2023 ASCO Key Studies

Breast and Gynecological Cancer

- NATALEE
- PALLAS
- PALMIRA
- SONIA
- MIRASOL

GU/GI Cancer

- PROSPECT*
- DESTINY-CRC02
- PEACE-1
- NeoCol
- CONTACT-03

Other Notable Studies

- ADAURA*
- INDIGO*
- SWOG1826*
- DESTINY-PanTumor02
- COMMANDS

* Plenary Session

cornerstone specialty network™

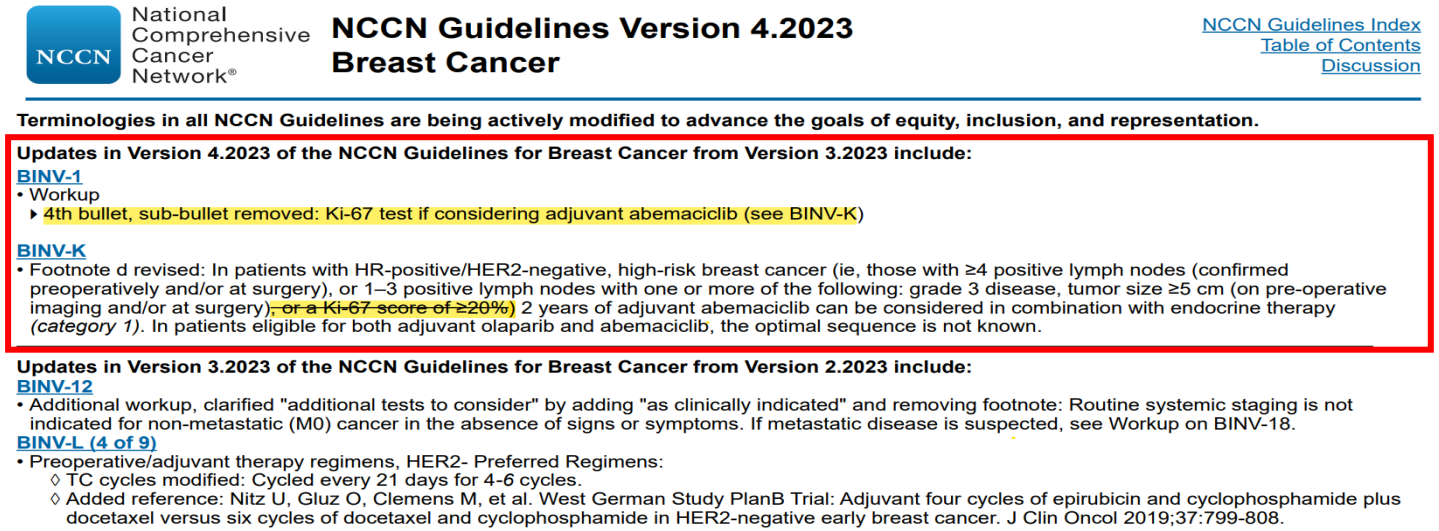
UPDATES

*On **October 12,2021**, the FDA approved abemaciclib (Verzenio, Eli Lilly and Company)with endocrine therapy (tamoxifen or an aromatase inhibitor) for adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20%, as determined by an FDA approved test.*

*On **March 3, 2023**, the Food and Drug Administration (FDA) approved abemaciclib (Verzenio, Eli Lilly and Company) with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence. Patients defined as high risk included those having either ≥4 pALN (pathologic axillary lymph nodes) or 1-3 pALN and either tumor grade 3 or a tumor size ≥50 mm.*

Abemaciclib was previously approved for the above high-risk population with the additional requirement of having a Ki-67 score ≥20%.

This new 2023 approval removes the Ki-67 testing requirement



National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2023
Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 4.2023 of the NCCN Guidelines for Breast Cancer from Version 3.2023 include:

BINV-1
- Workup
  - 4th bullet, sub-bullet removed: Ki-67 test if considering adjuvant abemaciclib (see BINV-K)

BINV-K
- Footnote d revised: In patients with HR-positive/HER2-negative, high-risk breast cancer (ie, those with ≥4 positive lymph nodes (confirmed preoperatively and/or at surgery), or 1–3 positive lymph nodes with one or more of the following: grade 3 disease, tumor size ≥5 cm (on pre-operative imaging and/or at surgery)~~, or a Ki-67 score of ≥20%~~) 2 years of adjuvant abemaciclib can be considered in combination with endocrine therapy *(category 1)*. In patients eligible for both adjuvant olaparib and abemaciclib, the optimal sequence is not known.

Updates in Version 3.2023 of the NCCN Guidelines for Breast Cancer from Version 2.2023 include:

BINV-12
- Additional workup, clarified "additional tests to consider" by adding "as clinically indicated" and removing footnote: Routine systemic staging is not indicated for non-metastatic (M0) cancer in the absence of signs or symptoms. If metastatic disease is suspected, see Workup on BINV-18.

BINV-L (4 of 9)
- Preoperative/adjuvant therapy regimens, HER2- Preferred Regimens:
  - ◊ TC cycles modified: Cycled every 21 days for 4-*6* cycles.
  - ◊ Added reference: Nitz U, Gluz O, Clemens M, et al. West German Study PlanB Trial: Adjuvant four cycles of epirubicin and cyclophosphamide plus docetaxel versus six cycles of docetaxel and cyclophosphamide in HER2-negative early breast cancer. J Clin Oncol 2019;37:799-808.

KEY QUESTIONS

CDK4/6 inhibitors

1. *Do all adjuvant CDK4/6 inhibition therapies benefit patients?*
2. *What to do after tumor progression on CDK4/6 inhibition and endocrine therapy?*
3. *Should a CDK4/6 inhibitor be combined with endocrine therapy for 1L or wait until 2L for metastatic breast cancer?*

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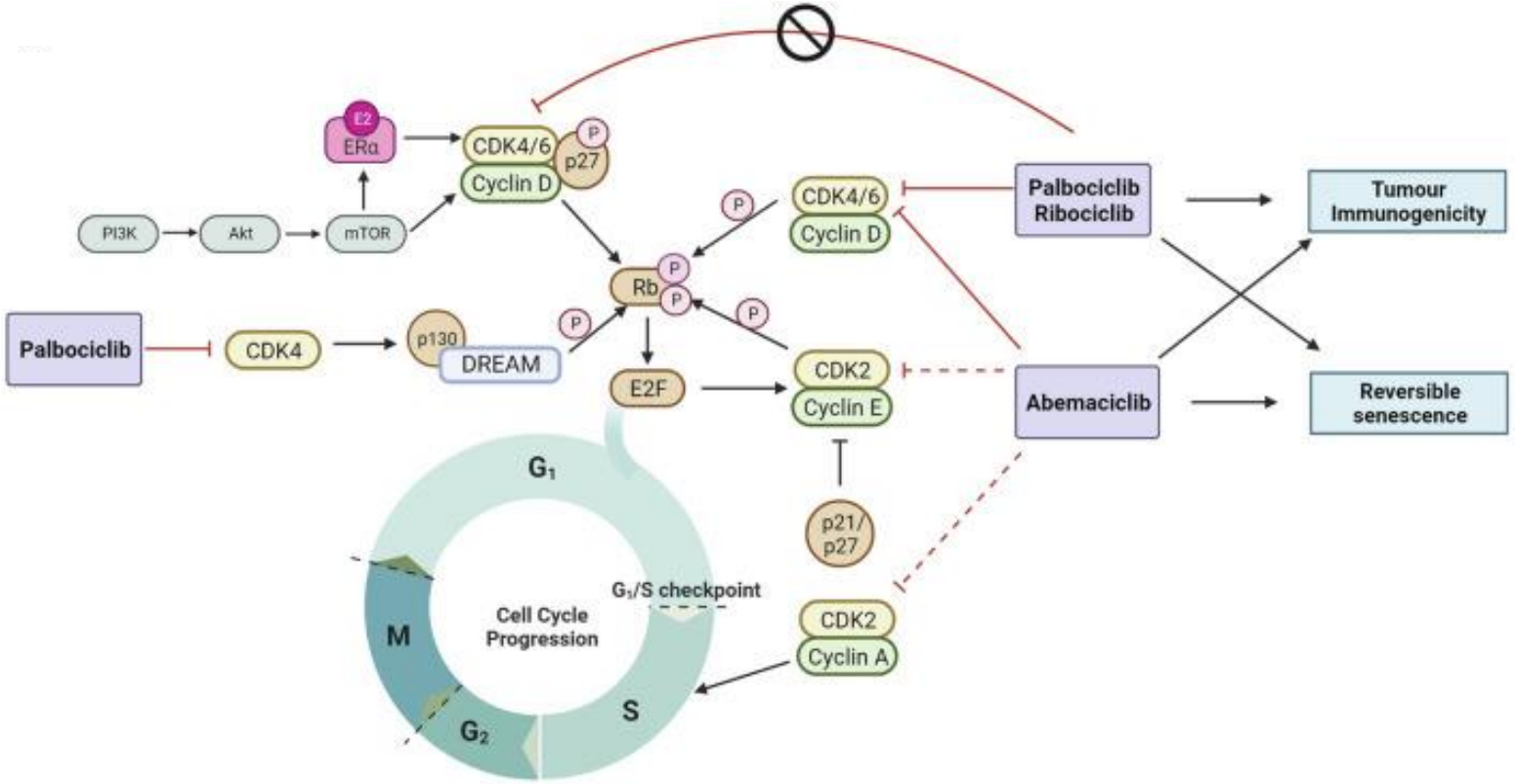
MOA



- CDK4/6 inhibitors act to block the cell cycle progression to DNA synthesis S phase and G2 phase but cannot inhibit tyrosine kinase phosphorylated p27-CDK4/6-CycD complexes in ER + breast cancer (Guiley et al., 2019; Hafner et al., 2019; Schade et al., 2019; Pack et al., 2021).
- Non-cell cycle effects of CDK4/6 inhibition include reversible senescence (Thangavel et al., 2011; Torres-Guzman et al., 2017; Vijayaraghavan et al., 2017; Marinelli et al., 2020; Maskey et al., 2021; Mayayo-Peralta et al., 2021) and enhanced tumor immunogenicity (Goel et al., 2017; Peuker et al., 2022)

Zhou et al., Front cell Dev Biol 2023; 11; 1148792 CDK4/6 inhibitor resistance in estrogen receptor positive breast cancer, a 2023 perspective
doi: 10.3389/fcell.2023.1148792

NATALEE

1. Does adding adjuvant ribociclib (Kisqali®) provide benefit to patients with Stage II-III HR+/HER2- early breast cancer?

NATALEE

Study Design: International, randomized, open-label phase III trial

Stratified by stage (II vs III), menopausal status (men and premenopausal vs postmenopausal women), prior (neo)adjuvant CT (yes vs no), geography (N America/W Europe/Oceania vs rest of world)

- Pre/postmenopausal women and men with HR+/HER2- EBC
- Stage IIA
  - Either N0 with grade 2 and Ki-67 ≥20%, Oncotype DX RS ≥26, or high risk via genomic risk profiling, N0 with grade 3, or N1
- Stage IIB (N0 or N1)
- Stage III disease (N0, N1, N2, or N3)
- Prior ET up to 12 mo permitted, prior (neo)adjuvant CT permitted

(N = 5101)

R 1:1

Ribociclib 400 mg
PO QD for 3 wk on/1 wk off for 3 yr
+ **Non steroidal AI** for ≥5 yr
(Letrozole or anastrozole. Men and premenopausal women also received goserelin 3.6 mg/28 days)
(n = 2549)

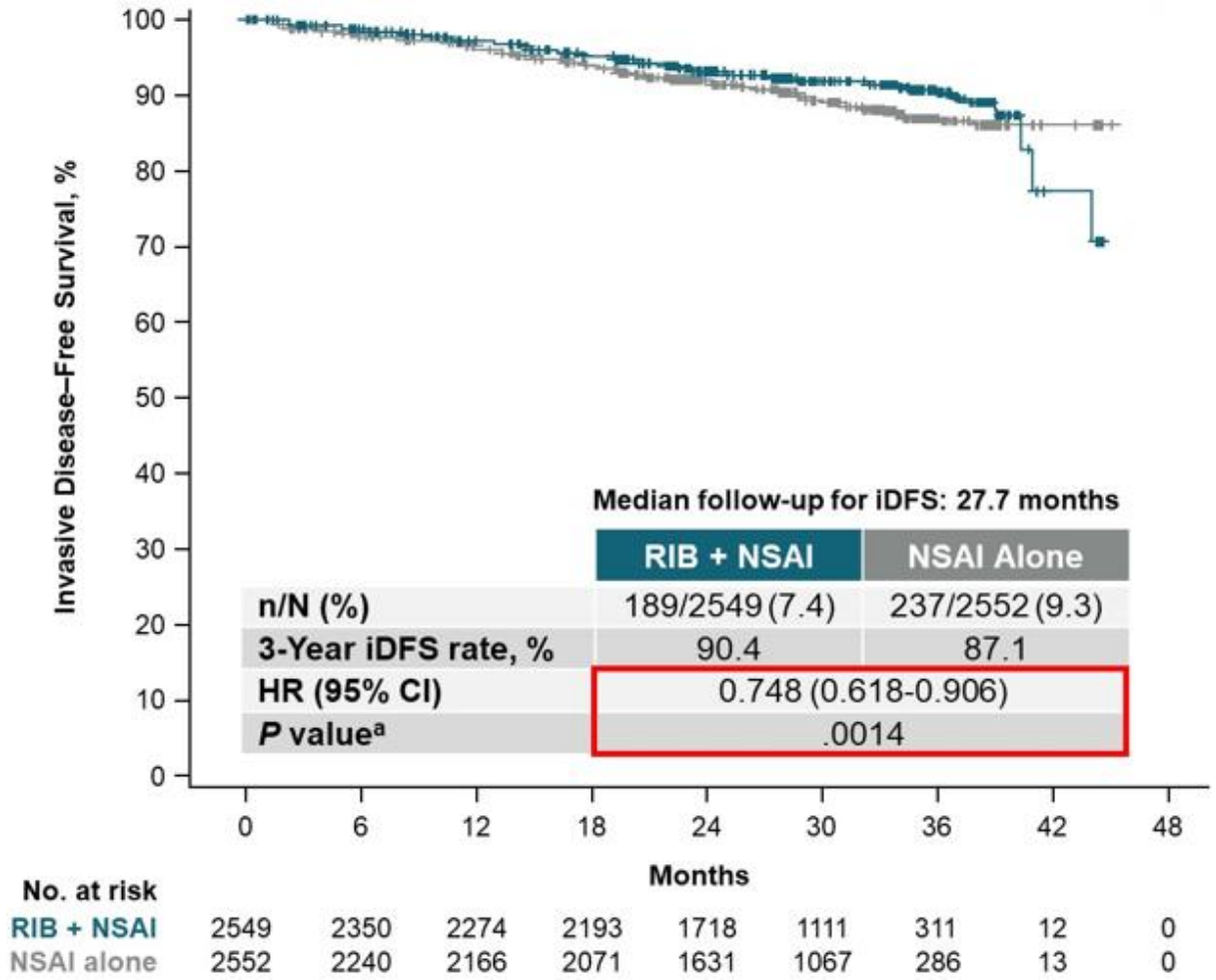
Non steroidal AI for ≥5 yr
(Letrozole or anastrozole. Men and premenopausal women also received goserelin 3.6 mg/28 days)
(n = 2552)

