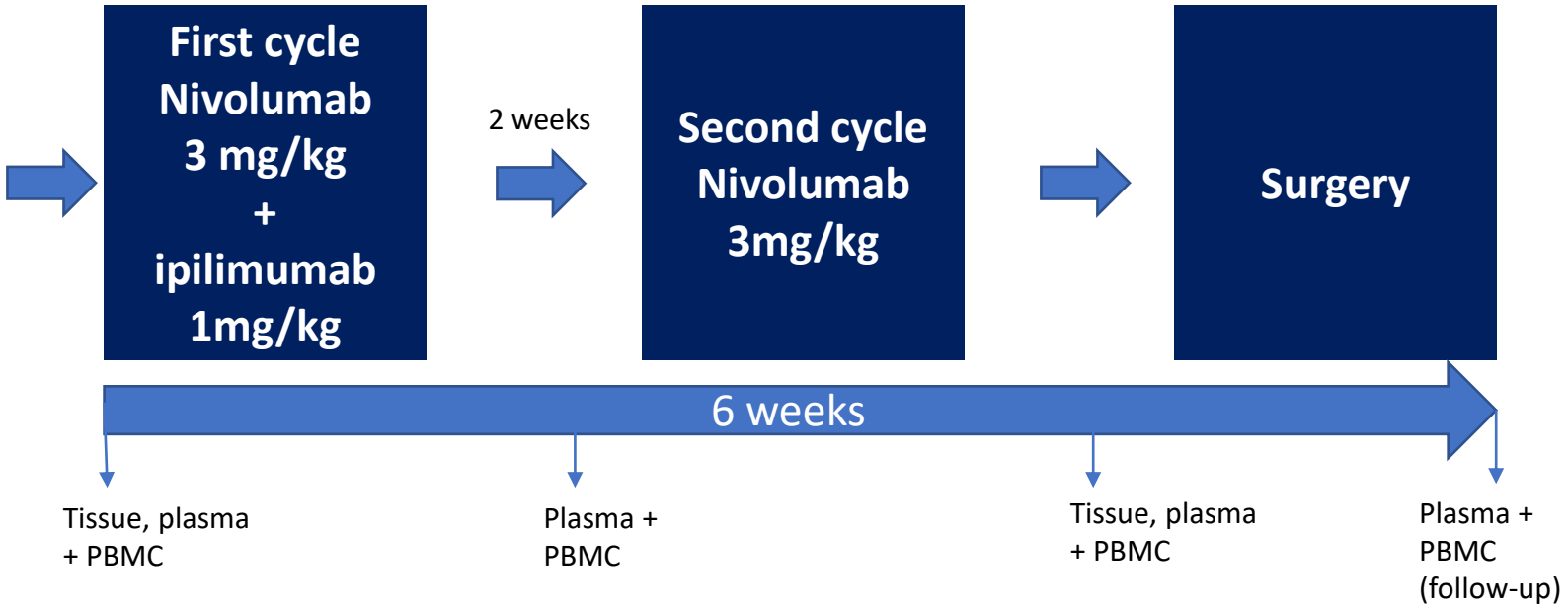
NICHE-2

Study Design: Investigator-initiated, non-randomized multicenter‡ study

‡6 participating hospitals in the Netherlands

- Non-metastatic, previously untreated dMMR colon adenocarcinoma
- cT3 and/or N+ disease based on radiologic staging*
- No clinical signs of obstruction
- No clinical symptoms or radiologic suspicion of perforation
- No active autoimmune disease or other medical conditions requiring systemic steroid or immunosuppressive medications

(N=112)



*Protocol revision October 2020 added a primary endpoint of 3-year DFS and a new cohort of 70 patients with at least T3 and/or N+ tumors
Current data combine n=30 from original cohort with new dMMR cohort

Primary endpoints: Safety and feasibility, 3-year disease-free survival (DFS)
Secondary endpoints: Major and complete pathologic response rate in post-treatment surgical specimen, Circulating tumor DNA dynamics, Translational research (DNA, RNA sequencing, single-cell sequencing, multiplex imaging)

Safety and feasibility endpoint is considered successful if surgery is performed on time (no more than 2 weeks delay) in 95% of patients, at a power of 80% and a two-sided significance level of 0.025. Timely surgery in less than 85% of patients would be deemed unacceptable • Survival: 3-year DFS of 93% would be deemed successful, at a power of 80% and a two-sided significance level of 0.025 (one-sample log-rank test assuming 82% DFS in the historical control group) • 95 patients needed

ESMO 2022. Abstr LBA7.

KEY DATA

NICHE-2

Baseline Characteristics

Characteristic	Number at risk (%) of intention to treat population (n=112)
Female sex, n (%)	65 (58%)
Median age, yr (range)	60 (20 – 82)
ECOG PS, n (%)	
• 0	97 (87%)
• 1	15 (13%)
Primary tumor location	
• Right colon	76 (68%)
• Left colon	19 (17%)
• Transverse colon	17 (15%)
Lynch syndrome	35 (31%)
• Unknown	10 (9%)

Characteristic	Number at risk (%) of intention to treat population (n=112)
Radiologic Stage	
• I/II	14 (13%)
• Low risk III	15 (13%)
• High risk III	83 (74%)
Radiologic T Stage	
• T2	17 (15%)
• T3 + T3/4a	25 (22%)
• T4a	39 (35%)
• T4b	31 (28%)
Radiologic N Stage	
• N0	14 (13%)
• N1	29 (26%)
• N2	69 (62%)
Radiologic high-risk with both T4 and N2	54 (48%)

63% clinical T4a or T4b tumors

ESMO 2022. Abstr LBA73.

NICHE-2

Adverse Events

Most common grade 1-2 AEs were infusion reactions, dry mouth, hyper- or hypothyroidism, fatigue and flu-like symptoms

Immune-related Adverse Events (n=112)		
Patients with any AE	68 (61%)	
Grade ≥3	**4 (4%)**	
	Grade 3	**Grade 4**
• Amylase increase	1	0
• Lipase increase	0	1
• Hepatitis	1	0
• Myositis	1	0
• Rash	1	0
AEs leading to delay in surgery ≥ 2 weeks	2 (2%)	

Five events observed in 4 (4%) patients. Amylase and lipase increases were asymptomatic and resolved without intervention. Rash and hepatitis were treated with prednisone and resolved completely. Myositis was treated with prednisone and mycophenolate and has resolved completely.

Surgery-related Adverse Events (n=112)	
Any	24 (21%)
Grade ≥3	15 (13%)
Anastomotic leakage or wound infections	6 (5%)

- All patients underwent surgery, with 100% R0 resections
  - 98% of patients underwent timely surgery, meeting the safety primary endpoint
- Median 5.4 weeks from first dose (nivolumab + ipilimumab) to surgery
- No new safety signals

KEY DATA

NICHE-2

Major pathologic response in 95% of patients; 67% pCR

Pathologic Responses (RVT)	Patients n=107
Yes (≤50%)	106 (99%)
Major (≤10%)	**102 (95%)**
Complete (0%)	**72 (67%)**
Partial (10% - 50%)	4 (4%)
No (≥50%)	1 (1%)

Adjuvant chemotherapy (CTx)

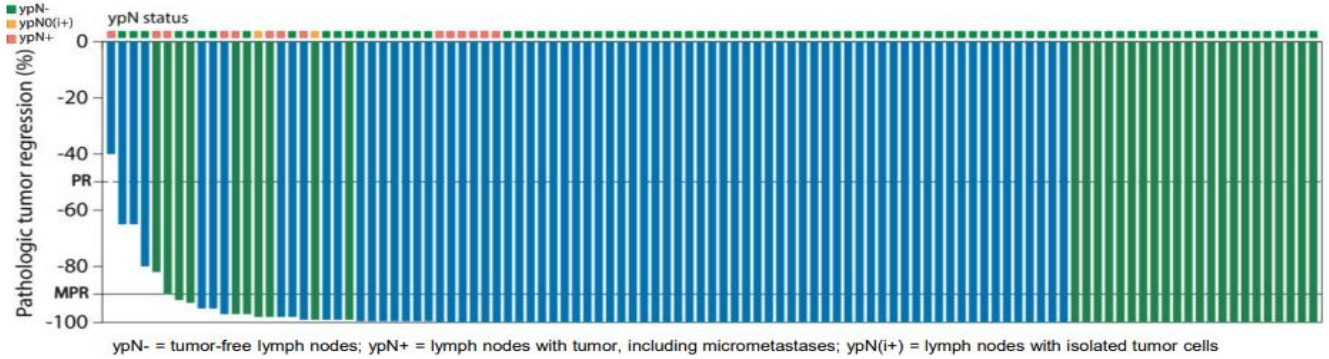
14 patients with ypN+ disease

- 3 patients received adjuvant CTx*
- 5 patients >70 years
- 6 patients refused

* 1 non-responder, 1 partial responder and 1 MPR

Disease recurrence

With a median follow-up of 13.1 months (1.4 - 57.4), there have been no disease recurrences



Green bars = NICHE-1 cohort; Blue bars = NICHE-2 cohort

pCR rate	No pCR	pCR
Sporadic tumor (n=65)	27 (42%)	38 (58%)
Lynch Syndrome (n=32)	7 (22%)	25 (78%)

ESMO 2022. Abstr LBA73.

SUMMARY

NICHE-2

- Neoadjuvant immunotherapy, in the form of one dose of ipi and two doses of nivo within 6 weeks prior to surgery, resulted in major pathologic responses in 95% of patients, including 67% pathologic complete responses, with dMMR colon cancer
- Treatment is well-tolerated with only 4% grade 3-4 immune-related adverse events
- No disease recurrences to date
- 3-year disease-free survival data expected in 2023

ESMO 2022. Abstr LBA7.

NICHE-2

Neoadjuvant immunotherapy (one dose of ipilimumab and two doses of nivolumab ≤6 weeks prior to surgery) has the potential to become standard of care for patients with dMMR colon cancer

More to come…

2022 ESMO Key Studies

Breast and Gynecological Cancer

- TROPiCS-02
- MONARCH 3

- SOLO1
- PAOLA-1

Lung Cancer

- CodeBreaK 200*
- IPSOS*
- DESTINY-Lung02
- CheckMate-816

- NADIM II‡
- IMpower010‡

GU/GI and Other Cancer

- NICHE-2*
- RADICALS-HD*
- COSMIC-313*
- EV-103 K

- EXPLORER/PATHFINDER

*ESMO Presidential Symposium
‡WCLC 2022

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RADICALS-HD

Does duration of androgen deprivation therapy (ADT) with post-operative radiotherapy impact patients with prostate cancer?