Primary endpoints: iDFS (using STEEP criteria)
Key secondary endpoints: recurrence-free survival, DDFS, OS, PROs, PK, safety
Exploratory Endpoints: Locoregional recurrence-free survival, gene expression and alternations in tumor ctDNA/ctRNA samples

Data cutoff: January 11, 2023
(median f/u: 34.0 mo with minimum of 21 mo)

NATALEE

Primary Endpoint: invasive Disease Free Survival



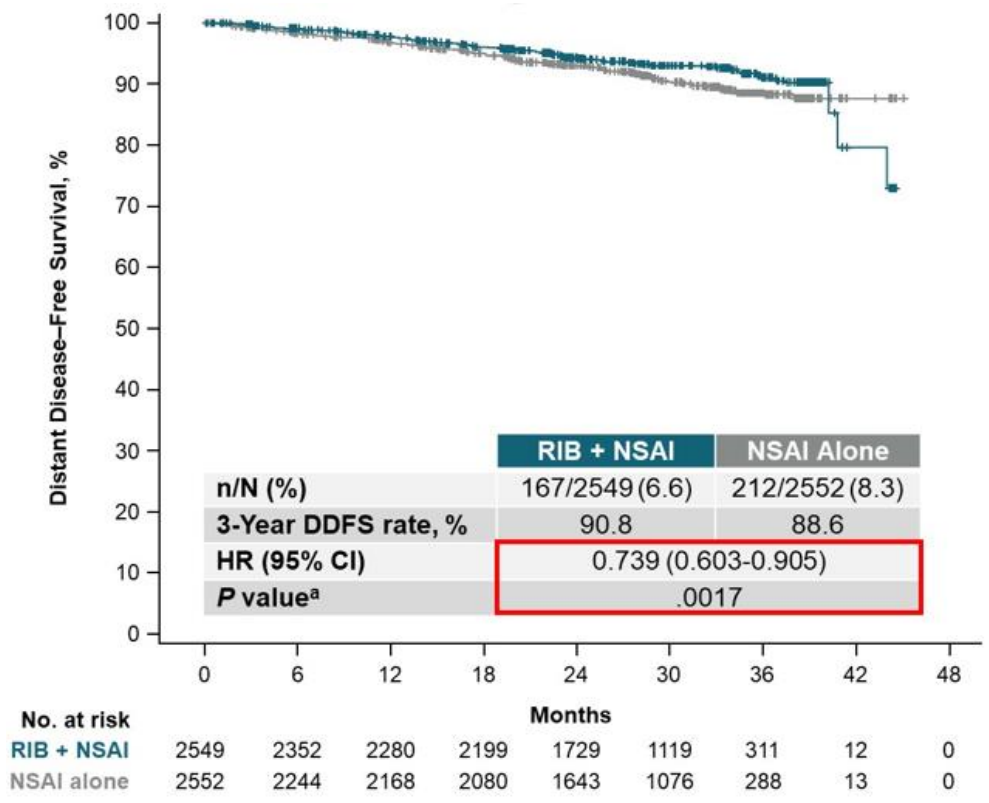
- Ribociclib + NSAI significantly improved iDFS vs NSAI alone
  - *P* value of .0014 met protocol-defined stopping boundary for superior efficacy (1-sided *P* <.0128)
- Absolute iDFS benefit at 3 yr: 3.3%
- Risk of invasive disease decreased by 25.2%

ASCO 2023. Abstr LBA500.

KEY DATA

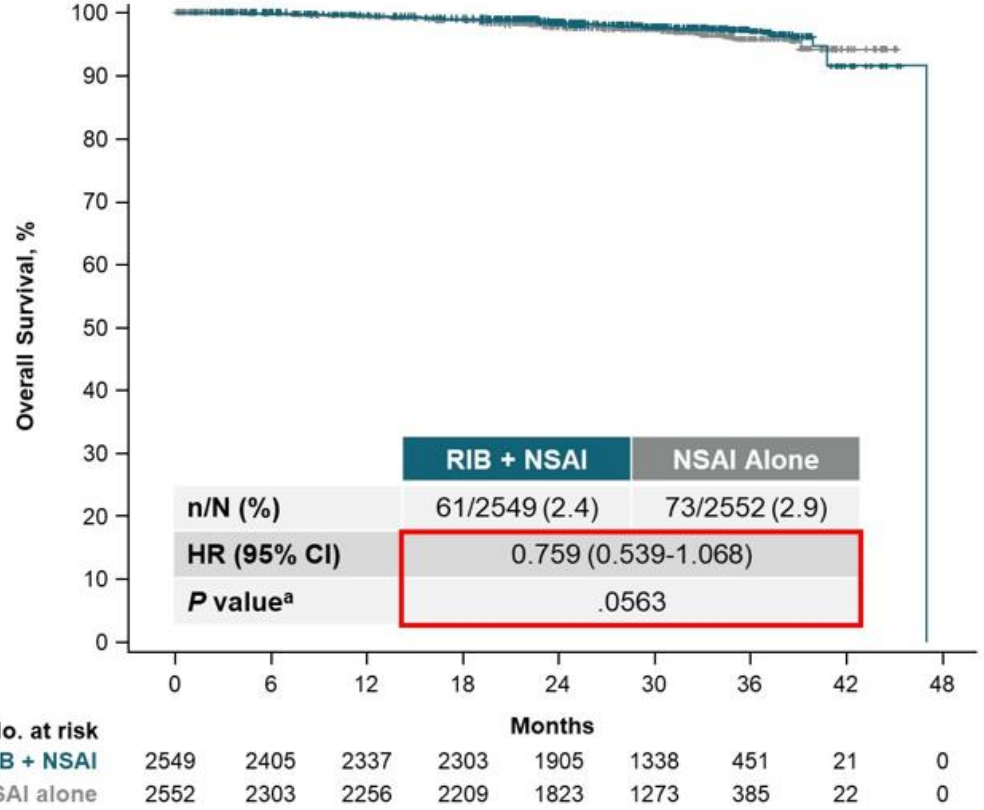
NATALEE

Distant disease free survival (DDFS)



- Absolute DDFS benefit at 3 yr: 2.2%
- Risk of distant disease decreased by 26.1%

Overall Survival (OS)



- Non-significant trend toward improved OS with ribociclib + NSAI
- Median follow-up OS was 30.4 months
- Further follow-up planned

ASCO 2023. Abstr LBA500.

NATALEE

Safety

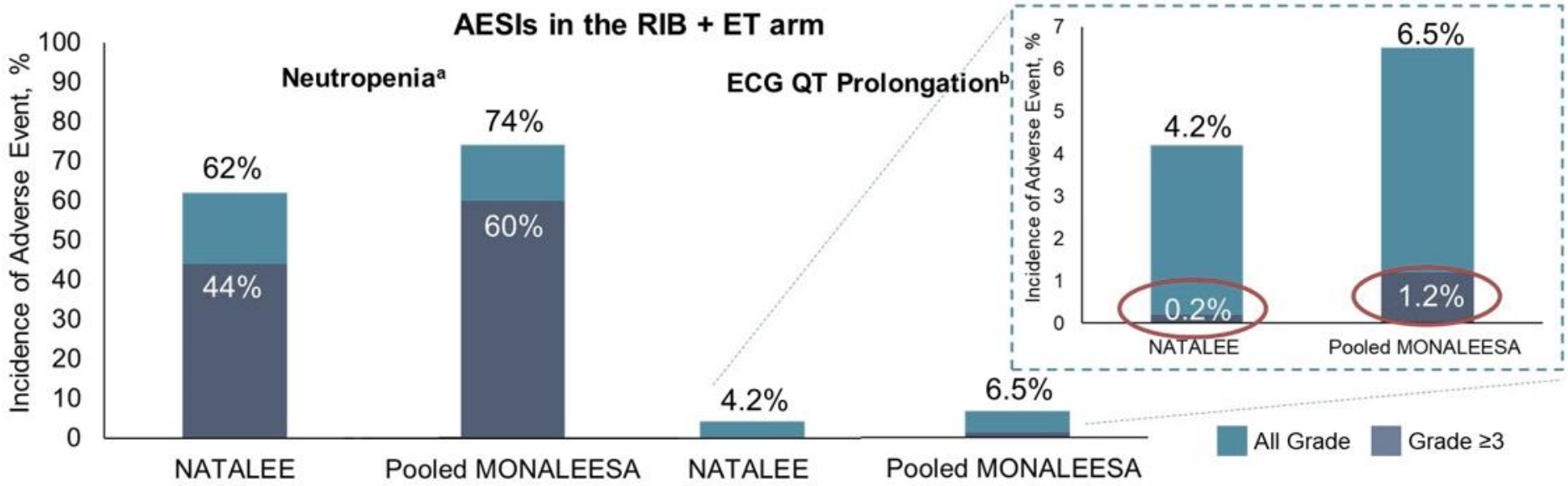
AEs (%)	Ribociclib + NSAI (n = 2524)		NSAI Alone (n = 2444)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
AEs of special interest				
Neutropenia	62.1	43.8	4.5	0.8
• Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs	25.4	8.3	10.6	1.5
QT interval prolongation	5.2	1.0	1.2	0.5
• ECG QT prolonged	4.2	0.2	0.7	0
ILD pneumonitis	1.5	0	0.8	0.1
Other clinically relevant AEs				
Arthralgia	36.5	1.0	42.5	1.3
Nausea	23.0	0.2	7.5	0.04
Headache	22.0	0.4	16.5	0.2
Fatigue	21.9	0.7	12.7	0.2
Diarrhea	14.2	0.6	5.4	0.1
VTE	1.4	0.6	0.6	0.2

ASCO 2023. Abstr LBA500.

NATALEE

Safety: 400 mg vs 600 mg

- Ribociclib 400 mg had lower rates of dose-dependent toxicities vs pooled analysis of MONALEESA trials using ribociclib 600 mg



[a]This is a grouped term that combines neutropenia and neutrophil count decreased
[b]This is a preferred term.

SUMMARY

NATALEE

- Ribociclib plus non-steroidal AI provided statistically significant improvement in iDFS compared to NSAI alone
  - *P* value of 0.0014 met protocol-defined stopping boundary for superior efficacy (1-sided *P* <.0128)
  - Absolute iDFS benefit at 3 yr: 3.3%
  - Relative risk of invasive disease decreased by 25.2%

- DDFS and OS improved with ribociclib + NSAI vs NSAI alone
  - OS improvement was not statistically significant; additional follow-up is planned

- The 3-year regimen of ribociclib at a starting dose of 400 mg was “well tolerated”

ASCO 2023. Abstr LBA500.

NATALEE

Ribociclib in combination with NSAI has potential as an adjuvant treatment option for patients with stage II-III HR+/HER2- EBC, including those with node-negative disease

Not yet approved by the FDA…

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* Plenary Session

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PALLAS

1. Does adjuvant Palbociclib (Ibrance®) provide benefit to patients with Stage II-III, ER+ breast cancer?

KEY DATA

PALLAS

Study Design: Randomized, open-label Phase III trial

- Stage II – III HR+/HER2-
- Completion of prior surgery, ± chemotherapy, RT
- Within 12 months of diagnosis, within 6 months of starting adjuvant ET
- FFPE tumor block submitted and received at biorespository

(N = 5,600)

Stage IIA enrollment capped at 1,000

Stratified by Stage (IIA vs IIB/III), Chemotherapy (yes or no), age (≤50 or >50), geographic region (N. America vs Europe vs Other)

R
1:1

Palbociclib x 2 years
125 mg QD, 3wks on/1 week off
+ ET
AI or tamoxifen, ± LHRH agonist
(duration, at least 5 years)

ET
AI or tamoxifen, ± LHRH agonist
(duration, at least 5 years)

Until PD, unacceptable toxicity, or study withdrawal

Primary Endpoint: iDFS
Secondary Endpoint: iBCFS, DRFS, LRFS, OS

Data cut-off date: Feb 2, 2023
Median follow-up: 13.2 months

ASCO 2023. Rapid Abstract Updates Abstr #390216.

PALLAS

Baseline Characteristics

Characteristic	Stage IIA (N=1,010 patients) randomized ITT		Stage IIB/III (N=4729)
	Palbociclib + ET (n = 503)	ET (n = 507)	
Median age, yr (range)	55 (29 -84)	53 (30-85)	51 (22-90)
Sex, n (%) • Female • Male	500 (99.4%) 3 (0.6%)	505 (99.6%) 2 (0.4%)	4,699 (99.4%) 30 (0.6%)
Menopausal Status • Postmenopausal, n (%) • Pre/Perimenopausal, n (%)	306 (54.2%) 194 (45.2%)	288 (53.3%) 216 (46.0%)	2,491 (52.7%) 2,206 (46.6%)
Histologic Grade • Grade 1/Grade 2 • Grade 3	346 (68.8%) 145 (28.8%)	364 (71.8%) 127 (25.0%)	3,170 (67.0%) 1,330 (28.1%)
Prior Chemotherapy	282 (56.1%)	279 (55.0%)	4,180 (88.4%)

ASCO 2023. Rapid Abstract Updates Abstr #390216.

PALLAS

Stage IIA vs IIB/III Cohorts: iDFS

Cohort		Palbociclib + ET	ET alone
Stage IIA	No. events	31	45
	iDFS at 4 yrs	92.9%	92.1%
	HR (95% CI)	0.75 (0.48 – 1.19), log rank p = 0.23	
Stage IIB/III	No. events	294	315
	iDFS at 4 yrs	85.3%	83.6%
	HR (95% CI)	0.91 (0.77-1.07), log rank p = 0.24	

ASCO 2023. Rapid Abstract Updates Abstr #390216.

KEY DATA

PALLAS

Secondary Endpoints at 4 years: iBCFS, DRFS, LRFS, OS

	Palbociclib + ET		ET alone	
iBCFS at 4 yrs	94.8%		94.2%	Δ 0.6%
HR (95% CI)		0.80 (0.47 – 1.36)		
DRFS at 4 yrs	95.3%		95.2%	Δ 0.1%
HR (95% CI)		0.92 (0.52 – 1.65)		
LRFS at 4 yrs	98.1%		98.2%	Δ -0.1%
HR (95% CI)		0.84 (0.35 – 2.00)		
OS at 4 yrs	97.7%		98.1%	Δ -0.4%
HR (95% CI)		1.28 (0.57 – 2.86)		

ASCO 2023. Rapid Abstract Updates Abstr #390216.

PALLAS

The combination of palbociclib with endocrine therapy does not provide additional benefit to patients with early breast cancer

COMPARISON

CDK4/6 Inhibitors in the Adjuvant Setting

	Palbociclib (IBRANCE®)		Ribociclib (KISQALI®)	Abemaciclib (VERZENIO®)
FDA approval	*Not in adjuvant*		*Not in adjuvant*	***Approved*** [in combination with ET (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence]
Study	**PENELOPE-B**	**PALLAS**	**NATALEE**	**MONARCH-E**
Study Design	Palbociclib + ET vs ET alone		Ribociclib + NSAI vs NSAI alone	Abemaciclib + ET vs ET alone
Sample Size	1250	5600	5000	4580
Duration of Rx	1 year	2 years	3 years	2 years

Eligibility	• HR+, HER2-negative primary breast cancer without a pathological complete response after taxane-containing NACT
	• At high risk of relapse
	  • clinical pathological staging-estrogen receptor grading score ≥ 3 or 2 and ypN+
		• Stage II – III HR+/HER2-
		• Completion of prior surgery, ± chemotherapy, RT
		• Within 12 months of diagnosis, within 6 months of starting adjuvant ET
			• Pre/postmenopausal women and men with HR+/HER2- EBC
			• Stage IIA
			  • Either N0 with grade 2 and Ki-67 ≥20%, Oncotype DX RS ≥26, or high risk via genomic risk profiling, N0 with grade 3, or N1
			• Stage IIB (N0 or N1)
			• Stage III disease (N0, N1, N2, or N3)
			• Prior ET up to 12 mo permitted, prior (neo)adjuvant CT permitted
				• Women or men with high-risk, node-positive, HR+/HER2- EBC
				• Prior (neo)adjuvant CT permitted
				• Pre- or postmenopausal
				• No distant metastasis
				• ≤16 mo from surgery to randomization
				• ≤12 wk of ET after last non-ET

Median follow-up (months)	42.8	43	17.7	42
iDFS HR (95% CI) (ITT)	**0.93** (0.74 – 1.17)	**0.96** (0.81-1.14)	**0.75** (0.62 – 0.91), *P* 0.0014	**0.65** (0.57 – 0.75), *P* 0.0001
iDFS HR (95% CI) (by Stage)	---	**IIA**: **0.75** (0.48 – 1.19), NS	**II**: **0.76** (0.53 – 1.1)	---
iDFS HR (95% CI) (by node)	---	---	**N0**: **0.63** (0.36-1.65)	---

NS: not significant

COMPARISON

No black box label warnings but…

KISQALI® (ribociclib)

----------WARNINGS AND PRECAUTIONS----------

• Interstitial Lung Disease (ILD)/Pneumonitis: Patients treated with CDK 4/6 inhibitors should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Interrupt and evaluate patients with new or worsening respiratory symptoms suspected to be due to ILD/pneumonitis. Permanently discontinue KISQALI in patients with recurrent symptomatic or severe ILD/pneumonitis. (2.2, 5.1)

• Severe Cutaneous Adverse Reactions (SCARs): Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), and drug-reaction with eosinophilia and systemic symptoms (DRESS) can occur with KISQALI treatment. Permanently discontinue KISQALI in patients with SCARs or other life-threatening cutaneous reactions. (2.2, 5.2)

• QT Interval Prolongation: Monitor electrocardiograms (ECGs) and electrolytes prior to initiation of treatment with KISQALI. Repeat ECGs at approximately Day 14 of the first cycle and at the beginning of the second cycle, and as clinically indicated. Monitor electrolytes at the beginning of each cycle for 6 cycles, and as clinically indicated. Avoid using KISQALI with drugs known to prolong QT interval and/or strong CYP3A inhibitors. (2.2, 5.3, 7.1, 7.4)

• Increased QT Prolongation with Concomitant Use of Tamoxifen: KISQALI is not indicated for concomitant use with tamoxifen. (5.4)

• Hepatobiliary Toxicity: Increases in serum transaminase levels have been observed. Perform liver function tests (LFTs) before initiating treatment with KISQALI. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated. (2.2, 5.5)

• Neutropenia: Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated. (2.2, 5.6)

• Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use effective contraception during therapy. (5.7, 8.1, 8.3)

VERZENIO® (abemaciclib)

----------WARNINGS AND PRECAUTIONS----------

• Diarrhea: VERZENIO can cause severe cases of diarrhea, associated with dehydration and infection. Instruct patients at the first sign of loose stools to initiate antidiarrheal therapy, increase oral fluids, and notify their healthcare provider. (2.2, 5.1)

• Neutropenia: Monitor complete blood counts prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. (2.2, 5.2)

• Interstitial Lung Disease (ILD)/Pneumonitis: Severe and fatal cases of ILD/pneumonitis have been reported. Monitor for clinical symptoms or radiological changes indicative of ILD/pneumonitis. Permanently discontinue VERZENIO in all patients with Grade 3 or 4 ILD or pneumonitis. (2.2, 5.3)

• Hepatotoxicity: Increases in serum transaminase levels have been observed. Perform liver function tests (LFTs) before initiating treatment with VERZENIO. Monitor LFTs every two weeks for the first two months, monthly for the next 2 months, and as clinically indicated. (2.2, 5.4)

• Venous Thromboembolism: Monitor patients for signs and symptoms of thrombosis and pulmonary embolism and treat as medically appropriate. (2.2, 5.5)

• Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. (5.6, 8.1, 8.3)

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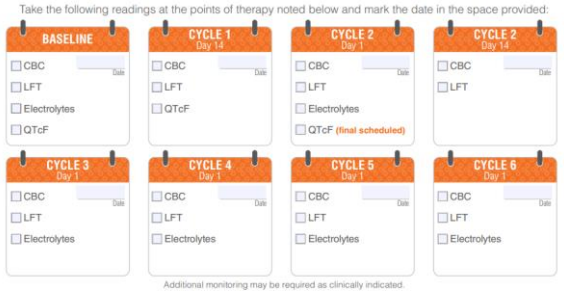
COMPARISON

Monitoring Checklist

KISQALI® (ribociclib)

kisqali-monitoring-checklist.pdf (novartis.com)


Take the following readings at the points of therapy noted below and mark the date in the space provided:

BASELINE: CBC, LFT, Electrolytes, QTcF

CYCLE 1 Day 14: CBC, LFT, QTcF

CYCLE 2 Day 1: CBC, LFT, Electrolytes, QTcF (final scheduled)

CYCLE 2 Day 14: CBC, LFT

CYCLE 3 Day 1: CBC, LFT, Electrolytes

CYCLE 4 Day 1: CBC, LFT, Electrolytes

CYCLE 5 Day 1: CBC, LFT, Electrolytes

CYCLE 6 Day 1: CBC, LFT, Electrolytes

Additional monitoring may be required as clinically indicated.

Hepatobiliary Toxicity: Perform liver function tests (LFTs) before initiating therapy with KISQALI. Monitor LFTs every 2 weeks for first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.

ILD or Pneumonitis: Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis which may include hypoxia, cough, and dyspnea.

Neutropenia: Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.

QT Interval Prolongation: Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values less than 450 ms. Repeat ECG at approximately Day 14 of the first cycle and the beginning of the second cycle, and as clinically indicated. Monitor serum electrolytes (including potassium, calcium, phosphorous and magnesium) prior to the initiation of treatment, at the beginning of the first 6 cycles, and as clinically indicated.

Severe Cutaneous Adverse Reactions: Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.

VERZENIO® (abemaciclib)

Diarrhea: At the first sign of loose stools, start treatment with antidiarrheal agents and increase intake of oral fluids.

Hematologic Toxicities: Monitor complete blood counts prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.

Hepatotoxicity: Monitor ALT, AST, and serum bilirubin prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.

ILD or Pneumonitis: Monitor patients for pulmonary symptoms indicative of ILD or pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations.

Neutropenia: Monitor complete blood counts prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.

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PALMIRA

2. Does 2nd-line endocrine therapy with palbociclib regimen after tumor progression to palbociclib benefit patients with HR+/HER2- advanced (metastatic) breast cancer?

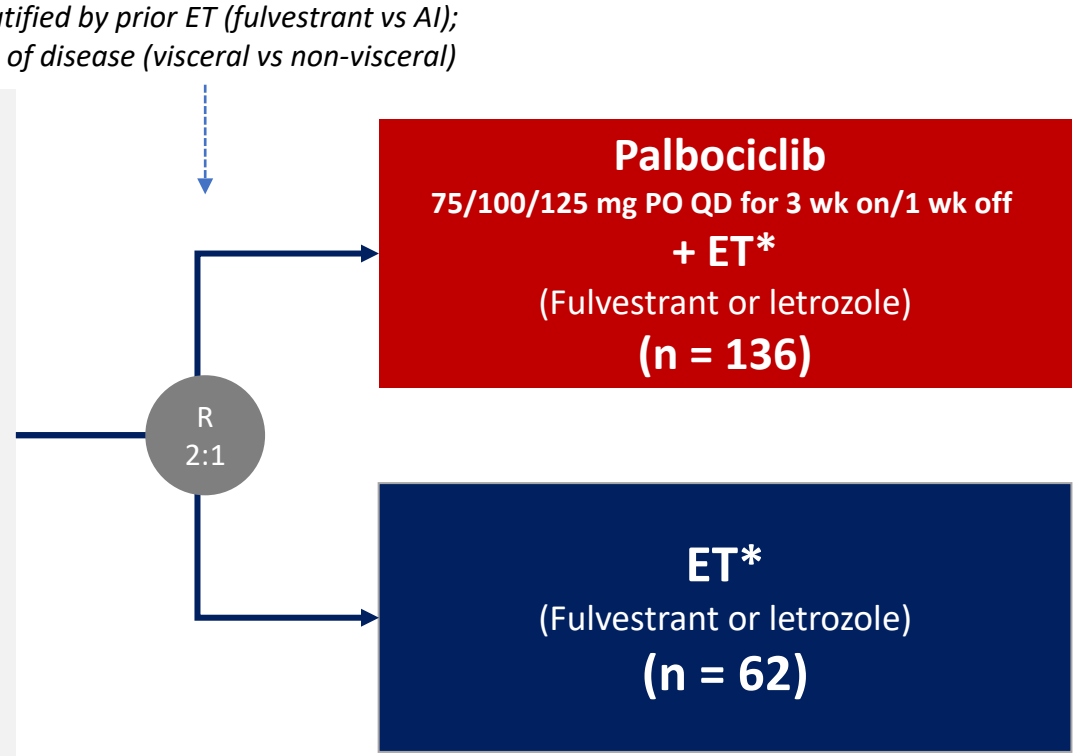
KEY DATA

PALMIRA

Study Design: International, randomized, open-label trial

- Women with HR+/HER2- ABC
- Premenopausal with ovarian suppression or postmenopausal
- Progresion on 1L palbociclib + ET (AI or fulvestrant) after clinical benefit or progression on palbociclib-based adjuvant tx after ≥12 mo of tx within 12 mo of completion
- Last dose of prior Palbociclib within 8 weeks from study entry (except for pts relapsing on a Palbociclib regimen in the adjuvant setting)
- Measurable disease
- ECOG PS 0/1

(N = 198)



Until PD, unacceptable toxicity, or study withdrawal

*Depending on prior agent, either fulvestrant 500 mg IM on D1/15/29 and QM thereafter, or letrozole 2.5 mg PO QD

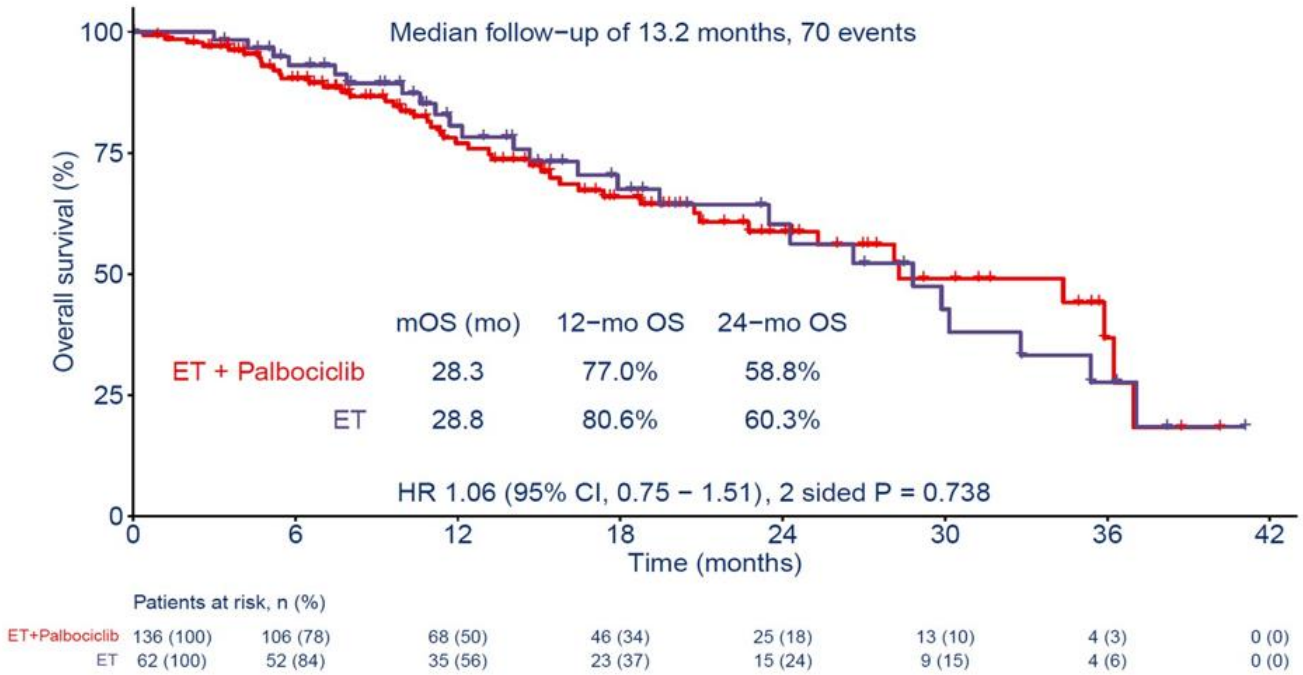
Primary endpoints: PFS per RECIST v1.1 by investigator
Trial has 80% power to detect mPFS increase of 2.74 mo over 4 mo with ET (2-sided α = 0.05; hazard ratio: 0.59)

Secondary endpoints: ORR, CBR, OS, DoR, TTR, time to progression, QoL, PFS by prior ET/site of disease/HER2 status, safety and tolerability

Data cut-off date: Feb 2, 2023
Median follow-up: 13.2 months

PALMIRA

Overall Survival (ITT population)



Characteristic, n (%)	Palbociclib + ET (n = 136)	ET (n = 62)
Overall response		
• CR	0	0
• PR	6 (4.4)	1 (1.6)
• SD	49 (36.0)	22 (35.5)
• Non-CR/Non-PD	34 (25.0)	13 (21.0)
• PD	39 (28.7)	24 (38.7)
• NE	8 (5.9)	2 (3.2)
Objective Response Rate	6 (4.4)	1 (1.6)
Clinical Benefit Rate	57 (41.9)	17 (27.4)
Measurable disease, n/N (%)	6/94 (6.4)	1/44 (2.3)

ASCO 2023. Abstr #1001.