Key Questions:

- *Who should have ADT added to their radiotherapy?*
- *What is the optimal duration of ADT?*

RADICALS-HD

Study Design: randomized, multicenter phase III trial

Inclusion: Due for post-op RT after radical prostatectomy for non-metastatic adenocarcinoma, Post-operative serum prostate-specific antigen (PSA) < 0.4 ng/mL
Exclusion: Prior pelvic RT, Prior hormone therapy, metastatic disease, PSA > 5ng/ml

Key
STHT = 6 months ADT
LTHT = 24 months ADT

2-way randomization
n=1150

RT alone vs RT+STHT

3-way randomization
n=492

RT alone vs RT+STHT vs RT+LTHT

2-way randomization
n=1197

RT+STHT vs RT+LTHT

RT alone vs RT+STHT
n=1480

268 MFS events observed
9 year median follow-up

RT+STHT vs RT+LTHT
n=1523

313 MFS events observed
9 year median follow-up

Primary endpoint of metastasis-free survival

Note: study start date Nov 2007 (standards of care have evolved during that time including particularly the imaging approaches employed). Additionally, hormonal treatments were not standardized and patients and investigators could choose which of the randomizations to participate in.

KEY DATA

RADICALS-HD: No ADT vs short course ADT

Baseline Characteristics: RT alone vs RT+STHT

	RT alone (n=737)	RT + STHT (n=743)
Age, median years (IQR)	66 (61 – 69)	66 (61 – 69)
PSA at randomization, median (IQR)	0.2 (0.1 – 0.4)	0.2 (0.1 – 0.4)
Stage		
T2	289 (40%)	305 (42%)
T3a	325 (44%)	303 (41%)
T3b/4	**112 (16%)**	**128 (17%)**
N+ve	25 (3%)	25 (3%)
Gleason		
≤7	654 (89%)	657 (89%)
8-10	**83 (11%)**	**86 (12%)**
Positive margins		
Present	452 (61%)	472 (64%)
Absent	285 (39%)	271 (36%)

Treatment: RT alone vs RT+STHT

	RT alone (n=737)	RT + STHT (n=743)
RT timing		
Adjuvant	**208 (28%)**	**215 (29%)**
Early salvage	529 (72%)	528 (71%)
Planned RT schedule		
52.5Gy / 20f	215 (29%)	222 (30%)
66.0Gy / 33f	510 (69%)	511 (69%)
Other	12 (2%)	10 (1%)
Planned RT target		
Prostate bed	700 (95%)	692 (93%)
Prostate bed + Pelvic LN	37 (5%)	51 (7%)
Planned hormone therapy		
LHRH	613 (83%)	624 (84%)
Bicalutamide	124 (17%)	119 (16%)

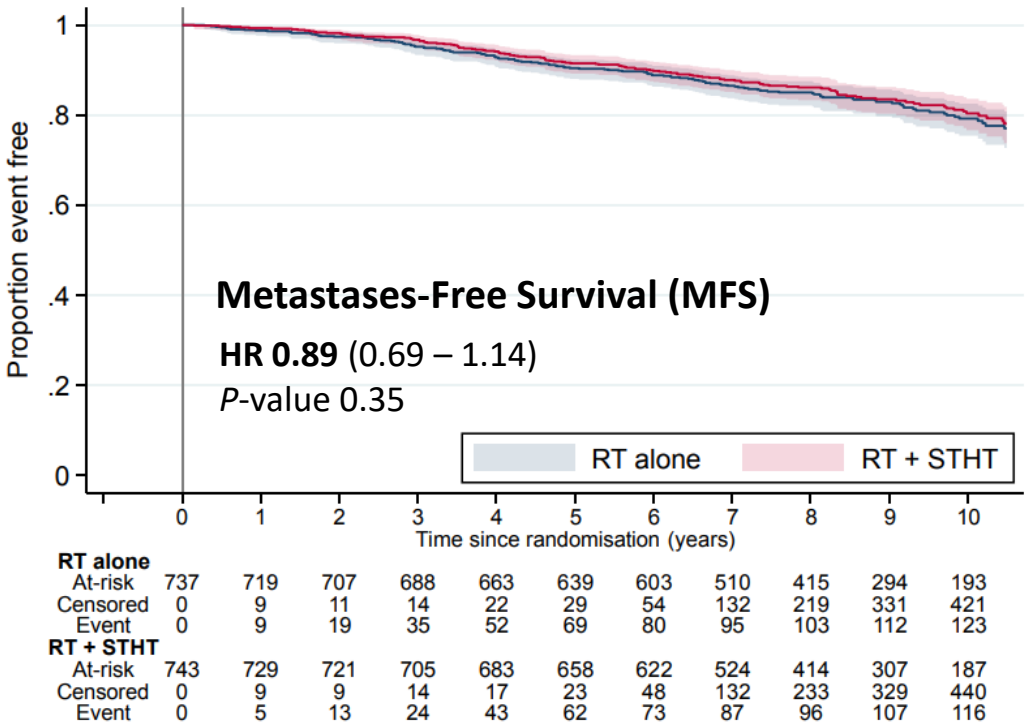
KEY DATA

RADICALS-HD : No ADT vs short course ADT

RT alone vs RT+STHT

	RT alone (n=737)	RT + STHT (n=743)
Metastases-Free Survival (MFS)		
Events	142	126
HR (95%CI)	0.89 (0.69 – 1.14)	
P-value	0.35	
10yr event free	79%	80%
Freedom-from-distant metastases (FFDM)		
Events	79	65
HR (95%CI)	0.82 (0.58 – 1.15)	
P-value	0.24	
10yr event free	88%	90%
Overall Survival (OS)		
Events	98	92
HR (95%CI)	0.88 (0.65 – 1.19)	
P-value	0.42	
10yr event free	86%	85%
Time to Salvage Hormone Therapy		
Events	176	109
HR (95%CI)	**0.54** (0.42 – 0.70)	
P-value	**<0.0001**	
10yr event free	**73%**	**82%**

- Short course ADT, compared with no ADT, did not meaningfully improve MFS



Note: HR < 1 favor RT+STHT
Note: predicted 10yr MFS = 80%

ESMO 2022. Abstr LBA9.

KEY DATA

RADICALS-HD: Short course ADT vs long course ADT

Baseline Characteristics: RT+STHT vs RT+LTHT

	RT + STHT (n=761)	RT + LTHT (n-=762)
Age, median years (IQR)	65 (60-69)	65 (61-69)
PSA at randomization, median (IQR)	0.2 (0.1-0.5)	0.2 (0.1-0.5)
Stage		
T2	206 (27%)	215 (29%)
T3a	327 (43%)	309 (41%)
T3b/4	**226 (29%)**	**235 (31%)**
N+ve	63 (8%)	66 (9%)
Gleason		
≤7	545 (72%)	543 (71%)
8-10	**215 (28%)**	**219 (29%)**
Positive margins		
Present	480 (63%)	484 (64%)
Absent	281 (37%)	278 (36%)

Treatment: RT+STHT vs RT+LTHT

	RT + STHT (n=761)	RT + LTHT (n=762)
RT timing		
Adjuvant	**328 (43%)**	**325 (43%)**
Early salvage	433 (57%)	437 (57%)
Planned RT schedule		
52.5Gy / 20f	145 (19%)	148 (19%)
66.0Gy / 33f	604 (79%)	600 (79%)
Other	11 (1%)	13 (2%)
Planned RT target		
Prostate bed	645 (85%)	642 (84%)
Prostate bed + Pelvic LN	115 (15%)	119 (16%)
Planned hormone therapy		
LHRH	640 (84%)	636 (84%)
Bicalutamide	119 (16%)	124 (16%)
LHRH antagonist	1 (<1%)	0 (0%)

KEY DATA

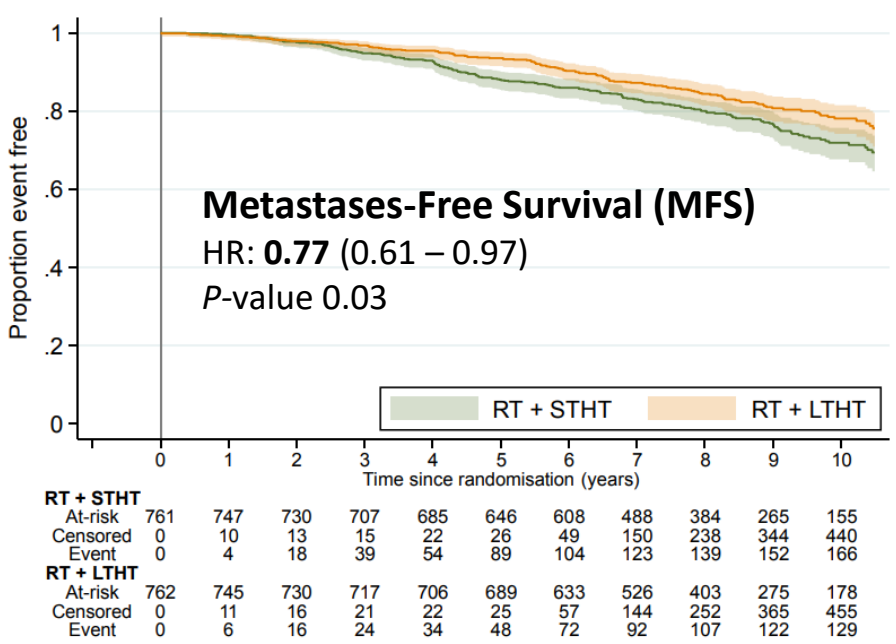
RADICALS-HD: Short course ADT vs long course ADT

RT + STHT vs RT + LTHT

	RT + STHT (n=761)	RT + LTHT (n-=762)
Metastases-Free Survival (MFS)		
Events	174	139
HR (95%CI)	**0.77** (0.61 – 0.97)	
P-value	**0.03**	
10yr event free	**72%**	**78%**
Freedom-from-distant metastases (FFDM)		
Events	117	76
HR (95%CI)	**0.63** (0.47 – 0.85)	
P-value	**0.002**	
10yr event free	81%	88%
Overall Survival		
Events	111	100
HR (95%CI)	0.88 (0.66 – 1.17)	
P-value	0.38	
10yr event free	82%	85%
Time to Salvage Hormone Therapy		
Events	200	157
HR (95%CI)	**0.73** (0.59 – 0.91)	
P-value	0.005	
10yr event free	**69%**	**75%**

Note: HR < 1 favor RT+LTHT
Note: predicted 10yr MFS = 75%

- Long course ADT, compared with short course ADT, did meaningfully improve MFS
- At 10 years:
  - MFS 72% with RT + short term ADT
  - MFS 78% with RT + long term ADT



RADICALS-HD

Safety: RTOG toxicity

Maximum Grade	RT alone	RT + STHT	RT + STHT	RT + LTHT
0 – 2	612 (83%)	635 (85%)	650 (85%)	615 (81%)
	P-value 0.25		*P*-value 0.06	
3	114 (16%)	90 (12%)	99 (13%)	138 (18%)
4	7 (1%)	10 (1%)	6 (1%)	4 (1%)

- No grade 5 events
- Most common grade 3+ adverse events reported within 2 years after randomization:
  - 6% Urethral stricture
  - 4% Hematuria

ESMO 2022. Abstr LBA9.