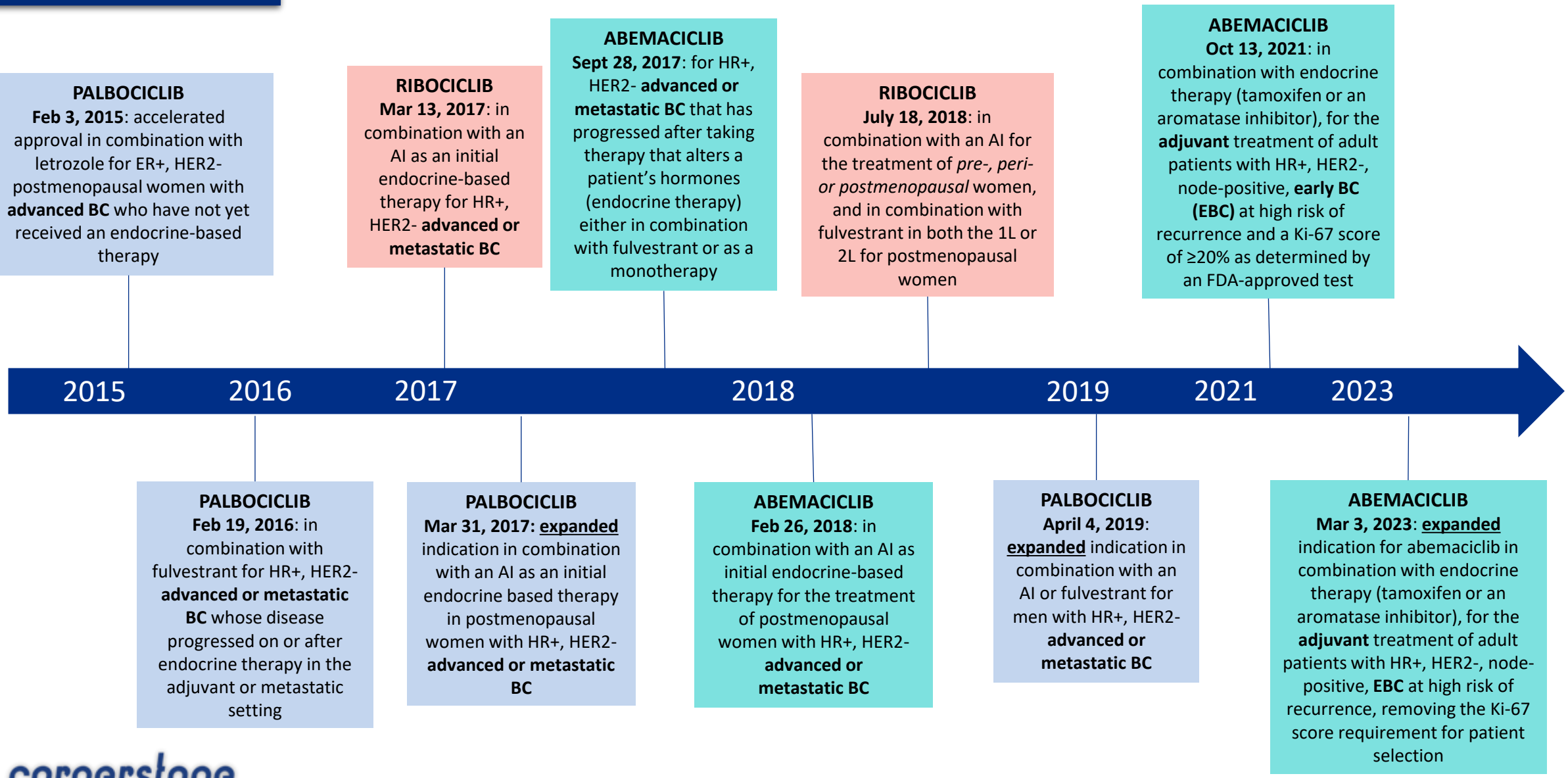
PALMIRA

Palbociclib maintenance following progression on a 1L palbociclib-based regimen does not benefit patients with HR+/HER2- advanced breast cancer

Alternative treatment options should be explored

FDA APPROVALS

CDK4/6 INHIBITORS: metastatic and adjuvant



PALBOCICLIB
Feb 3, 2015: accelerated approval in combination with letrozole for ER+, HER2- postmenopausal women with **advanced BC** who have not yet received an endocrine-based therapy

PALBOCICLIB
Feb 19, 2016: in combination with fulvestrant for HR+, HER2- **advanced or metastatic BC** whose disease progressed on or after endocrine therapy in the adjuvant or metastatic setting

RIBOCICLIB
Mar 13, 2017: in combination with an AI as an initial endocrine-based therapy for HR+, HER2- **advanced or metastatic BC**

PALBOCICLIB
Mar 31, 2017: <u>expanded</u> indication in combination with an AI as an initial endocrine based therapy in postmenopausal women with HR+, HER2- **advanced or metastatic BC**

ABEMACICLIB
Sept 28, 2017: for HR+, HER2- **advanced or metastatic BC** that has progressed after taking therapy that alters a patient's hormones (endocrine therapy) either in combination with fulvestrant or as a monotherapy

ABEMACICLIB
Feb 26, 2018: in combination with an AI as initial endocrine-based therapy for the treatment of postmenopausal women with HR+, HER2- **advanced or metastatic BC**

RIBOCICLIB
July 18, 2018: in combination with an AI for the treatment of *pre-, peri- or postmenopausal* women, and in combination with fulvestrant in both the 1L or 2L for postmenopausal women

PALBOCICLIB
April 4, 2019: **<u>expanded</u>** indication in combination with an AI or fulvestrant for men with HR+, HER2- **advanced or metastatic BC**

ABEMACICLIB
Oct 13, 2021: in combination with endocrine therapy (tamoxifen or an aromatase inhibitor), for the **adjuvant** treatment of adult patients with HR+, HER2-, node-positive, **early BC (EBC)** at high risk of recurrence and a Ki-67 score of ≥20% as determined by an FDA-approved test

ABEMACICLIB
Mar 3, 2023: **<u>expanded</u>** indication for abemaciclib in combination with endocrine therapy (tamoxifen or an aromatase inhibitor), for the **adjuvant** treatment of adult patients with HR+, HER2-, node-positive, **EBC** at high risk of recurrence, removing the Ki-67 score requirement for patient selection

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2023 ASCO Key Studies

Breast and Gynecological Cancer

- NATALEE
- PALLAS
- PALMIRA
- SONIA

- MIRASOL

GU/GI Cancer

- PROSPECT*
- DESTINY-CRC02
- PEACE-1
- NeoCol
- CONTACT-03

Other Notable Studies

- ADAURA*
- INDIGO*
- SWOG1826*
- DESTINY-PanTumor02
- COMMANDS

* Plenary Session

cornerstone specialty network™

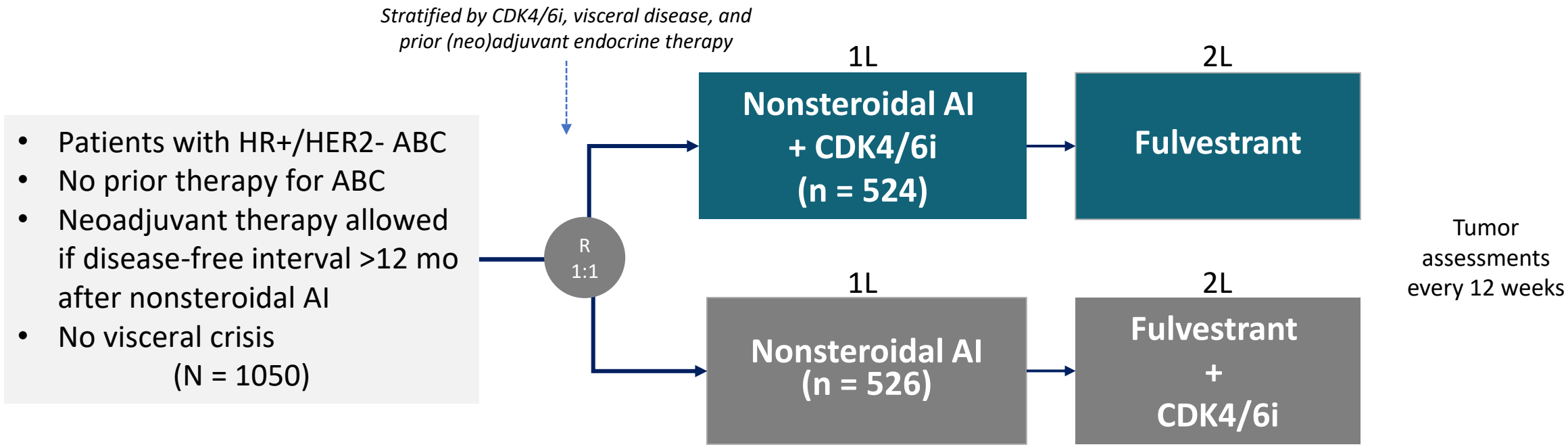
SONIA

3. Is it better to add a CDK4/6 inhibitor in the 1st line or 2nd line for patients with HR+/HER2- advanced (metastatic) breast cancer?

KEY DATA

SONIA

Study Design: Investigator initiated, randomized phase III trial



Primary endpoints: PFS2 (time from randomization to second disease progression or death) per RECIST V1.1
Planned primary analysis after 574 PFS2 events; 89% power to detect superiority with 2-sided α = 5%

Secondary endpoints: OS, QoL, cost-effectiveness

Inclusion period: Nov 23, 2017 – Sept 1, 2021
Data cut-off date: Dec 1 , 2022
Median follow-up: 37.3 months

SONIA

Baseline Characteristics

Characteristic, n (%)	First-line CDK4/6i (n = 524)	Second-line CDK4/6i (n = 526)
Median age, yr (range)	64 (24-88)	63 (25-87)
WHO PS		
• 0	257 (49)	257 (49)
• ≥1	267 (51)	269 (51)
Menopausal status		
• Pre/peri	69 (13)	76 (14)
• Post	455 (87)	450 (86)
Disease-free interval		
• Newly diagnosed	182 (35)	182 (35)
• ≤24 mo	96 (18)	98 (19)
• >24 mo	246 (47)	246 (47)

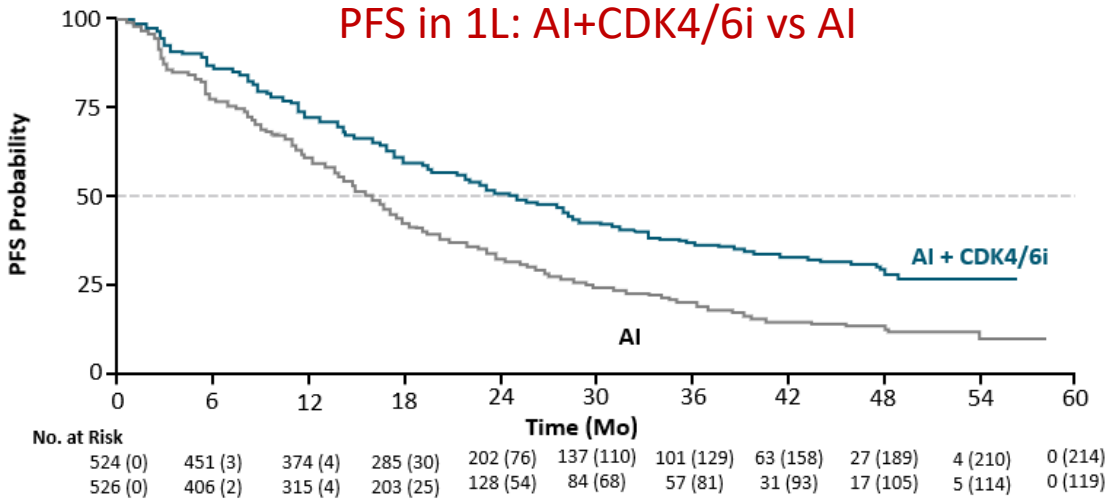
Characteristic	First-line CDK4/6i (n = 524)	Second-line CDK4/6i (n = 526)
Prior (neo)adjuvant tx		
• CT	212 (40)	210 (40)
• ET	258 (49)	254 (48)
Metastatic site		
• Visceral	291 (56)	292 (56)
• Bone only	91 (17)	91 (17)
Measurable disease	315 (60)	312 (59)
CDK4/6 inhibitor		
• Palbociclib	479 (91)	479 (91)
• Ribociclib	42 (8)	44 (8)
• Abemaciclib	3 (1)	3 (1)

KEY DATA

SONIA

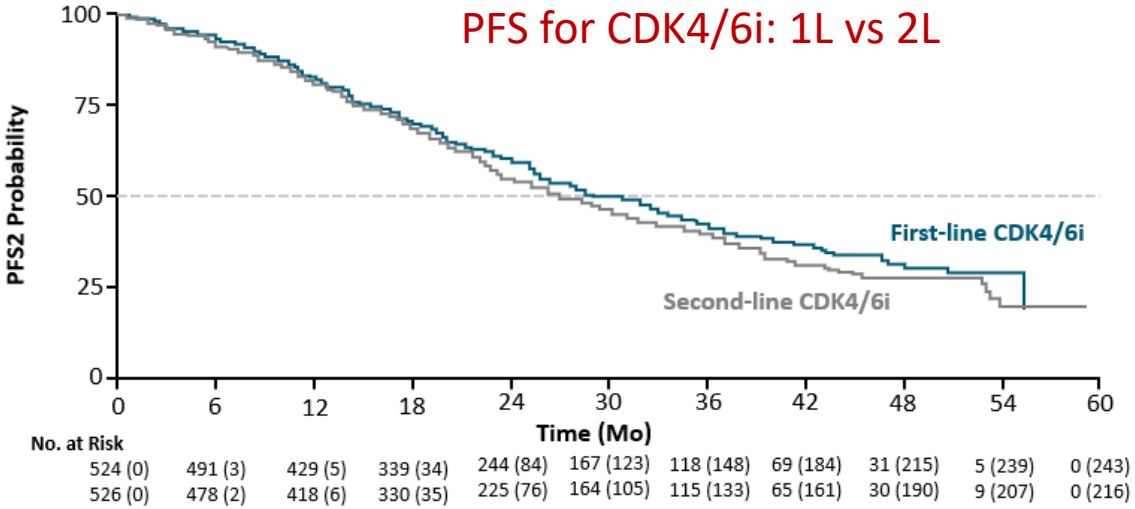
Progression Free Survival

PFS in 1L: AI+CDK4/6i vs AI



Characteristic	AI + CDK4/6i (n = 524)	AI (n = 526)
Events, n	310	407
Median PFS1, mo	24.7	16.1
Hazard ratio (95% CI)	**0.59** (0.51-0.69)	
2-sided P value	<0.0001	

PFS for CDK4/6i: 1L vs 2L



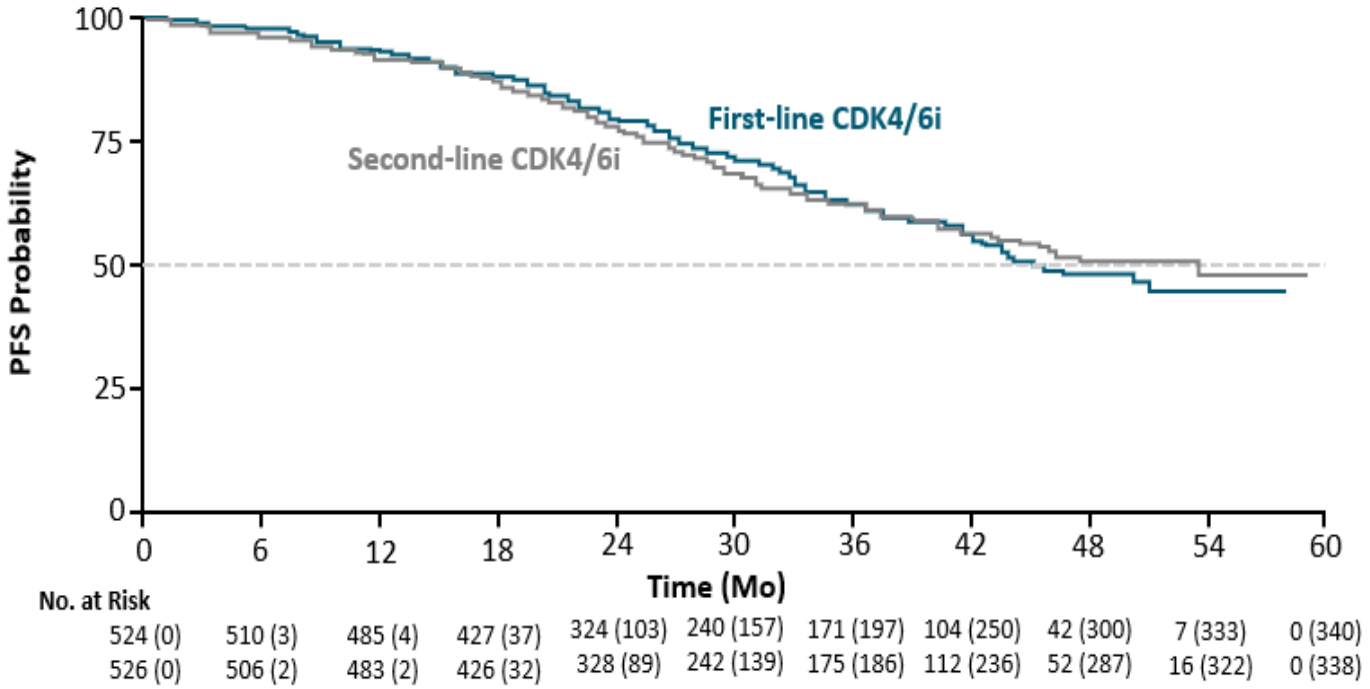
Characteristic	1L CDK4/6i (n = 524)	2L CDK4/6i (n = 526)
Events, n	281	310
Median PFS2, mo	31.0	26.8
Hazard ratio (95% CI)	**0.87** (0.74-1.03)	
2-sided P value	0.10	

ASCO 2023. Abstr LBA1000.

KEY DATA

SONIA

Overall Survival



Characteristic	1L CDK4/6i (n = 524)	2L CDK4/6i (n = 526)
Events, n	184	188
Median OS, mo	45.9	53.7
Hazard ratio (95% CI)	**0.98** (0.80-1.20)	
2- sided P value	0.83	

ASCO 2023. Abstr LBA1000.

SUMMARY

SONIA

- Use of CDK4/6 inhibitors in the first-line setting or the second-line setting provides benefit to patients with advanced breast cancer

- CDK4/6 inhibitor in the 1L compared to the 2L setting:

  - The use of CDK4/6 inhibitors in the first-line setting prolongs time on therapy and therefore is associated with higher drug costs

  - The use of CDK4/6 inhibitors in the first-line setting increases toxicity

ASCO 2023. Abstr LBA1000.

SONIA

Use of endocrine therapy with a CDK4/6 inhibitor is a beneficial treatment option in either the first-line or second-line setting for patients with CDK4/6i treatment naïve advanced breast cancer

Toxicity and drug cost can impact treatment decisions on a patient-by-patient basis

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- SONIA

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GU/GI Cancer

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- SWOG1826*
- DESTINY-PanTumor02
- COMMANDS

* Plenary Session

cornerstone specialty network™

MIRASOL

Does mirvetuximab soravtansine provide benefit to patients with FRα-High Expression, Platinum-Resistant Advanced Ovarian, Primary Peritoneal, or Fallopian Tube Cancer?

Mirvetuximab soravtansine is an ADC comprising a FRα-binding antibody, a cleavable linker, and matansinoid DM4 (a potent tubulin-targeting agent)

FDA APPROVAL AND TESTING

On November 14, 2022, the FDA granted accelerated approval to mirvetuximab soravtansine-gynx (Elahere, ImmunoGen, Inc.) for adult patients with folate receptor alpha (FRα) positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens.

The FDA also approved the VENTANA FOLR1 (FOLR-2.1) RxDx Assay (Ventana Medical Systems, Inc.) as a companion diagnostic device to select patients for the above indication.

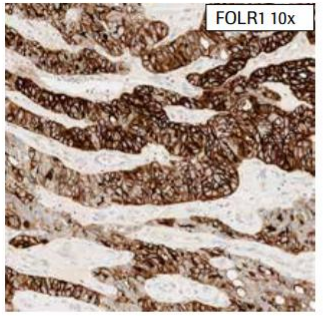
The scoring algorithm for the VENTANA FOLR1 Assay

IHC Interpretation	Staining Description
Positive for FOLR1*	≥ 75% of viable tumor cells with moderate (2+) and/or strong (3+) membrane staining
Negative for FOLR1*	< 75% of viable tumor cells with moderate (2+) and/or strong (3+) membrane staining
Not Evaluable	Artifacts making interpretation not possible

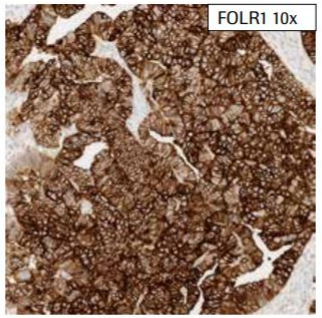
* Re-reading by Additional Pathologists for FOLR1 Scoring : To decrease variability of FOLR1 results for cases with %TC near the threshold of 75% (65% to 85%), re-reading of the slide by a second pathologist is recommended

Interpretation guide FOLR1 RxDx assay 11.14.22 BG FINAL.pdf (roche.com)

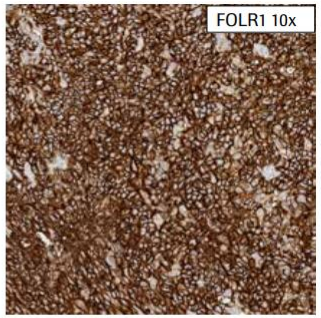
Clinical Diagnosis Positive



Exhibits 95% moderate and strong membrane staining or ≥ 75% moderate or strong membrane staining with complete circumferential pattern*

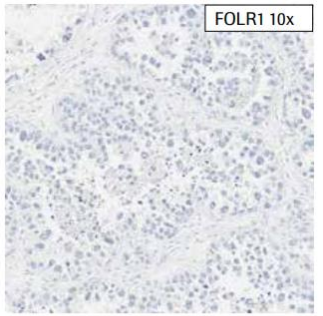


Exhibits 98% moderate and strong membrane staining or ≥ 75% tumor cells membrane staining with complete circumferential pattern*

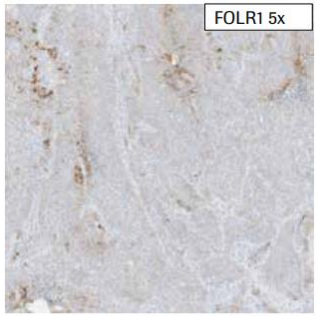


Exhibits 98% moderate and strong membrane staining or ≥ 75% tumor cells membrane staining with complete circumferential pattern*

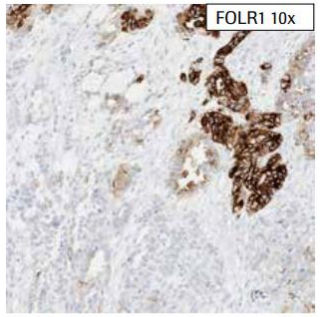
Clinical Diagnosis Negative



Exhibits no moderate or strong tumor cell membrane staining or < 75% moderate and/or strong tumor cell membrane staining



Exhibits 7% moderate and strong membrane staining or < 75% moderate and/or strong tumor cell membrane staining



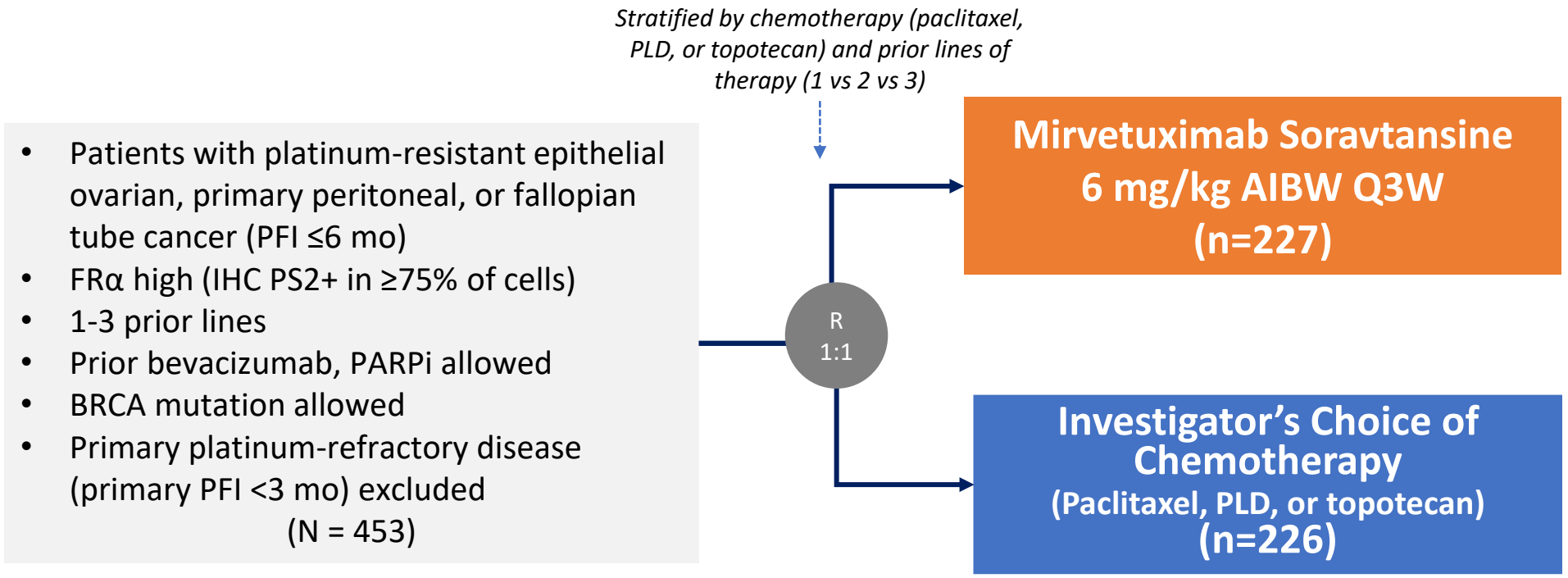
Exhibits 20% moderate and strong membrane staining or < 75% moderate and/or strong tumor cell membrane staining

- Negative (0) signal intensity is characterized by an absence of any detectable signal. Negative cases may still exhibit pale grey cytoplasmic and/or membranous discoloration.
- Weak (1+) signal intensity is characterized by a faint gold/light brown hue that may be partial or circumferential.
- Moderate (2+) or Strong (3+) signal intensity is characterized by a chocolate brown to thickened dark brown, black hue that may be partial or circumferential.

KEY DATA

MIRASOL

Study Design: global, randomized, open-label, confirmatory phase III trial



Primary endpoints: PFS by investigator (BICR for sensitivity analysis)

Secondary endpoints: ORR by investigator, OS, PROs, Safety, DoR, CA-125 response, PFS2

MIRASOL

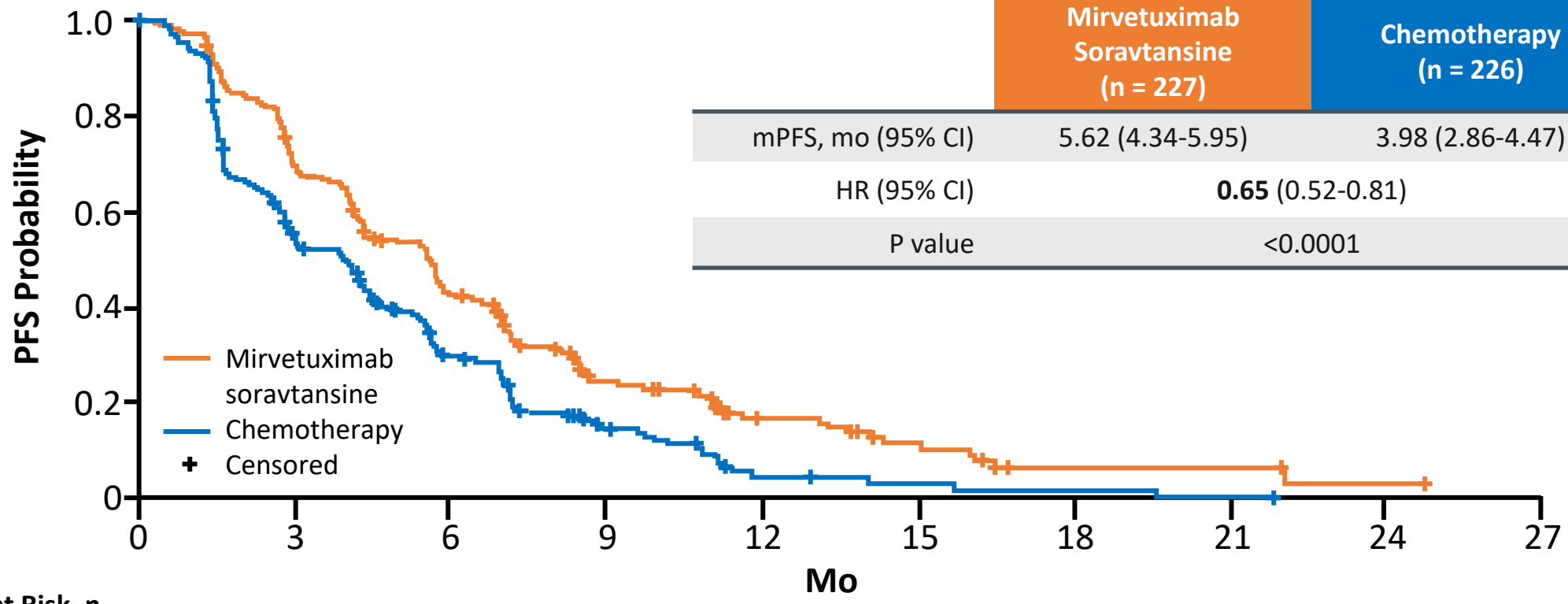
Baseline Characteristics

	Mirvetuximab Soravtansine (n = 227)	Chemotherapy (n = 226)
Median age, yr (range)	63 (32-88)	62 (29-87)
Stage at initial diagnosis, n (%)		
• I-II	9 (4)	9 (4)
• III	137 (60)	147 (65)
• IV	76 (33)	65 (29)
BRCA mutation, n (%)	29 (13)	36 (16)
Prior systemic therapies, n (%)		
• 1	29 (13)	34 (15)
• 2	90 (40)	88 (39)
• 3	108 (48)	104 (46)
Prior exposure, n (%)		
• Bevacizumab	138 (61)	143 (63)
• PARPi	124 (55)	127 (56)
• Taxanes	227 (100)	224 (99)
Primary platinum-free interval, n (%)		
• ≤12 mo/>12 mo	146 (64)/80 (35)	142 (63)/84 (37)
Platinum-free interval, n (%)		
• ≤3 mo/>3 to ≤6 mo	88 (39)/138 (61)	99 (44)/124 (55)