SUMMARY

RADICALS-HD

- Long term (24 months) ADT when added to post-operative radiotherapy for prostate cancer improved metastasis-free survival compared to short course (6 months) ADT
  - Patients included in the none versus short-term ADT comparison had less aggressive disease than those in the short-term versus long-term ADT comparison

- Overall survival data immature

ESMO 2022. Abstr LBA9.

RADICALS-HD

Some patients will benefit from either short-term ADT versus no ADT or from long-term ADT versus short-term ADT

Need to personalize therapy – consider a combination of clinical factors to determine addition and length of ADT

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*ESMO Presidential Symposium
‡WCLC 2022

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CLINICAL QUESTION

COSMIC-313

Does nivolumab + ipilimumab in combination with a TKI (cabozntinib) provide benefit for patients with previously untreated advanced renal cell carcinoma of IMDC intermediate or poor-risk?

CABOMETYX (cabozntinib) is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (RCC) as a monotherapy (CABOSUN), the only single-agent TKI with NCCN preferred recommendation in Category 2A: 1L intermediate-/poor-risk clear-cell aRCC; and for patients with advanced renal cell carcinoma, as a first-line treatment in combination with nivolumab (CheckMate-9ER)

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COSMIC-313

Study Design: randomized, double-blind phase III trial

- Patients with advanced RCC
- No prior systemic therapy*
- Clear cell component
- Intermediate or poor IMDC risk
- Measurable disease per RECIST v1.1
- Karnofsky PS ≥70%

(N = 855)

Stratified by IMDC risk and region

R 1:1

Cabozantinib 40 mg PO QD + **Nivolumab** 3 mg/kg IV Q3W x 4 + **Ipilimumab** 1 mg/kg IV Q3W x 4 (n = 428)

→ **Cabozantinib** 40 mg PO QD + **Nivolumab** 480 mg IV Q4W†

Placebo PO QD + **Nivolumab** 3 mg/kg IV Q3W x 4 + **Ipilimumab** 1 mg/kg IV Q3W x 4 (n = 427)

→ **Placebo** PO QD + **Nivolumab** 480 mg IV Q4W†

Tumor assessment every 8 weeks per RECIST v1.1‡
Treatment until loss of clinical benefit or intolerable toxicity§
No crossover allowed

*One prior systemic adjuvant therapy allowed for completely resected RCC and if recurrence occurred ≥6 mo after last dose of adjuvant therapy; adjuvant PD-1 or PD-L1 inhibitor in combination with CTLA-4 inhibitor not permitted.
†Nivolumab given for maximum of 2 yr.
‡Tumor assessment (RECIST v1.1) at Wk 10, then every 8 wk through 50 wk, then every 12 wk. §Discontinuation of 1 agent did not necessitate discontinuing all agents.

Primary endpoint: PFS per RECIST v1.1 by BIRC (analyzed after 249 events in PITT population [first 550 patients randomized])

Secondary endpoint: OS

Additional endpoints: ORR, DoR, safety

Median follow-up: ITT: 17.7 mo, PITT: 20.2 mo

PITT, progression-free survival ITT

COSMIC-313

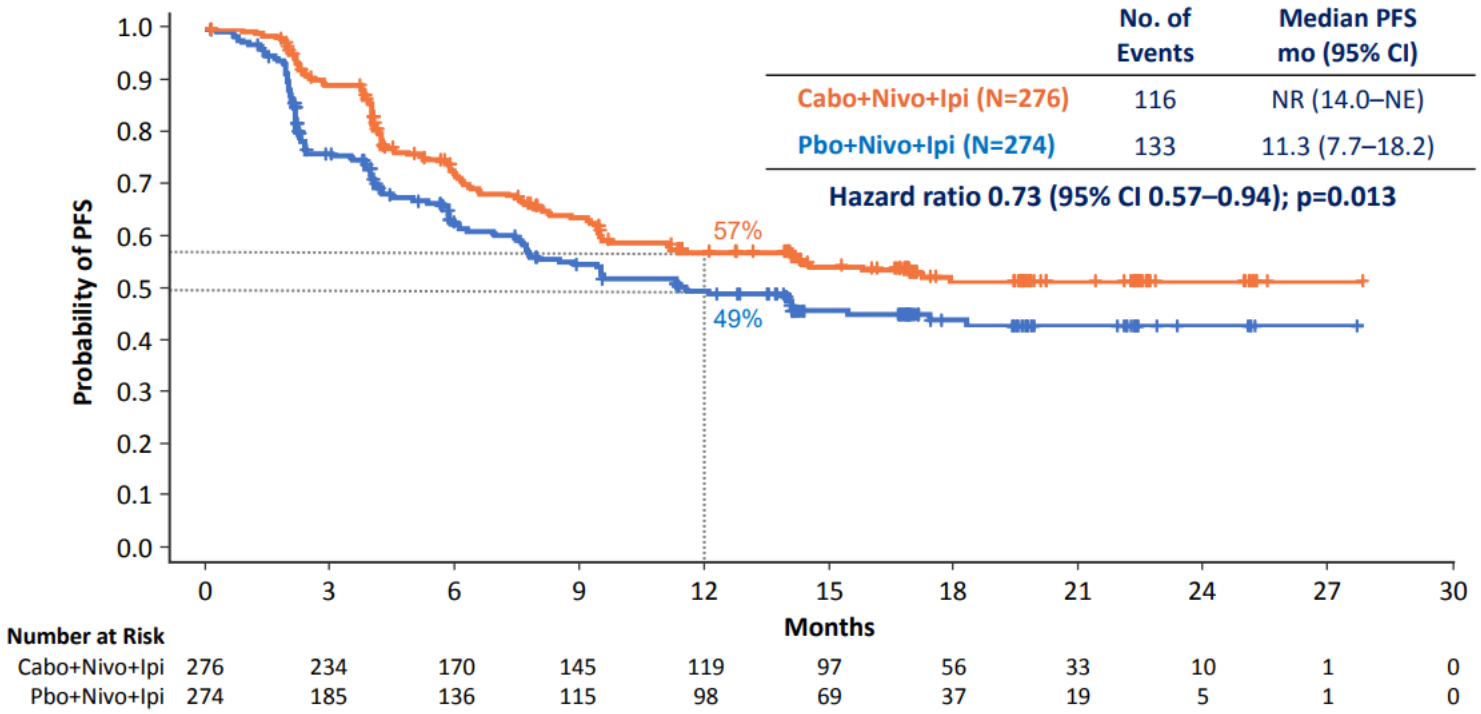
Baseline Characteristics

Characteristic	Cabozantinib + Nivolumab + Ipilimumab (n = 428)	Placebo + Nivolumab + Ipilimumab (n = 427)
Median age, yr (range)	61 (19-85)	60 (28-87)
Male, %	76	73
Region, %		
• US, Canada, Europe, Australia, New Zealand	65	65
• Latin America, Asia	35	35
IMDC intermediate/poor risk, %	75/25	75/25
Tumor PD-L1 status, %		
• <1%	64	62
• ≥1%	20	22
• Indeterminate/missing	17	16

Characteristic	Cabozantinib + Nivolumab + Ipilimumab (n = 428)	Placebo + Nivolumab + Ipilimumab (n = 427)
Karnofsky PS 100 or 90/70 or 80, %	59/41	63/37
Prior nephrectomy, %	65	65
1/≥2 sites with target/nontarget lesions per BIRC, %	19/80	19/80
Most common target/nontarget metastatic sites per BIRC, %		
• Lung	68	71
• Lymph node	54	50
• Liver	20	19
• Bone	17	21

COSMIC-313

PFS per RECIST v1.1 by BIRC



ESMO 2022. Abstr LBA8.

COSMIC-313

Tumor Response

BIRC Analysis	Cabozantinib + Nivolumab + Ipilimumab (n = 276)	Placebo + Nivolumab + Ipilimumab (n = 274)
ORR, % (95% CI)	**43** (37.2-49.2)	**36** (30.1-41.8)
Best overall response, n (%)		
• CR	7 (3)	9 (3)
• PR	112 (41)	89 (32)
• SD	119 (43)	100 (36)
• PD	23 (8)	55 (20)
• NE	15 (5)	21 (8)
Disease control rate, %*	**86**	**72**
Median time to objective response, mo (range)	2.4 (1.5-17.1)	2.3 (1.9-16.8)
Median DoR, mo (95% CI)	NR (20.2-NE)	NR (NE-NE)

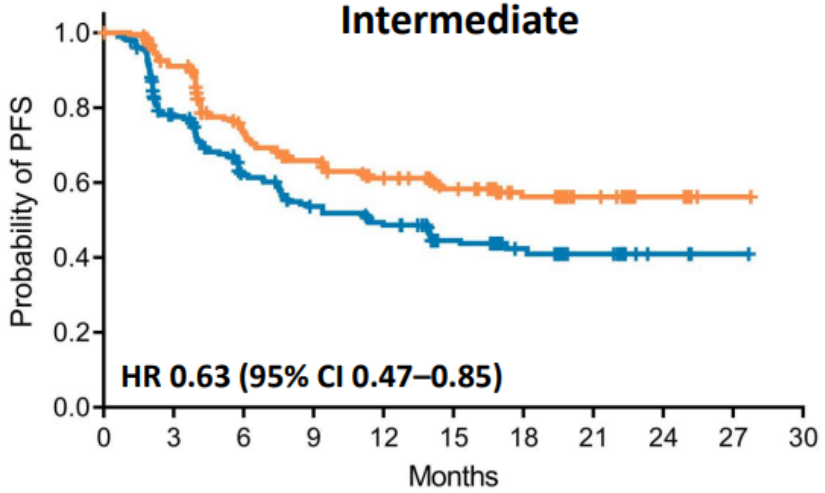
Tumor response per RECIST v1.1 by BIRC
*Disease control rate = complete response + partial response + stable disease