MIRASOL

Primary Endpoint: PFS by investigator

	Mirvetuximab Soravtansine (n = 227)	Chemotherapy (n = 226)
mPFS, mo (95% CI)	5.62 (4.34-5.95)	3.98 (2.86-4.47)
HR (95% CI)	**0.65** (0.52-0.81)	
P value	<0.0001	



Patients at Risk, n

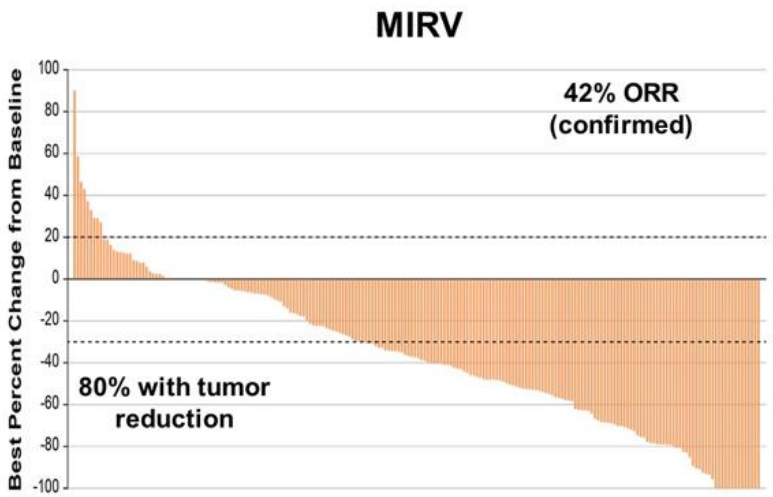
Mirvetuximab soravtansine	227	151	89	38	18	10	3	3	1	0
Chemotherapy	226	98	48	19	5	3	2	1	0	

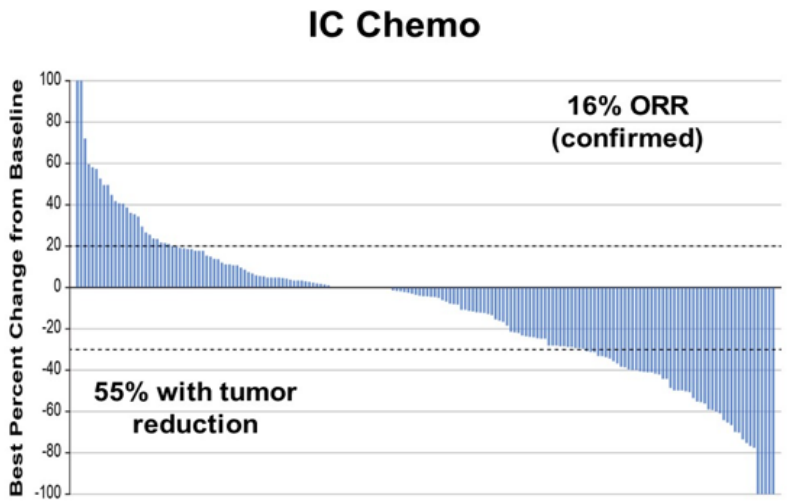
ASCO 2023. Abstr LBA5507.

MIRASOL

Overall Response Rate by investigator

Best Overall Response, n (%)	Mirvetuximab Soravtansine (n = 227)	Chemotherapy (n = 226)
ORR	**96 (42)**	**36 (16)**
• **CR**	12 (5)	0
• **PR**	84 (37)	36 (16)
• **SD**	86 (38)	91 (40)
• **PD**	31 (14)	62 (27)
• **NE**	14 (6)	37 (16)

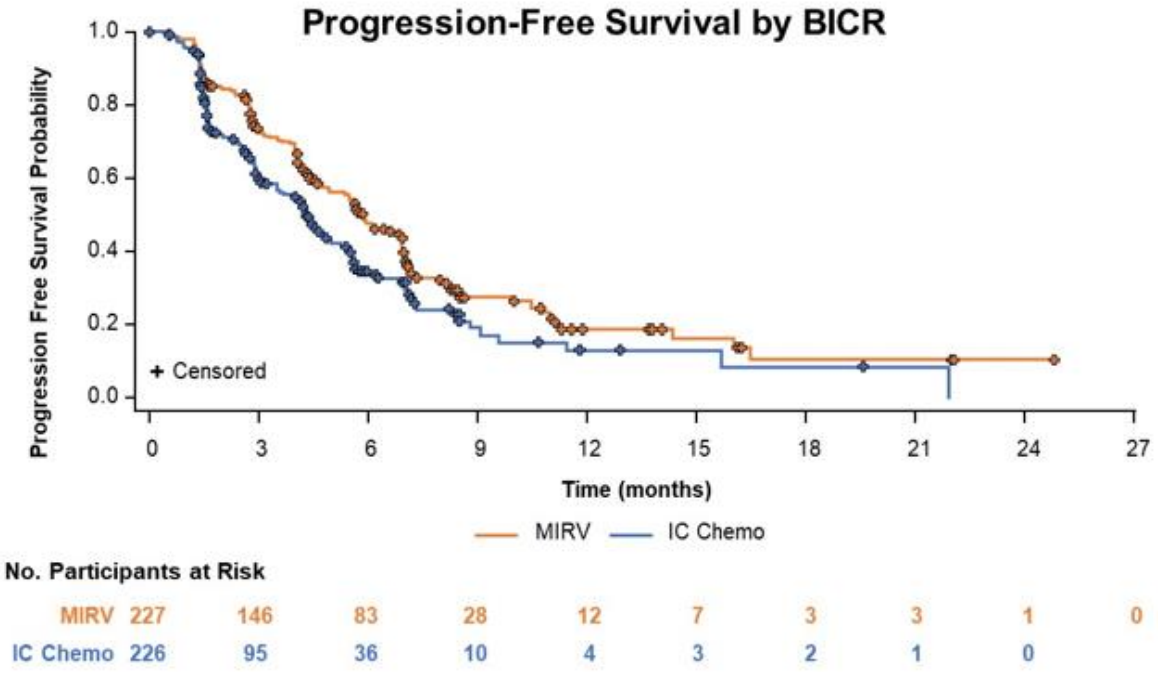




ASCO 2023. Abstr LBA5507.

MIRASOL

PFS and ORR by Blinded Independent Central Review



	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	5.9 (4.9, 7.0)	4.3 (3.5, 5.0)
Events, n (%)	146 (64)	123 (54)
HR (95% CI)	0.72 (0.56, 0.92)	
p-value	0.0082	

	MIRV (n=227)	IC Chemo (n=226)
ORR, n (%) (95% CI)	82 (36) (30, 43)	33 (15) (10, 20)
OR (95% CI)	3.22 (2.04, 5.09)	
p-value	<0.0001	

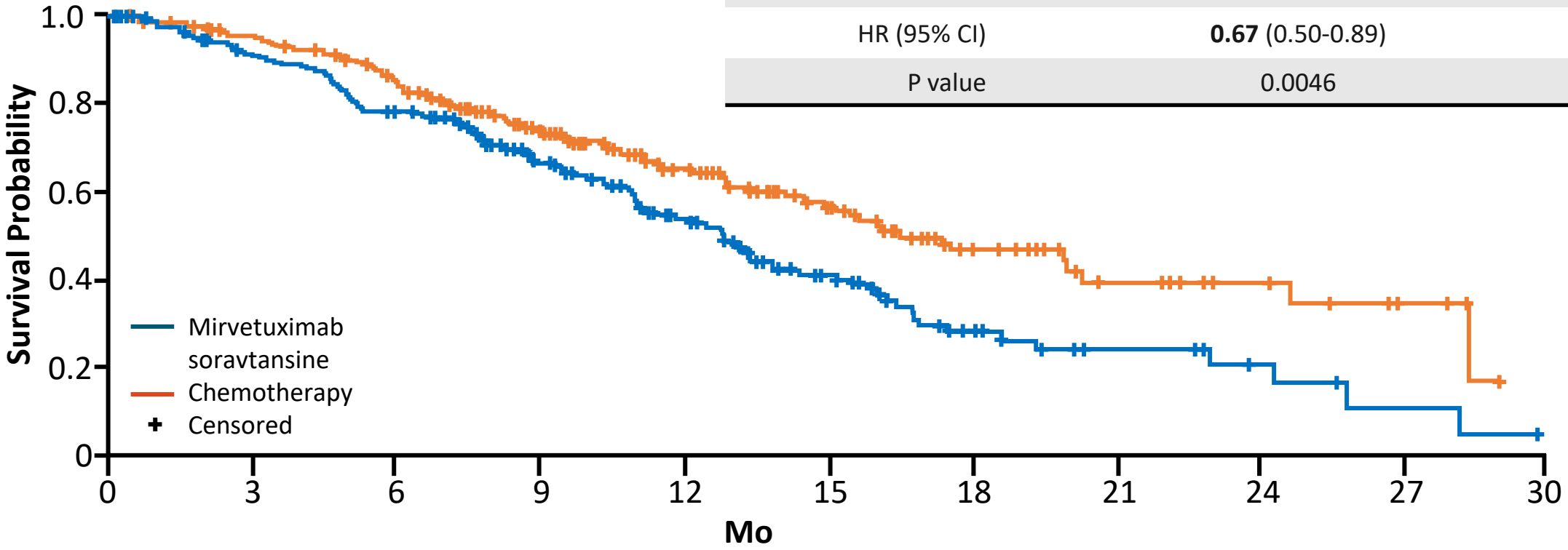
ASCO 2023. Abstr LBA5507.

KEY DATA

MIRASOL

Overall Survival

	Mirvetuximab Soravtansine (n = 227)	Chemotherapy (n = 226)
mOS, mo (95% CI)	16.46 (14.46-24.57)	12.75 (10.91-14.36)
HR (95% CI)	**0.67** (0.50-0.89)	
P value	0.0046	



227	204	175	128	82	53	28	15	9	4	0
226	185	157	107	68	39	18	9	5	2	0

ASCO 2023. Abstr LBA5507.

MIRASOL

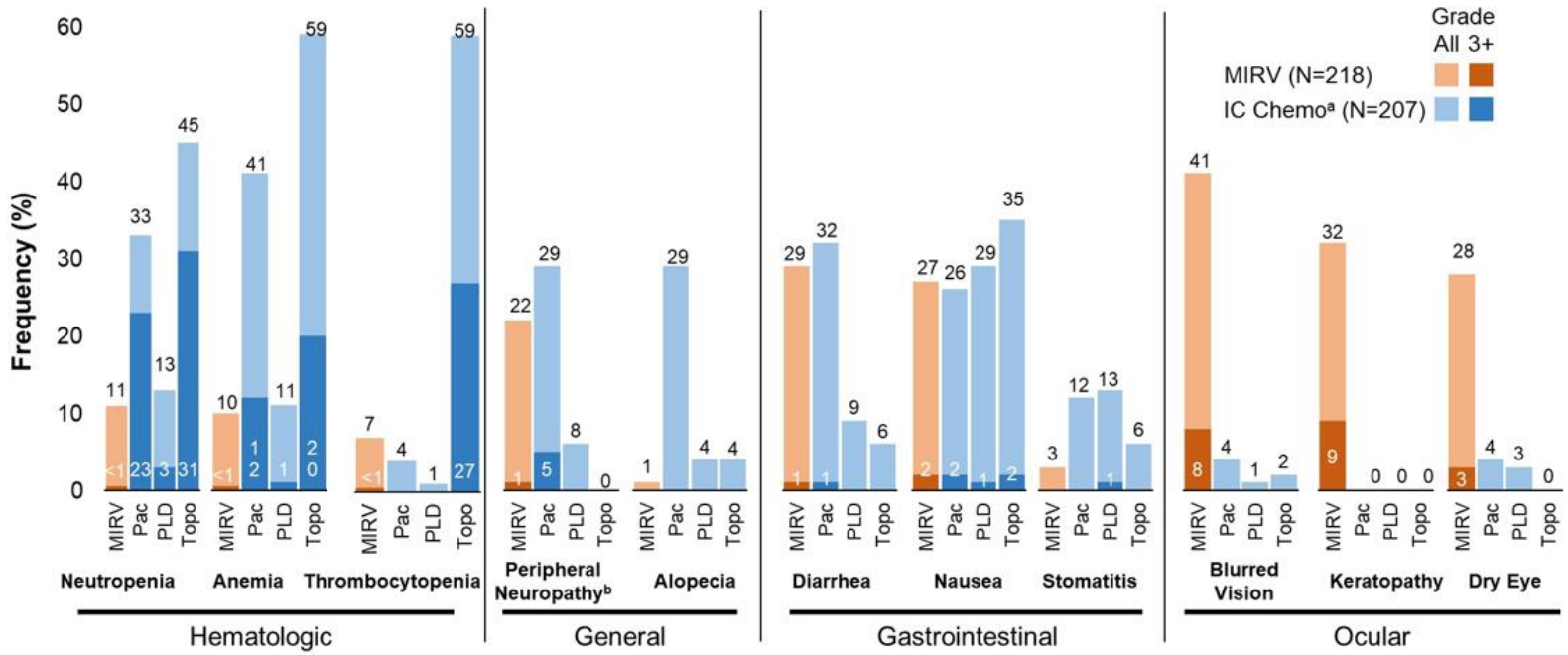
PFS and OS in bevacizumab-naïve and prior bevacizumab-treated subsets by investigator