Data cut-off: Jan 31, 2022

COSMIC-313

PFS and ORR by IMDC Risk Group (PITT Population)

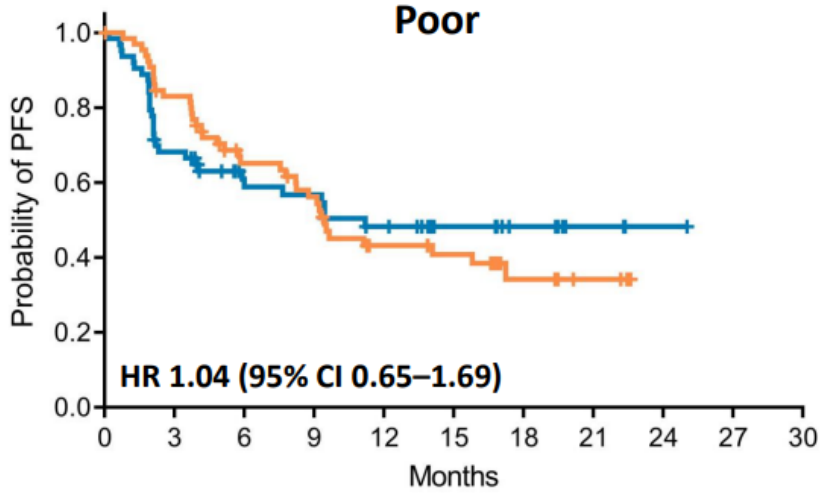
Intermediate



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=209)	79	NR (16.9–NE)
Pbo+Nivo+Ipi (N=208)	103	11.4 (7.6–17.3)

ORR: 45% (95% CI, 38.1–52.0) for Cabo+Nivo+Ipi vs 35% (95% CI, 28.6–42.0) for Pbo+Nivo+Ipi

Poor



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=67)	37	9.5 (7.8–17.3)
Pbo+Nivo+Ipi (N=66)	30	11.2 (4.0–NE)

ORR: 37% (95% CI, 25.8–50.0) for Cabo+Nivo+Ipi vs 38% (95% CI, 26.2–50.7) for Pbo+Nivo+Ipi

PFS and ORR per RECIST v1.1 by BIRC. IMDC risk group is per IxRS

Date of the 249th PFS event: Aug 23, 2021
Data cut-off for ORR: Jan 31, 2022

COSMIC-313

Treatment Exposure and Discontinuation

Parameter	Cabozantinib + Nivolumab + Ipilimumab (n = 426)	Placebo + Nivolumab + Ipilimumab (n = 424)
Median exposure to study treatment, mo (range)	10.9 (0.2-28.5)	10.3 (0.1-28.1)
Median average daily dose of Cabo or Pbo, mg (range)	23.2 (3.6-40.0)	36.1 (0.8-40.0)
Median number of Nivo infusions (range)	10 (1-27)	9 (1-27)
Doses of Ipi received, %		
• 4	58	73
• 3	13	14
• 2	22	7
• 1	7	6

Parameter	Cabozantinib + Nivolumab + Ipilimumab (n = 426)	Placebo + Nivolumab + Ipilimumab (n = 424)
Any dose hold due to AE, %	90	70
Any dose reduction of cabozantinib or placebo due to AE, %	54	20
Treatment-related AE leading to discontinuation, %		
• Any study treatment	45	24
• Cabo or Pbo	28	14
• Nivo	26	18
• Ipi	30	12
• All treatment components (due to same AE)	12	5

PFS and ORR per RECIST v1.1 by BIRC. IMDC risk group is per IxRS

Date of the 249th PFS event: Aug 23, 2021
Data cut-off for ORR: Jan 31, 2022

COSMIC-313

Safety Summary

TRAEs, %	Cabozantinib + Nivolumab + Ipilimumab (n = 426)		Placebo + Nivolumab + Ipilimumab (n = 424)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any event occurring in ≥20% in either group	99	73	91	41
• Alanine aminotransferase increased	46	26	17	6
• Aspartate aminotransferase increased	44	20	16	5
• Diarrhea	41	4	18	3
• Palmar–plantar erythrodysesthesia	28	3	4	0
• Hypothyroidism	24	<1	15	0
• Hypertension	23	8	5	2
• Fatigue	22	2	21	1
• Lipase increased	22	9	13	6
• Amylase increased	20	5	12	2
• Rash	20	2	20	1
• Pruritis	20	0	26	<1

- Grade 5 TRAEs:
  - ≤30 days after last dose: 3 patients (1%) in cabozantinib + nivolumab + ipilimumab arm (gastrointestinal hemorrhage, hepatic failure, respiratory failure) and 3 patients (1%) in placebo + nivolumab + ipilimumab arm (renal failure, myocarditis, sudden death)
  - Through 100 days after last dose: 2 patients in cabozantinib + nivolumab + ipilimumab arm (immune-mediated hepatitis and hepatic failure) and 1 patient in placebo + nivolumab + ipilimumab arm (perforated ulcer)
- 58% and 35% of patients in cabozantinib + nivolumab + ipilimumab vs placebo + nivolumab + ipilimumab arms, respectively, used high-dose corticosteroids (≥40 mg of prednisone or equivalent) for AEs

SUMMARY

COSMIC-313

- The triplet combination of cabozantinib with nivolumab plus ipilimumab demonstrated a significant benefit in PFS for previously untreated patients with advanced RCC of IMDC intermediate or poor risk versus the doublet of nivolumab and ipilmumab
  - The first study to use an immuno-oncology doublet standard of care as the control group
  - Subgroup analysis were consistent with greater benefit in the cabozantinib with nivolumab plus ipilimumab arm
  - Benefit greater for IMDC intermediate vs poor risk
- Improved ORR and disease control rate with cabozantinib with nivolumab plus ipilimumab
- Safety profile consistent with the individual treatment components; increase in some adverse events in the triplet versus the doublet as expected

ESMO 2022. Abstr LBA9.

COSMIC-313

The additional of cabozantinib to nivolumab and ipilimumab provided benefit in previously untreated patients with IMDC intermediate or poor risk advanced RCC

More to come…OS follow-up ongoing

2022 ESMO Key Studies

Breast and Gynecological Cancer

- TROPiCS-02
- MONARCH 3
- SOLO1
- PAOLA-1

Lung Cancer

- CodeBreaK 200*
- IPSOS*
- DESTINY-Lung02
- CheckMate-816
- NADIM II‡
- IMpower010‡

GU/GI and Other Cancer

- NICHE-2*
- RADICALS-HD*
- COSMIC-313*
- EV-103 K
- EXPLORER/PATHFINDER

*ESMO Presidential Symposium
‡WCLC 2022

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CLINICAL QUESTION

EV-103

Does enfortumab vedotin with or without pembrolizumab provide benefit to 1L cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer?

Cohort K

On July 9, 2021, the FDA approved enfortumab vedotin-ejfv (Padcev) for adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 or programmed death-ligand inhibitor and platinum-containing chemotherapy, or are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy

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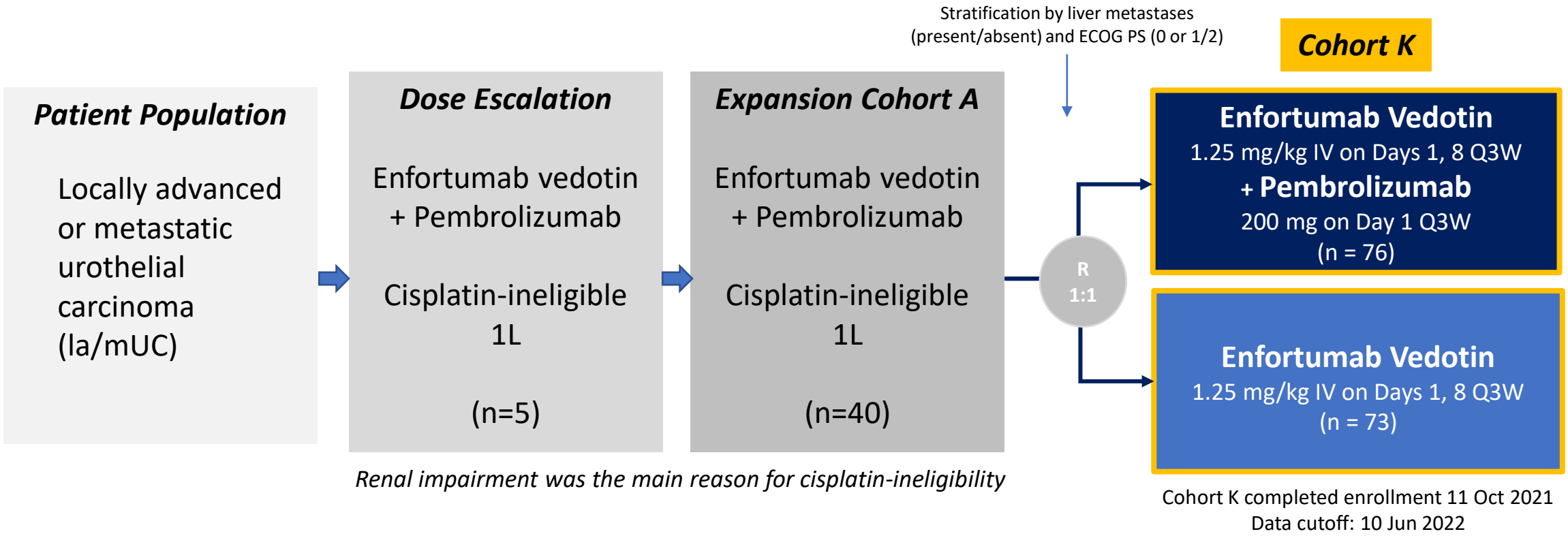
KEY DATA

EV-103

Study Design: open-label, multiple cohort, phase Ib/2 study



Renal impairment was the main reason for cisplatin-ineligibility

Cohort K completed enrollment 11 Oct 2021
Data cutoff: 10 Jun 2022

Primary endpoint: confirmed ORR by RECIST v1.1 per BICR

Secondary endpoints: confirmed ORR per RECIST v1.1 by investigator, DOR, DCR, PFS, OS, safety/ tolerability, and lab abnormalities

Exploratory endpoints: pharmacokinetics, antitherapeutic antibody, biomarkers of activity including baseline PD-L1 status and Nectin-4 expression, progression-free survival on subsequent therapy by investigator, patient reported outcomes

Statistical considerations: The sample size was based on precision of the estimate for ORR characterized by 95%CIs; No formal statistical comparisons between the 2 treatment arms

EV-103

Baseline Characteristics

Characteristic	Enfortumab Vedotin + Pembrolizumab (n = 76)	Enfortumab Vedotin (n = 73)
Male sex, n (%)	54 (71.1)	56 (76.7)
Median age, yr (range)	71 (51-91)	74 (56-89)
White race, n (%)	61 (80.3)	55 (75.3)
ECOG PS, n (%)		
• 0	33 (43.4)	28 (38.4)
• 1	33 (43.4)	35 (47.9)
• 2	10 (13.2)	10 (13.7)
Primary tumor location		
• Lower tract	46 (60.5)	51 (69.9)
• Upper tract	30 (39.5)	21 (28.8)
Metastatic disease sites, n (%)		
• Bone	19 (25.0)	21 (28.8)
• Liver	13 (**17.1**)	13 (**17.8**)
• Lung	37 (48.7)	30 (41.1)

Characteristic	Enfortumab Vedotin + Pembrolizumab (n = 76)	Enfortumab Vedotin (n = 73)
Metastasis category, n (%)		
• Lymph node only	10 (13.2)	12 (16.4)
• Visceral disease	64 (84.2)	60 (82.2)
• Not applicable*	2 (2.6)	1 (1.4)
PD-L1 status by CPS, n (%)		
• <10	44 (**57.9**)	38 (**52.1**)
• ≥10	31 (40.8)	28 (38.4)
• Not evaluable	1 (1.3)	7 (9.6)
Meeting ≥1 Galsky criterion for cisplatin ineligibility, n (%)†	76 (100)	72 (98.6)
• CrCl < 60 and ≥30 mL/min[1]	48 (**63.2**)	44 (**60.3**)
• Grade ≥2 hearing loss	11 (14.5)	11 (15.1)
• ECOG PS 2	6 (7.9)	9 (12.3)
• CrCl <60 and ≥30 mL/min[1] and grade ≥2 hearing loss	7 (9.2)	7 (9.6)
• CrCl <60 and ≥30 mL/min[1] and ECOG PS 2	4 (5.3)	1 (1.4)

EV-103

Primary Endpoint: ORR by BICR

BICR Analysis	Enfortumab Vedotin + Pembrolizumab (n = 76)	Enfortumab Vedotin (n = 73)
Confirmed ORR, n (%)	**49 (64.5)**	**33 (45.2)**
• 95% CI	52.7 – 75.1	33.5 – 57.3
Best overall response, n (%)		
• CR	8 (**10.5**)	3 (4.1)
• PR	41 (**53.9**)	30 (41.1)
• SD	17 (22.4)	25 (34.2)
• PD	6 (7.9)	7 (9.6)
• NE	3 (3.9)	5 (6.8)
• NA	1 (1.3)	3 (4.1)
Median time to objective response, mo (range)	2.07 (1.1-6.6)	2.07 (1.9-15.4)
Median number of treatment cycles (range)	11.0 (1-29)	8.0 (1-33)

<u>Enfortumab Vedotin + Pembrolizumab</u>

- 41/49 (85.7%) of responses observed at first assessment (week 9 ± 1 week)
- Confirmed ORRs were consistent across all pre-specified subgroups
- 7/13 (53.8%) of confirmed ORRs observed in patients with liver metastases

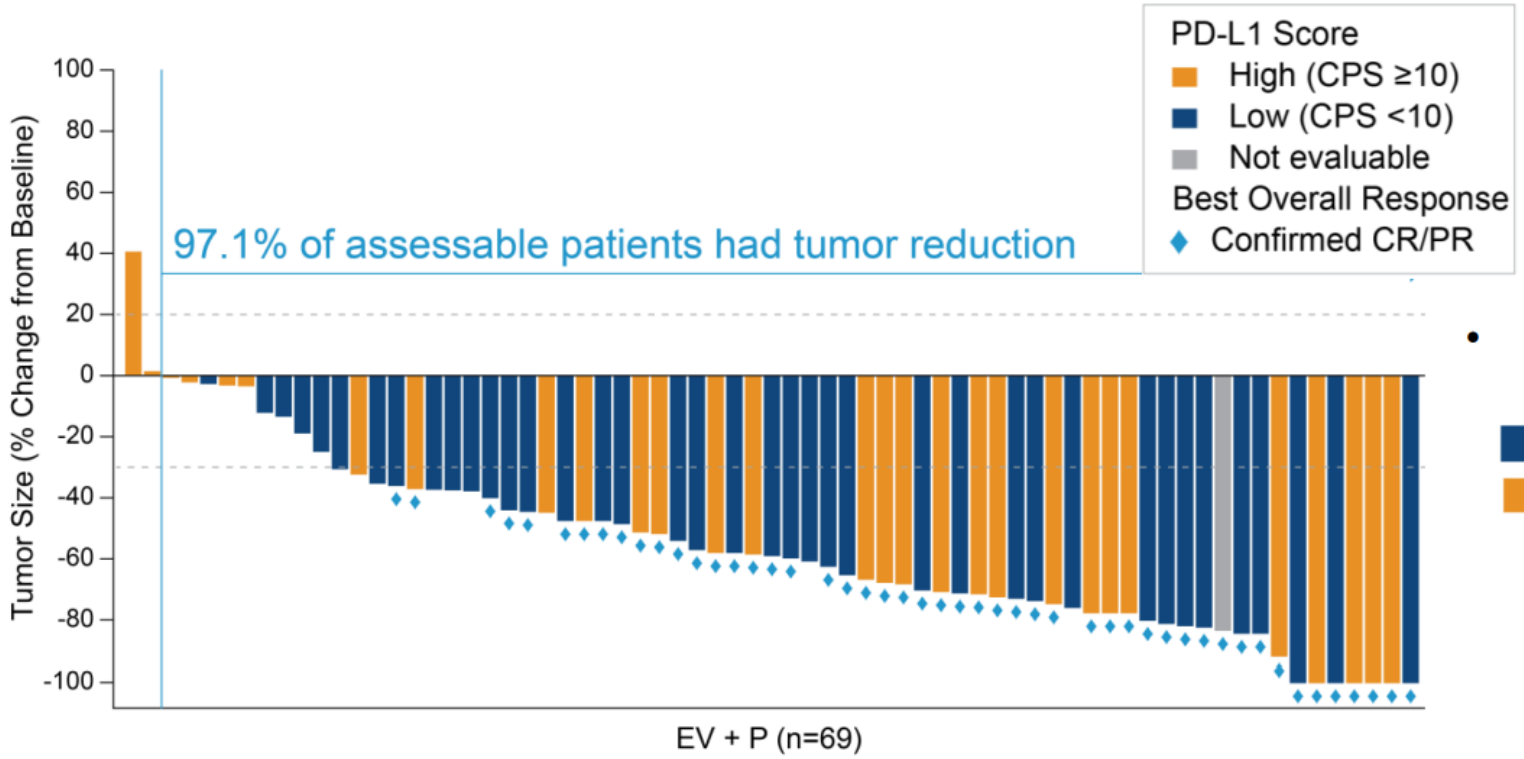
<u>Enfortumab Vedotin Monotherapy</u>

- Activity is consistent with prior results in 2L+ la/mUC

ESMO 2022. Abstr LBA73.

EV-103

Maximum percent reduction from baseline of target lesion by BICR



BICR: Blinded Independent Central Review; CPS: Combined Positive Score; CR: Complete Response; PD-L1: Programmed Death-Ligand 1 PR: Partial Response

- Activity seen regardless of PD-L1 status
  - 27/44 (61.4%) cORR in CPS<10
  - 21/31 (67.7%) cORR in CPS≥10

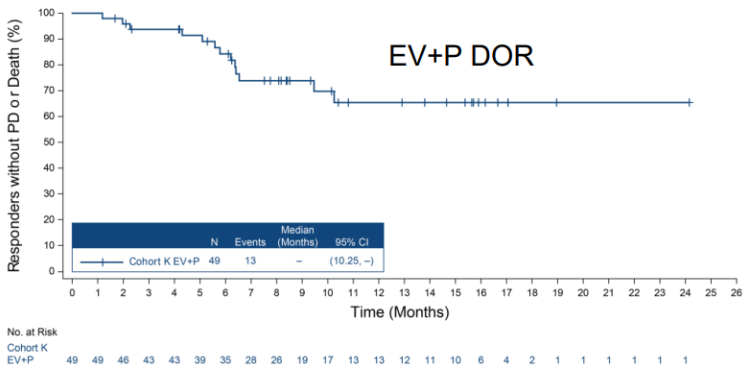
ESMO 2022. Abstr LBA73.

KEY DATA

EV-103

DOR by BICR

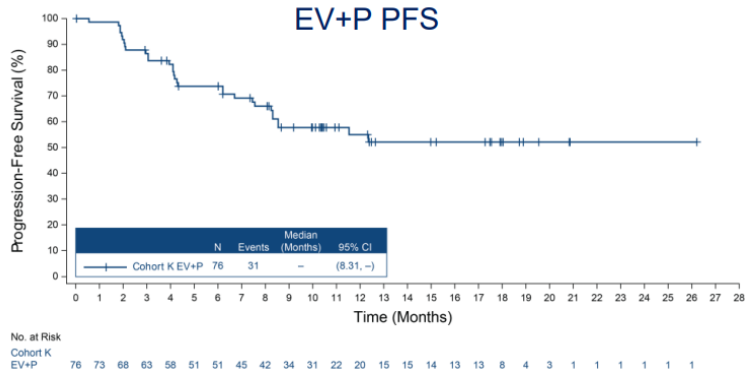
	EV + P (n = 76)	EV (n = 73)
Responders, n	49	33
Progression events, n	13	14
mDOR (95% CI), months	**NR** (10.25 - NR)	13.2 (6.14 – 15.97)
DOR ≥ 12 months, %	**65.4%**	**56.3%**



Longer follow up to come

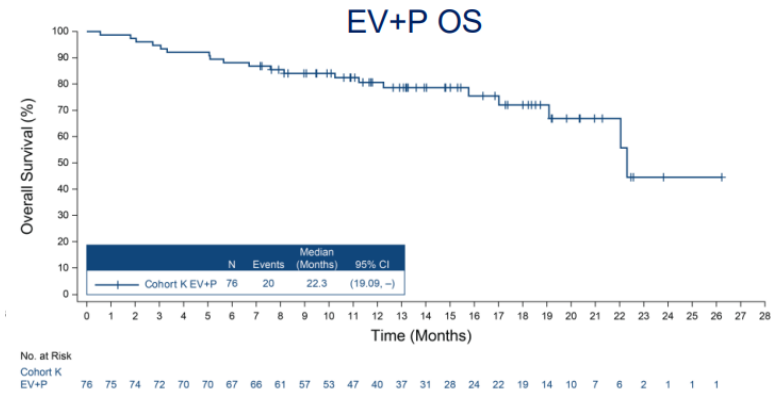
PFS by BICR

	EV + P (n = 76)	EV (n = 73)
PFS events, n	31	38
mPFS (95% CI), months	NR (8.31 – NR)	8.0 (6.05 – 10.35)
PFS at 12 months, %	55.1%	35.8%



OS

	EV + P (n = 76)	EV (n = 73)
OS events, n	20	26
mOS (95% CI), months	22.3 (19.09 – NR)	21.7 (15.21 – NR)
OS at 12 months, %	80.7%	70.7%
Median follow-up time, months	14.8	15.0



ESMO 2022. Abstr LBA73.