	Bev-Naive		Prior Bev	
	MIRV	IC Chemo	MIRV	IC Chemo
mPFS (95% CI)	7.0 (5.6 – 8.4)	5.6 (3.0 – 6.5)	4.4 (4.0 – 5.8)	3.0 (2.5 – 4.3)
• Events, n (%)	65 (73.0)	57 (69.0)	111 (80.4)	109 (76.2)
• HR (95% CI)	**0.66** (0.46 – 0.94)		**0.64** (0.49 – 0.84)	
• Nominal *p*-value	0.0210		0.0011	
mOS (95% CI)	20.2 (14.8 – NE)	14.4 (11.8 – 16.7)	15.4 (11.3 – 17.5)	10.9 (9.4 – 13.3)
• Events, n (%)	23 (25.8)	38 (47.0)	67 (48.6)	75 (52.4)
• HR (95% CI)	**0.51** (0.31 – 0.86)		**0.74** (0.54 – 1.04)	
• Nominal *p*-value	0.0099		0.0789	

MIRASOL

Safety

Parameter, n (%)	Mirvetuximab Soravtansine (n = 218)	Chemotherapy (n = 207)
Any TEAE	210 (96)	194 (94)
• Grade ≥3	91 (42)	112 (54)
SAEs	52 (24)	68 (33)
Discontinuations due to TEAEs	20 (9)	33 (16)
Deaths on study drug or within ≤ 30 days of last dose	5 (2)	5 (2)
Dose reductions due to TEAEs	74 (34)	50 (24)
Dose delays due to TEAEs	117 (54)	111 (54)
Discontinuations due to TEAEs	20 (9)	33 (16)



SUMMARY

MIRASOL

- Mirvetuximab soravtansine is the first novel treatment to demonstrate a benefit in OS in platinum-resistant ovarian cancer in a phase 3 setting
  - First ADC approved by FDA for platinum-resistant ovarian cancer
- Mirvetuximab soravtansine was associated with significant improvements in PFS, ORR, and OS vs investigator's choice of CT in patients with high FRα-expressing, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer
  - Median PFS was 5.62 mo vs 3.98 mo with investigator's choice of CT (P <0.0001)
  - Median OS was 16.46 mo vs 12.75 mo with investigator's choice of CT (P <0.0046)
- Safety profile demonstrated primarily low-grade peripheral neuropathy and ocular and gastrointestinal AEs

ASCO 2023. Abstr LBA5507.

MIRASOL

Mirvetuximab soravtansine provides benefit to patients with high FRα-expressing, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer and should be considered as a new standard of care

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Other Notable Studies

- ADAURA*
- INDIGO*
- SWOG1826*
- DESTINY-PanTumor02
- COMMANDS

* Plenary Session

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CLINICAL QUESTION

PROSPECT

Does neoadjuvant FOLFOX (with selective chemoradiation) benefit patients with locally advanced rectal cancer?

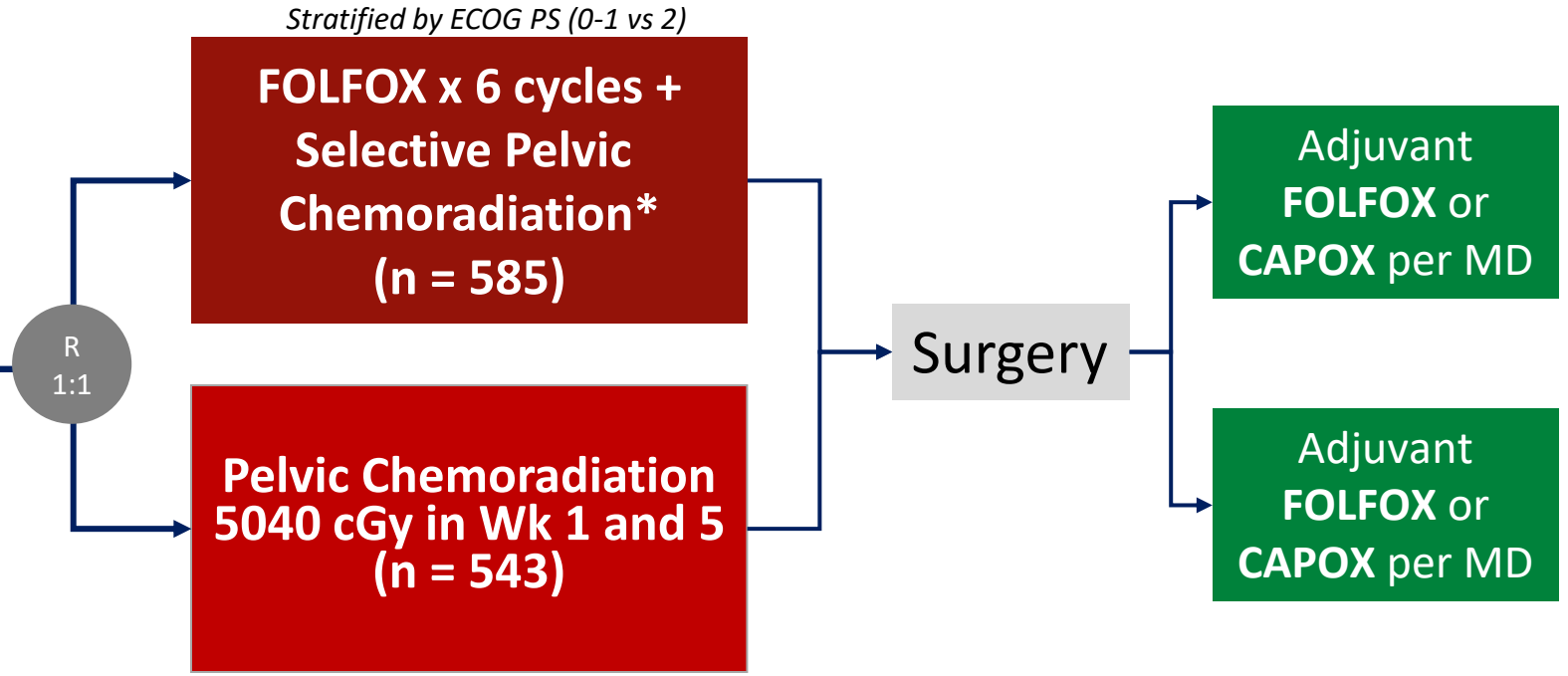
* Plenary Session

PROSPECT

Study Design: Multicenter, unblinded, noninferiority, randomized phase III trial

- Adults with rectal cancer staged as T2 node positive, T3 node negative, or T3 node positive†
- Indicated for neoadjuvant CRT
- Candidate for sphincter-sparing surgery

(N = 1128)



At MD discretion: staging with pelvic MRI or ERUS, IMRT or EBRT, capecitabine or 5-FU IV, open or laparoscopic TME.

†Could not have ≥4 pelvic lymph nodes ≥1 cm in short axis.

*Chemoradiotherapy given only if primary tumor decreased in size by <20% or FOLFOX was discontinued because of toxicity.

Primary endpoint: DFS

Secondary endpoints: local recurrence, OS, complete surgical resection, complete pathologic response, toxicity, QoL

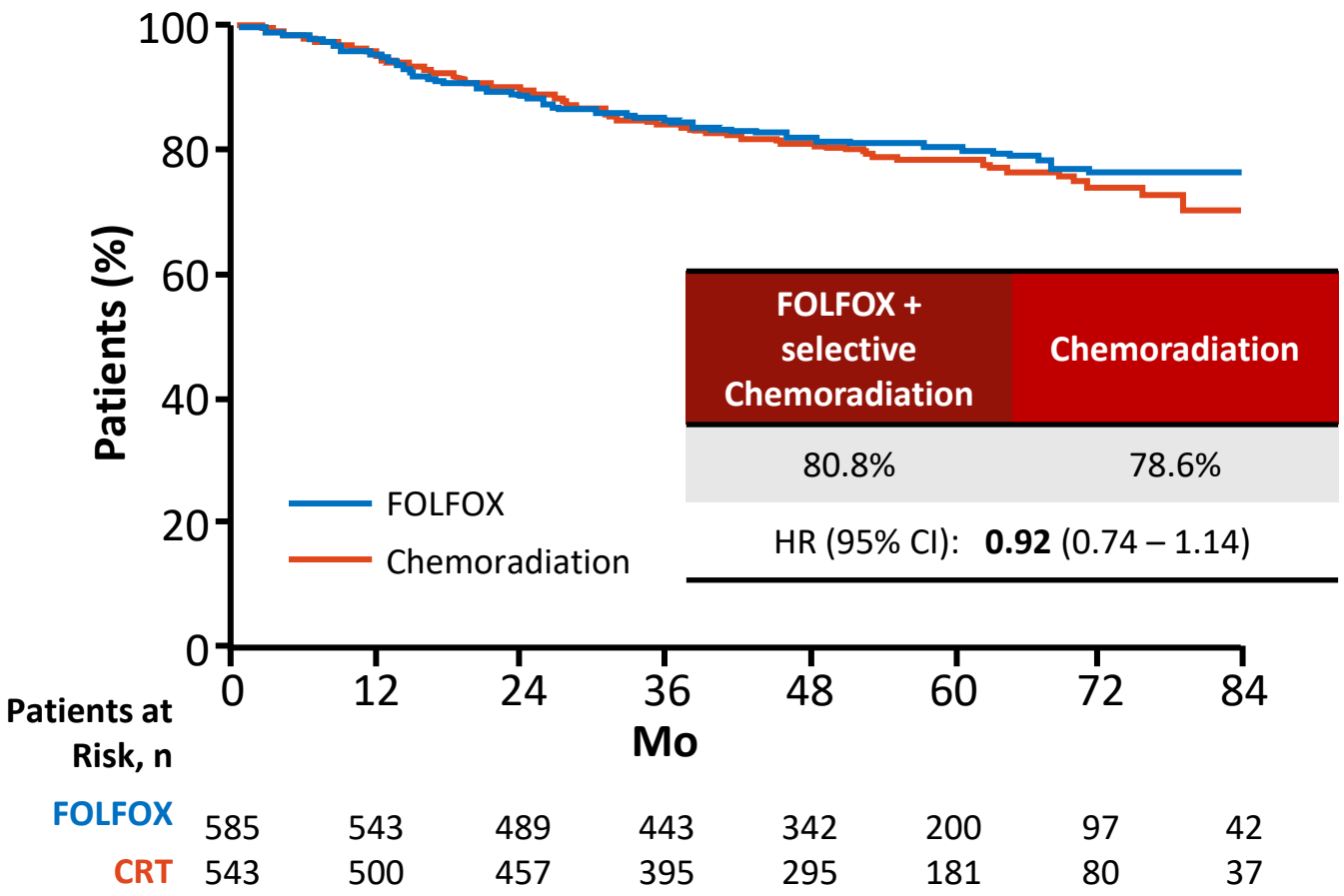
PROSPECT

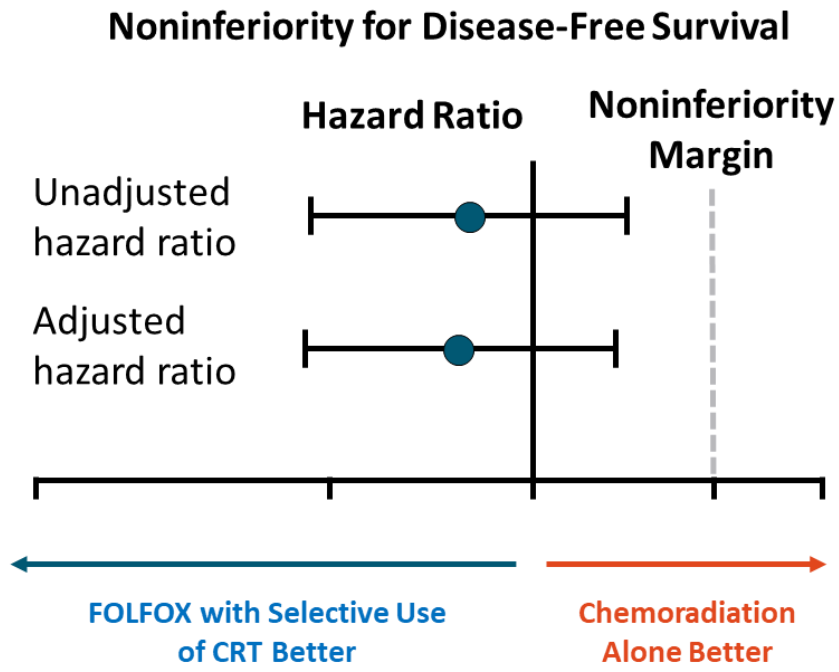
Baseline Characteristics

Characteristic	FOLFOX/Selective Chemoradiation (n = 585)	Chemoradiation (n = 543)
Mean age, yr (SD)	57 (11)	57 (11)
Male, %	63	68
Tumor distance from anal verge, cm (SD)	8 (3)	8 (3)
Baseline MRI staging, %	84	84
Clinical stage at baseline, %		
▪ cT2N+	11	7
▪ cT3N-	40	37
▪ cT3N+	50	57

PROSPECT

Primary Endpoint: Disease Free Survival





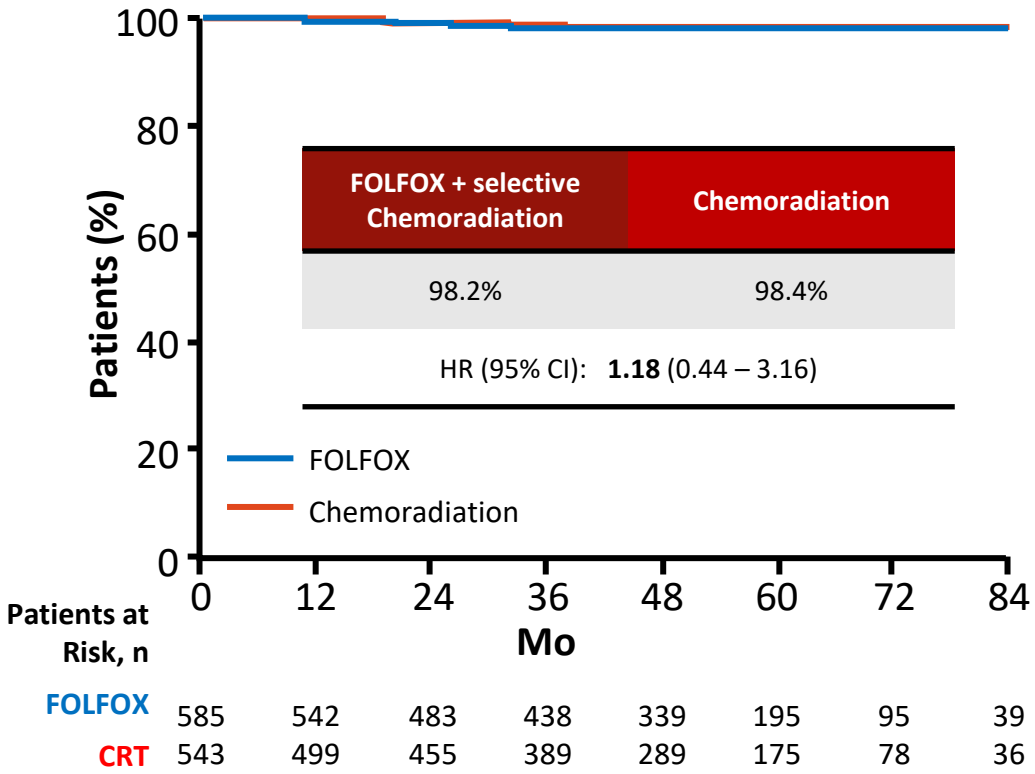
Median follow-up: 58 months

ASCO 2023. Abstr LBA2.