EV-103

Treatment-related Adverse Events (TRAEs)

TRAEs in ≥20% of Patients, n (%)	Enfortumab Vedotin + Pembrolizumab (n = 76)		Enfortumab Vedotin (n = 73)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Overall	76 (100.0)	48 (63.2)	68 (93.2)	35 (47.9)
• Fatigue	43 (56.6)	7 (9.2)	29 (39.7)	6 (8.2)
• Peripheral Sensory Neuropathy	39 (51.3)	1 (1.3)	32 (43.8)	2 (2.7)
• Alopecia	35 (46.1)	0	26 (35.6)	0
• Maculopapular rash	35 (46.1)	13 (17.1)	21 (28.8)	1 (1.4)
• Pruritis	30 (39.5)	3 (3.9)	19 (26.0)	1 (1.4)
• Dysgeusia	23 (30.3)	0	25 (34.2)	0
• Weight decreased	23 (30.3)	3 (3.9)	21 (28.8)	1 (1.4)
• Diarrhea	22 (28.9)	5 (6.6)	20 (27.4)	4 (5.5)
• Decreased appetite	20 (26.3)	0	28 (38.4)	0
• Nausea	19 (25.0)	0	25 (34.2)	1 (1.4)
• Dry eye	15 (19.7)	0	8 (11.0)	0

Serious TRAEs

- EV + P: 18 (23.7%)
- EV: 11 (15.1%)

TRAEs leading to death, per investigator

- EV + P: 3 (3.9%)
  - Pneumonitis, respiratory failure, sepsis
- EV: 2 (2.7%)
  - Multiple organ dysfunction, respiratory failure

No new safety signals observed: mostly grade 1 or 2

ESMO 2022. Abstr LBA73.

KEY DATA

EV-103

TRAEs of Special Interest* With EV

AE, n (%)	EV + P (n = 76)		EV (n = 73)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Skin reactions	51 (67.1)	16 (21.1)	33 (45.2)	6 (8.2)
Peripheral neuropathy	46 (60.5)	2 (2.6)	40 (54.8)	2 (2.7)
Ocular disorders				
• Dry eye	20 (26.3)	0	21 (28.8)	0
• Blurred vision	18 (23.7)	0	9 (12.3)	0
	9 (11.8)	0	10 (13.7)	0
• Corneal disorders	0	0	4 (5.5)	0
Hyperglycemia	11 (14.5)	5 (6.6)	8 (11.0)	7 (9.6)
Infusion-related reactions	3 (3.9)	0	4 (5.5)	0

Note: *Differences in rates of skin reactions with enfortumab vedotin treatment-related AESIs and pembrolizumab TEAEs of special interest due to using different reporting methodologies developed for these agents.

TEAEs of Special Interest With Pembro

TEAE, n (%)	EV + P(n = 76)	
	Any Grade	Grade ≥3
Severe skin reactions	21 (27.6)	15 (19.7)
Hypothyroidism	10 (13.2)	0
Pneumonitis	7 (9.2)	4 (5.3)
Adrenal insufficiency	3 (3.9)	0
Colitis	3 (3.9)	1 (1.3)
Hyperthyroidism	3 (3.9)	0
Infusion reactions	3 (3.9)	0
Hepatitis	2 (2.6)	2 (2.6)
Myasthenic syndrome	2 (2.6)	2 (2.6)
Myositis	2 (2.6)	0
Pancreatitis	2 (2.6)	1 (1.3)
Hypophysitis	1 (1.3)	0
Myocarditis	1 (1.3)	0
Nephritis	1 (1.3)	1 (1.3)
Thyroiditis	1 (1.3)	0

ESMO 2022. Abstr LBA73.

SUMMARY

EV-103

- Enfortumab vedotin + pembrolizumab showed promising activity in 1L cisplatin ineligible patients with la/mUC
- ORR by BICR: 64.5%
- Median DOR not reached
- PFS and OS expected to continue to evolve
- No new safety concerns emerged
  - Safety profile for EV+P was manageable, including skin reactions and peripheral neuropathy

ESMO 2022. Abstr LBA73.

EV-103

Enfortumab vedotin in combination with pembrolizumab has the potential to become a 1L treatment option for patients with la/mUC

More to come…

2022 ESMO Key Studies

Breast and Gynecological Cancer

- TROPiCS-02
- MONARCH 3
- SOLO1
- PAOLA-1

Lung Cancer

- CodeBreaK 200*
- IPSOS*
- DESTINY-Lung02
- CheckMate-816
- NADIM II‡
- IMpower010‡

GU/GI and Other Cancer

- NICHE-2*
- RADICALS-HD*
- COSMIC-313*
- EV-103 K
- EXPLORER/PATHFINDER

*ESMO Presidential Symposium
‡WCLC 2022

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Does avapritinib benefit patients with advanced Systemic Mastocytosis (SM)?

Advanced systemic mastocytosis (AdvSM) is a rare myeloproliferative neoplasm commonly distinguished by the accumulation of neoplastic mast cells in bone marrow and other tissues and organs
The majority (>90%) of patients with AdvSM harbor the KIT D816V mutation

On June 16, 2021, the Food and Drug Administration approved avapritinib (Ayvakit™) for adult patients with advanced systemic mastocytosis (AdvSM), including patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL)

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EXPLORER/PATHFINDER

Study Design: Multicenter, observational and retrospective study

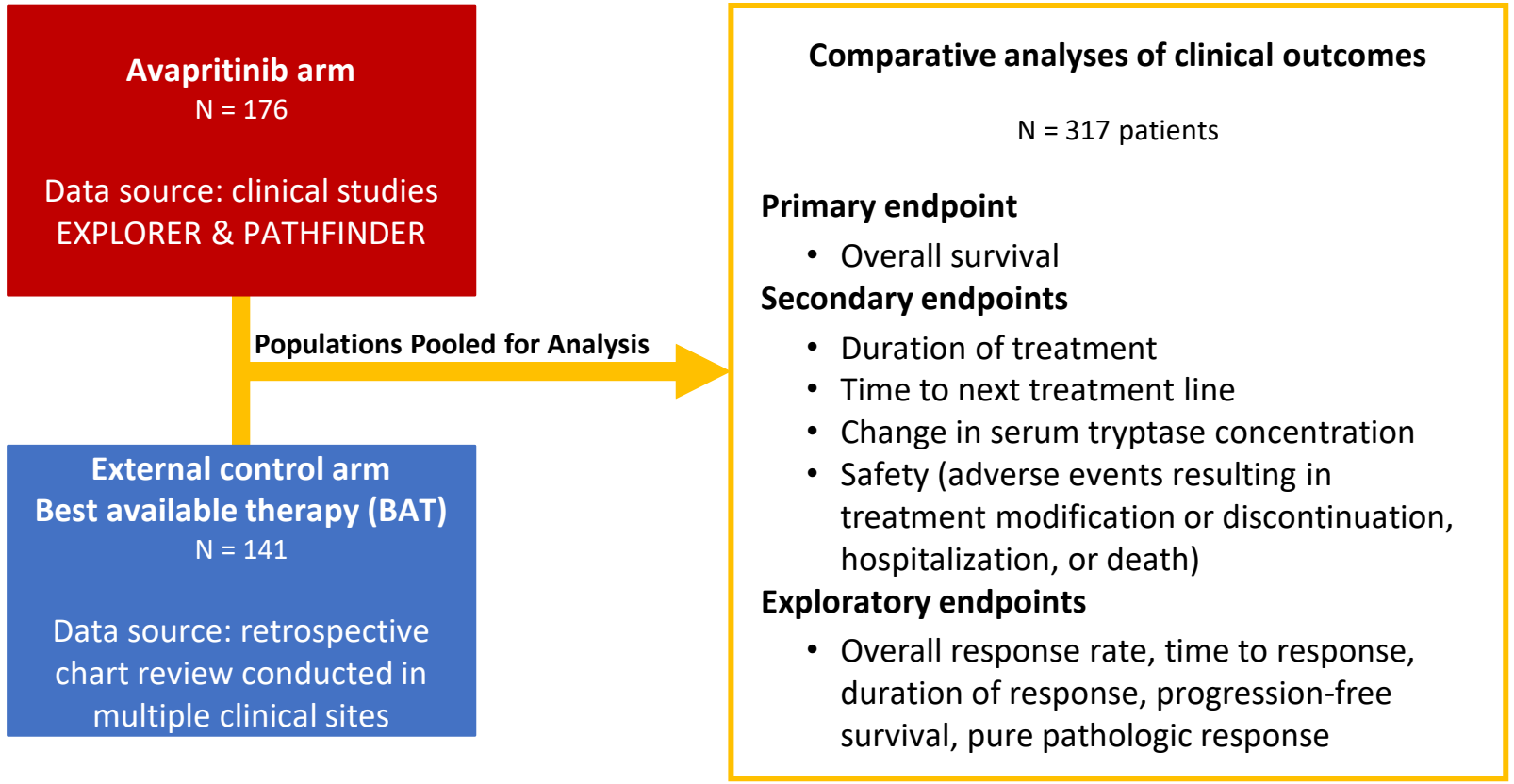
Real-world patients treated with best available therapy (BAT) were identified based on inclusion and exclusion criteria similar to those from EXPLORER and PATHFINDER single-arm trials.

Inclusion criteria

- Adults (aged ≥18 years) with a diagnosis of AdvSM and documented subtype in their chart (ASM, SM-AHN, or MCL)
- Received ≥1 line of systemic therapy (not necessarily as first line) for AdvSM at a participating site on or after January 1, 2009
- The date of initiation of each line of therapy at the participating site was defined as the index date
- Had an index date ≥3 months prior to the start of data collection, unless earlier death

Exclusion

- History of another primary malignancy that was diagnosed or required therapy within 3 years before the index date (excluding completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, and completely resected carcinoma *in situ* in any site)
- Received avapritinib as the first therapy for AdvSM at a participating site



Reiter A, et al. Efficacy of Avapritinib versus Best Available Therapy for AdvSM. Leukemia. Published Online 2022.

KEY DATA

EXPLORER/PATHFINDER

Baseline Characteristics

	IPTW-weighted sample		
	Avapritinib	BAT	Standardized Difference[1]
Number of unique patients	**Effective N = 172**	**Effective N = 134[2]**	
Number of lines of therapy	**Effective N = 172**	**Effective N = 210**	
Age (years), mean (SD)	66.4 (10.5)	65.3 (12.4)	9.2%
Male, n (%)	60.0%	62.6%	5.3%
ECOG category, n (%)			
0	16.3%	19.2%	7.4%
1	59.0%	56.2%	5.8%
≥2	24.6%	24.7%	0.1%
Anemia, n (%)	55.4%	57.8%	5.0%
Thrombocytopenia, n (%)	38.9%	43.9%	10.2%*
AdvSM subtype diagnosis, n (%)			
SM-AHN	58.4%	58.2%	0.5%
ASM	26.5%	25.2%	3.0%
MCL	15.1%	16.6%	4.3%
Any skin involvement, n (%)	30.3%	32.5%	4.8%
Leukocyte count ≥16 × 10^9/L, n (%)	18.5%	19.8%	3.3%
Serum tryptase[10] ≥125 ng/mL, n (%)	72.5%	71.0%	3.2%
SRSF2/ASXL1/RUNX1 (S/A/R) mutation panel testing	100% of patients tested	70.8% of patients tested	
Number of mutated genes within panel, n (%) 0	55.3%	26.7%	
1	28.7%	30.1%	3.1%
≥2	16.0%	13.9%	5.8%
Number of prior lines of systemic therapy received			
0	47.2%	50.4%	6.4%
1	33.1%	32.4%	1.5%
2	14.6%	12.6%	5.6%
≥3	5.1%	4.6%	2.7%
Prior treatments received, n (%)			
TKI therapy	37.1%	29.9%	15.2%*
Cytotoxic therapy	20.1%	22.1%	4.8%
Biologic or other systemic therapy	14.9%	15.2%	0.7%

Unweighted BAT sample	
Number of unique patients	**N = 141**
Number of lines of therapy	**N = 222**
Agents used in each included line of therapy,[1] n (%)	
TKI therapy	120 (54.1%)
Cytotoxic therapy	91 (41.0%)
Biologic therapy	25 (11.3%)
Agent-level information available[1]	**N = 196**
TKI	
Midostaurin	99 (50.5%)
Dasatinib	2 (1.0%)
Ibrutinib	3 (1.5%)
Imatinib	2 (1.0%)
Ripretinib	4 (2.0%)
Cytotoxic therapy	
Cladribine	49 (25.0%)
Azacitidine	3 (1.5%)
Hydroxyurea	17 (8.7%)
Biologic	
Brentuximab vedotin	4 (2.0%)
Gemtuzumab ozogamicin	1 (0.5%)
Interferon-alpha	11 (5.6%)
Pegylated interferon	8 (4.1%)

KIT mutation

- Patients tested, n (%): Avapritinib vs BAT
  - 170 (96.6%) vs 140 (99.3%)
- Tested positive for KIT D816V, n (%): Avapritinib vs BAT
  - 156 (91.8%) vs 128 (91.4%)

Abbreviations: *ASM, aggressive mastocytosis; ECOG, Eastern Cooperative Oncology Group; IPTW, inverse probability of treatment weighting; MCL, mast cell leukemia; SD, standard deviation; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm, TKI, tyrosine-kinase inhibitor.*

Notes:

1. A standardized difference of greater than 10% indicates meaningful imbalance between the two cohorts even after IPTW, denoted by a star (
2. Real-world patients with unknown ECOG score were excluded (N=20).

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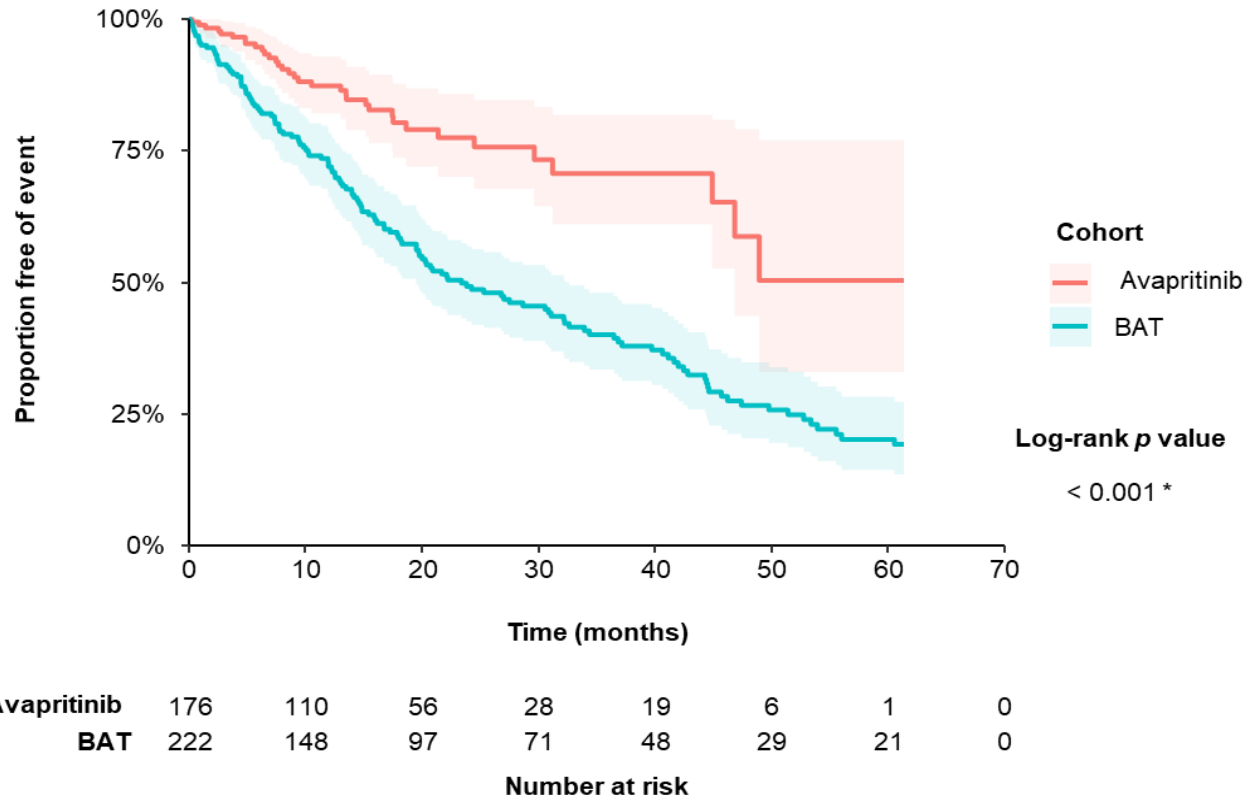
Primary Endpoint: Overall Survival



Overall Survival (OS) weighted by IPTW	Avapritinib	BAT
Number of unique patients	Effective N=172	Effective N=136
Number of lines of therapy	Effective N=172	Effective N=210
Median OS, months (95% CI)	**49.0** (46.9, NE)	**26.8** (18.2, 39.7)
Adjusted HR (95% CI)	**0.48** (0.29, 0.79)	
p value	0.004*	

OS rates were higher among avapritinib patients at all time points:

- 6 months: 96.4% vs. 84.8%
- 12 months: 86.4% vs. 73.8%
- 24 months: 74.6% vs. 50.9%
- 36 months: 68.0% vs. 42.7%
- 48 months: 61.9% vs. 30.0%

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KEY DATA

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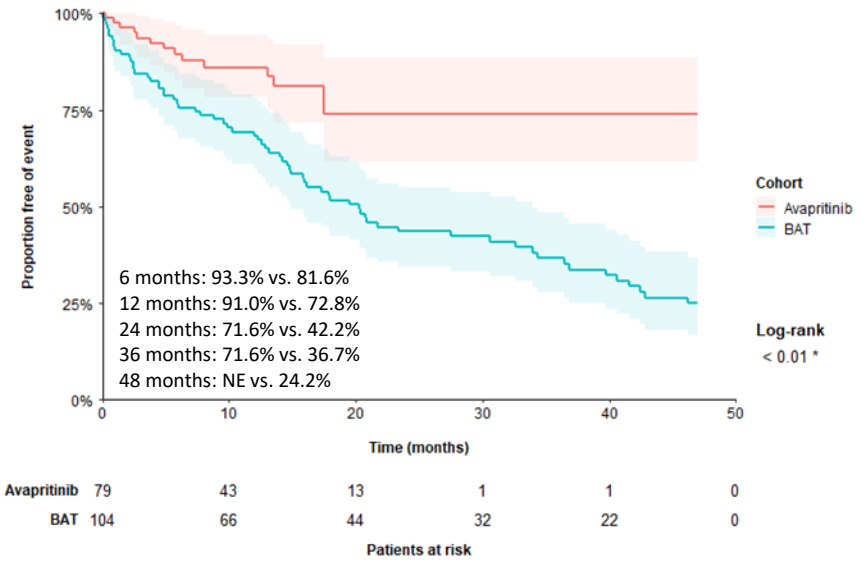
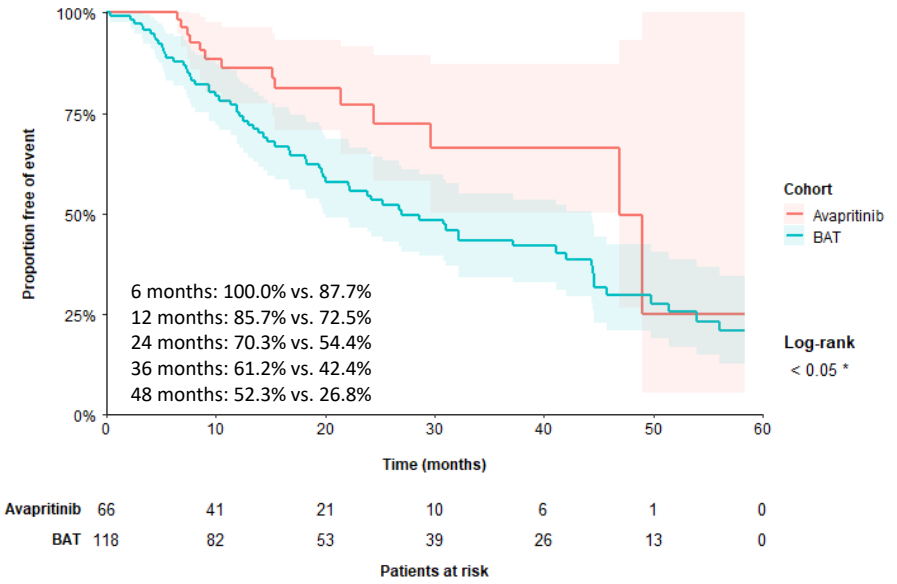
Adjusted OS rates were higher with avapritinib vs. BAT amongst pre-treated AdvSM patients

at least one prior line of therapy



Overall Survival (OS) weighted by IPTW	Avapritinib	BAT
Number of unique patients	Effective N=77	Effective N=66
Number of lines of therapy	Effective N=77	Effective N=96
Mean follow-up time, months	12.6	25.2
Median OS, months (95% CI)	NR (NE, NE)	17.2 (14.6, 36.5)
Adjusted HR (95% CI)	**0.37** (0.18, 0.75)	
p value	0.006	

Adjusted OS rates were higher with avapritinib vs. BAT amongst AdvSM patients receiving 1st line therapies



Overall Survival (OS) weighted by IPTW	Avapritinib	BAT
Number of unique patients	Effective N=62	Effective N=115
Number of lines of therapy	Effective N=62	Effective N=115
Mean follow-up time, months	17.8	26.1
Median OS, months (95% CI)	49.0 (29.6, NE)	27.0 (19.7, 44.3)
Adjusted HR (95% CI)	**0.40** (0.22, 0.74)	
p value	0.003	

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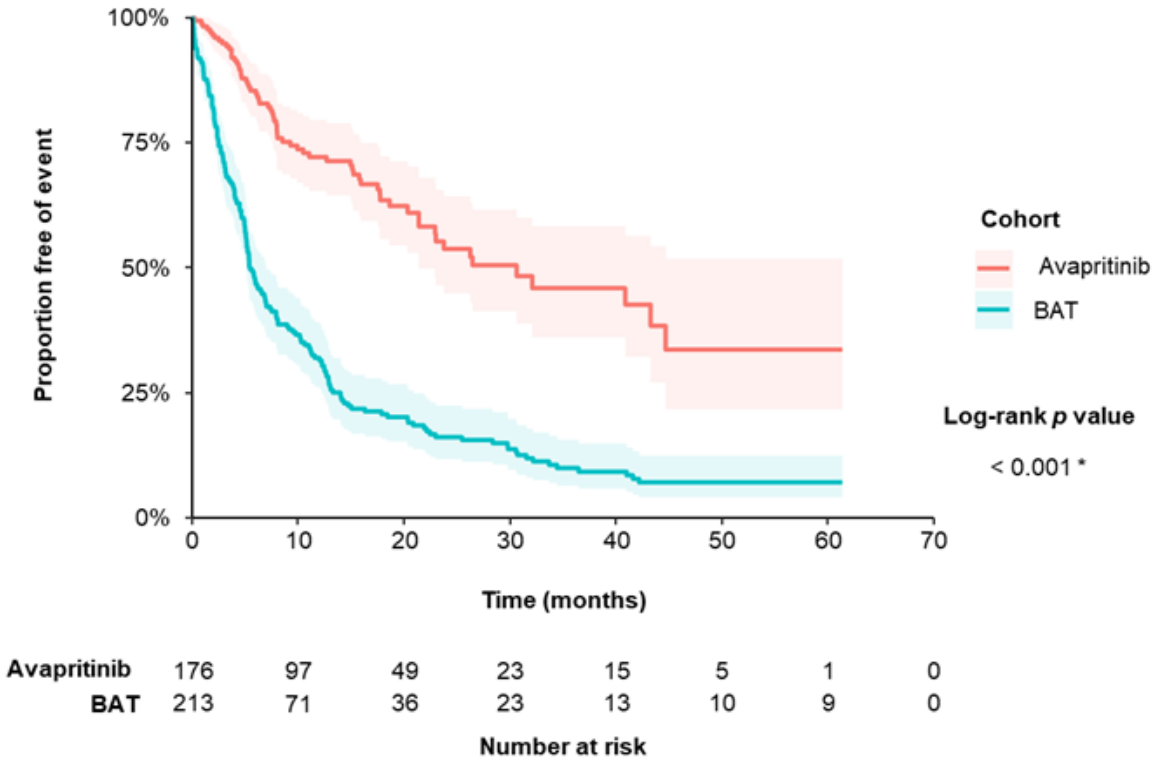
Duration of Treatment



Duration of Treatment (DOT) weighted by IPTW	Avapritinib	BAT
Number of unique patients	Effective N=173	Effective N=131
Number of lines of therapy	Effective N=173	Effective N=201
Median DOT, months (95% CI)	23.8 (20.3, 40.9)	5.4 (5.0, 7.5)
Adjusted HR (95% CI)	**0.36** (0.26, 0.51)	
p value	<0.001*	

Rates of ongoing response were higher for the avapritinib cohort versus BAT cohort at all time points:

- 6 months: 85.6% vs. 45.0%
- 12 months: 67.7% vs. 32.5%
- 24 months: 48.8% vs. 16.1%
- 36 months: 34.7% vs. 11.1%
- 48 months: 24.7% vs. 8.2%

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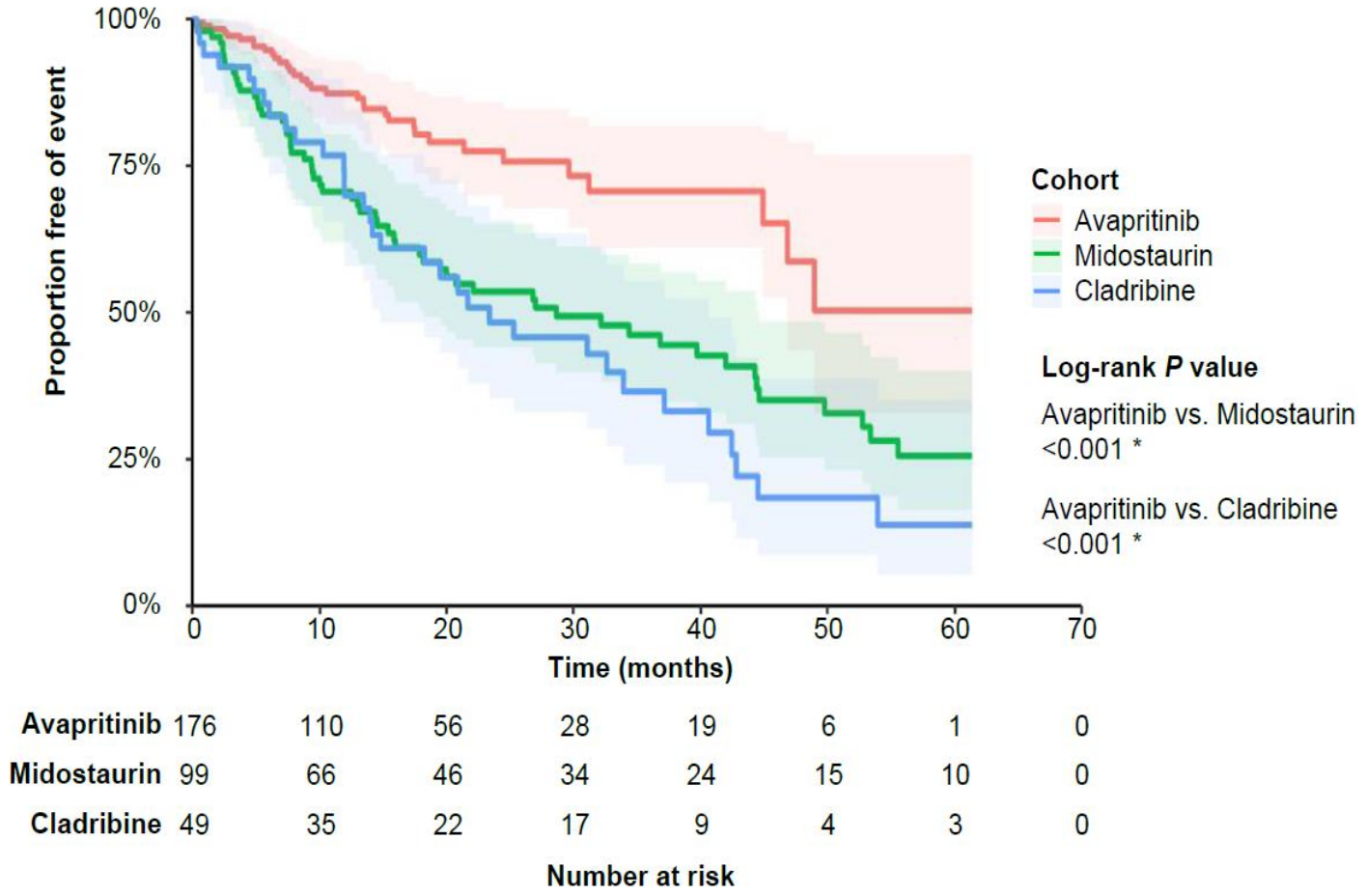
OS was significantly improved in Avapritinib vs. Midostaurin or Cladribine



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Reduction in serum tryptase levels

Maximum Reduction in Serum Tryptase Weighted by IPTW	Avapritinib	BAT
Number of unique patients	Effective N=173	Effective N=106
Number of lines of therapy	Effective N=173	Effective N=150
Absolute reduction	-278.4 (245.8)	-114.7 (245.1)
Percentage reduction	-87.1 (17.2)	-18.0 (123.9)
Adjusted mean difference in percentage change (95% CI)	**-60.34** (-72.81 – -47.86)	
p value	**<0.001***	
Time to maximum reduction, mean months	8.8	8.5

Abbreviations: *CI, confidence interval; IPTW, inverse probability of treatment weighting; HR, hazard ratio.*
 # Negative values indicated reduction.
** p* value less than 0.05.

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SUMMARY

EXPLORER/PATHFINDER

- Patients with advanced SM treated with avapritinib (200 mg orally once daily) compared to patients treated with best available therapy experienced:
  - Significantly improved overall survival
  - Longer duration of treatment
  - Greater reductions in serum tryptase levels

- Monitor platelet counts
  - AYVAKIT is not recommended in patients with AdvSM with platelet counts < 50 X 10^9 /L
  - Supportive therapies recommended

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EXPLORER/PATHFINDER

Avapritinib provides benefit to patients with advanced Systemic Mastocytosis and should be considered as standard of care

Need for high sensitivity diagnostic testing: KIT D816V assay