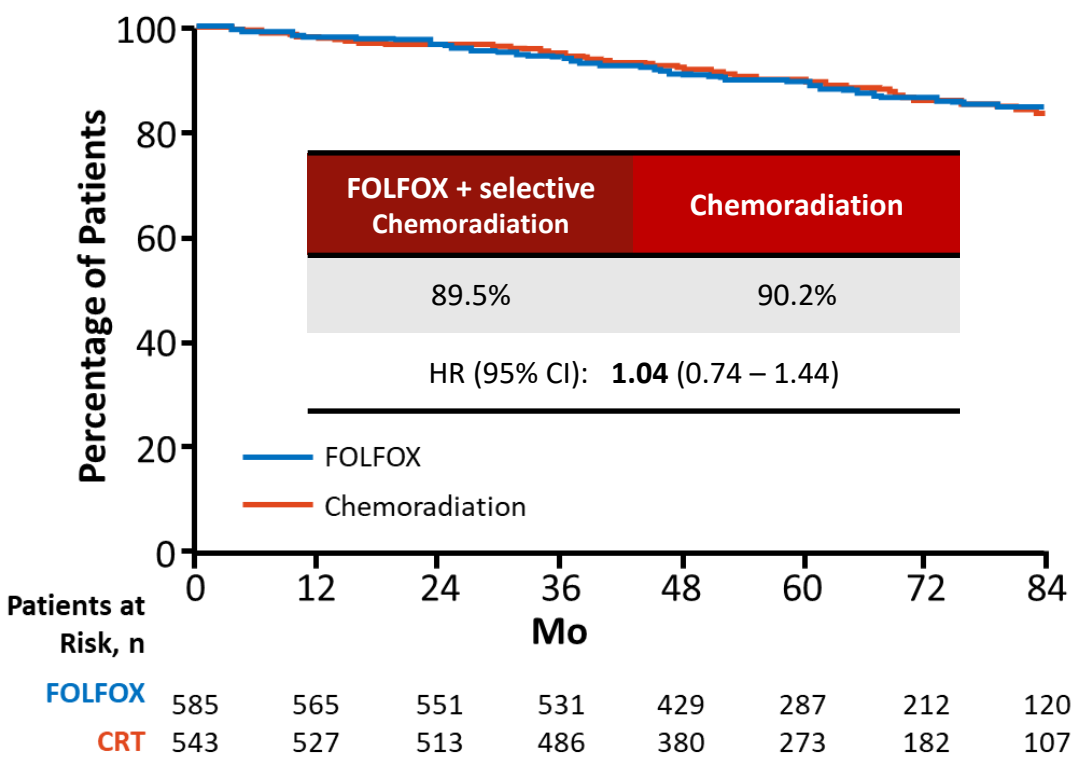
PROSPECT

Secondary Endpoints

Freedom from local recurrence



Overall survival



Median follow-up: 58 months

PROSPECT

Secondary Endpoints

Endpoint	FOLFOX/Selective Chemoradiation (n = 535)	Chemoradiation (n = 510)
Complete (R0) rectal resection, %	99	97
Low anterior resection rate, %	98	98
Pathologic complete response, %	22	24
Positive radial margin, %	1.2	1.5
Received any adjuvant chemotherapy, %	82	83
Received neoadjuvant chemoradiation*, %	9	NA
Received any adjuvant chemotherapy, %	82	83
Median duration from randomization to last dose of postoperative therapy, wk (IQR)	35 (33-39)	37 (34-40)

***9% of participants randomized to FOLFOX received neoadjuvant chemoradiation either because (1) restaging demonstrated clinical response <20% or (2) they did not tolerate at least 5 cycles of FOLFOX**

NA: not applicable

PROSPECT

Safety: Clinician Reported Toxicity

Most Severe Toxicity During Observation Period Based on CTCAE v4.0, %	FOLFOX/Selective Chemoradiation* (n = 535)	Chemoradiation (n = 510)†
Neoadjuvant grade ≥3 AE	41	23
Adjuvant grade ≥3 AE	25	39

*At 12 wk (22 wk if also treated with chemoradiation).
†At 6 wk.

During neoadjuvant treatment:

- More diarrhea in chemoradiation group
- More neuropathy in FOLFOX group

During adjuvant treatment:

- More diarrhea and neuropathy in chemoradiation group

PROSPECT

Safety: Patient Reported Adverse Events

AEs, %	During Neoadjuvant Treatment		At 12 Mo	
	FOLFOX/Selective CRT*	CRT†	FOLFOX/Selective CRT	CRT
Anxiety	11	6	3	2
Appetite loss	22	9	1	1
Constipation	27	11	3	4
Depression	10	3	2	3
Diarrhea	6	20	2	4
Dysphagia	12	1	1	0
Dyspnea	7	1	0	0
Edema	2	2	1	1
Fatigue	42	20	3	7
Mucositis	11	2	0	0
Nausea	21	7	1	0
Neuropathy	19	5	3	8
Pain	22	18	5	4
Vomiting	4	2	0	0

Quality of life:

- Trend toward improved QoL with FOLFOX and selective chemoradiation vs chemoradiation alone, but differences not significant
- Bowel function and sexual function favor FOLFOX and selective chemoradiation group

PROSPECT

- FOLFOX chemotherapy with selective use of pelvic chemoradiation is safe and noninferior for DFS compared with pelvic chemoradiation alone for neoadjuvant treatment of locally advanced rectal cancer (stage cT2, node positive; cT3, node negative or positive)
  - Similar 5-yr DFS, RFS, and OS

- Investigators noted the caveat that novel treatment approaches emerged for this population of patients during this trial, including shorter courses of adjuvant FOLFOX, short-course radiation, total neoadjuvant therapy, nonoperative management, and immunoablative therapy for those with MSI-H disease

PROSPECT

Neoadjuvant chemotherapy (with selective use of chemoradiation) as well as chemoradiation alone, benefits patients with locally advanced rectal cancer providing confidence in multiple treatment options to achieve a high cure rate

2023 ASCO Key Studies

Breast and Gynecological Cancer

- NATALEE
- PALLAS
- PALMIRA
- SONIA
- MIRASOL

GU/GI Cancer

- PROSPECT*
- DESTINY-CRC02
- PEACE-1
- NeoCol
- CONTACT-03

Other Notable Studies

- ADAURA*
- INDIGO*
- SWOG1826*
- DESTINY-PanTumor02
- COMMANDS

* Plenary Session

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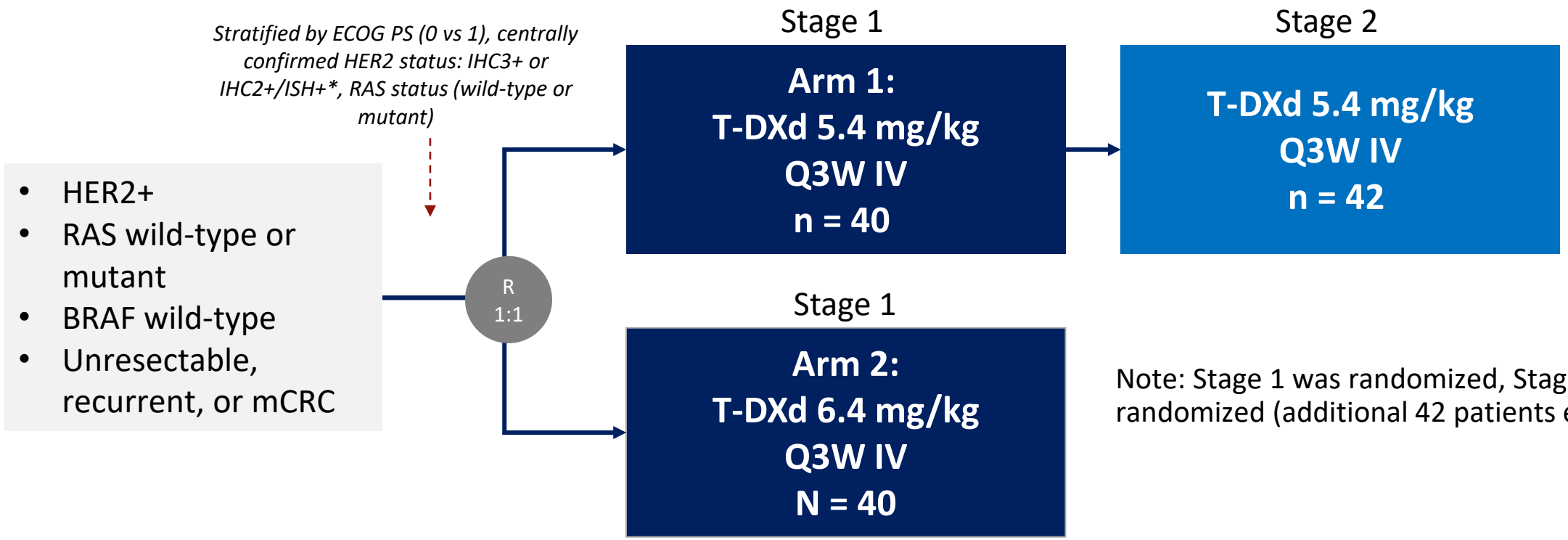
CLINICAL QUESTION

DESTINY-CRC02

Does trastuzumab deruxtecan (T-DXd) benefit previously treated patients with HER2-overexpressing/amplified (HER2+) metastatic colorectal cancer?

DESTINY-CRC02

Study Design: randomized, blinded, 2-stage, 2-arm, multicenter, global phase II trial



Note: Stage 1 was randomized, Stage 2 was not randomized (additional 42 patients enrolled)

Primary analysis‡ data cutoff: Nov 1, 2022

Primary endpoint: cORR by BICR
Secondary endpoints†: cORR by investigator, DoR, DCR, CBR, PFS, OS, Safety

*HER2 status was assessed with the Roche VENTANA HER2 Dual ISH DNA probe cocktail assay
† Exploratory endpoints included best percent change in the sum of diameters of measurable tumors based on BICR and investigator
‡Primary analysis occurred ≥6 months after the last pt had been enrolled or when all patients discontinued from the study, whichever occurred first

DESTINY-CRC02

Baseline Characteristics

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
Median age, years (range)	58.2 (26-78)	60.6 (30-84)	59.1 (26-84)	62.3 (35-81)
Sex, n (%)				
Male	21 (52.5)	24 (57.1)	45 (54.9)	19 (47.5)
Region, n (%)				
Asia-Pacific	25 (62.5)	22 (52.4)	47 (57.3)	24 (60.0)
US	5 (12.5)	1 (2.4)	6 (7.3)	2 (5.0)
Europe	10 (25.0)	19 (45.2)	29 (35.4)	14 (35.0)
HER2 status, n (%)				
IHC 3+	32 (80.0)	32 (76.2)	64 (78.0)	34 (85.0)
IHC 2+/ISH+	8 (20.0)	10 (23.8)	18 (22.0)	6 (15.0)
ECOG PS, n (%)				
0	22 (55.0)	24 (57.1)	46 (56.1)	22 (55.0)
1	18 (45.0)	18 (42.9)	36 (43.9)	18 (45.0)
***RAS* status, n (%)**				
Wild-type	34 (85.0)	34 (81.0)	68 (82.9)	34 (85.0)
Mutant	6 (15.0)	8 (19.0)	14 (17.1)	6 (15.0)

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.

DESTINY-CRC02

Baseline Characteristics (Contd)

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
HER2/*RAS* status, n (%)				
IHC 2+ ISH+/wild-type	7 (17.5)	5 (11.9)	12 (14.6)	6 (15.0)
IHC 2+ ISH+/mutant	1 (2.5)	5 (11.9)	6 (7.3)	0
IHC 3+/wild-type	27 (67.5)	29 (69.0)	56 (68.3)	28 (70.0)
IHC 3+/mutant	5 (12.5)	3 (7.1)	8 (9.8)	6 (15.0)
Liver metastases at baseline, n (%)	29 (72.5)	30 (71.4)	59 (72.0)	26 (65.0)
CNS metastases at baseline, n (%)	3 (7.5)	0	3 (3.7)	1 (2.5)
Primary tumor site, n (%)				
Left colon[a]	32 (80.0)	29 (69.0)	61 (74.4)	34 (85.0)
Rectum	15 (37.5)	12 (28.6)	27 (32.9)	19 (47.5)
Right colon[b]	8 (20.0)	13 (31.0)	21 (25.6)	6 (15.0)

[a] includes rectum, sigmoid, and descending
[b] include cecum, ascending and transverse

DESTINY-CRC02

Prior Treatment

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
Median prior lines of systemic therapy, n (range)	4 (1-12)	3 (1-7)	3 (1-12)	4 (1-8)
Systemic chemotherapy, n (%)	**40 (100)**	**42 (100)**	**82 (100)**	**40 (100)**
Irinotecan	39 (97.5)	40 (95.2)	79 (96.3)	40 (100)
Fluoropyrimidines[a]	40 (100)	42 (100)	82 (100)	40 (100)
Oxaliplatin	40 (100)	41 (97.6)	81 (98.8)	40 (100)
Anti-EGFR, n (%)	29 (72.5)	28 (66.7)	57 (69.5)	31 (77.5)
Anti-HER2, n (%)	**11 (27.5)**	**6 (14.3)**	**17 (20.7)**	**10 (25.0)**
HER2 TKI[b]	6 (15.0)	4 (9.5)	10 (12.2)	7 (17.5)
Anti-HER2 antibodies[c]	10 (25.0)	6 (14.3)	16 (19.5)	10 (25.0)
Anti-VEGF, n (%)	36 (90.0)	38 (90.5)	74 (90.2)	38 (95.0)
Regorafenib and tipiracil/trifluridine, n (%)	20 (50.0)	14 (33.3)	34 (41.5)	13 (32.5)
Other systemic therapy, n (%)	5 (12.5)	6 (14.3)	11 (13.4)	10 (25.0)

[a]Includes 5FU, capecitabine, S1, or tegafur. [b]Includes tucatinib and lapatinib. [c]Includes trastuzumab, trastuzumab duocarmazine, trastuzumab emtansine, pertuzumab, and zanidatamab (ZW25).

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DESTINY-CRC02

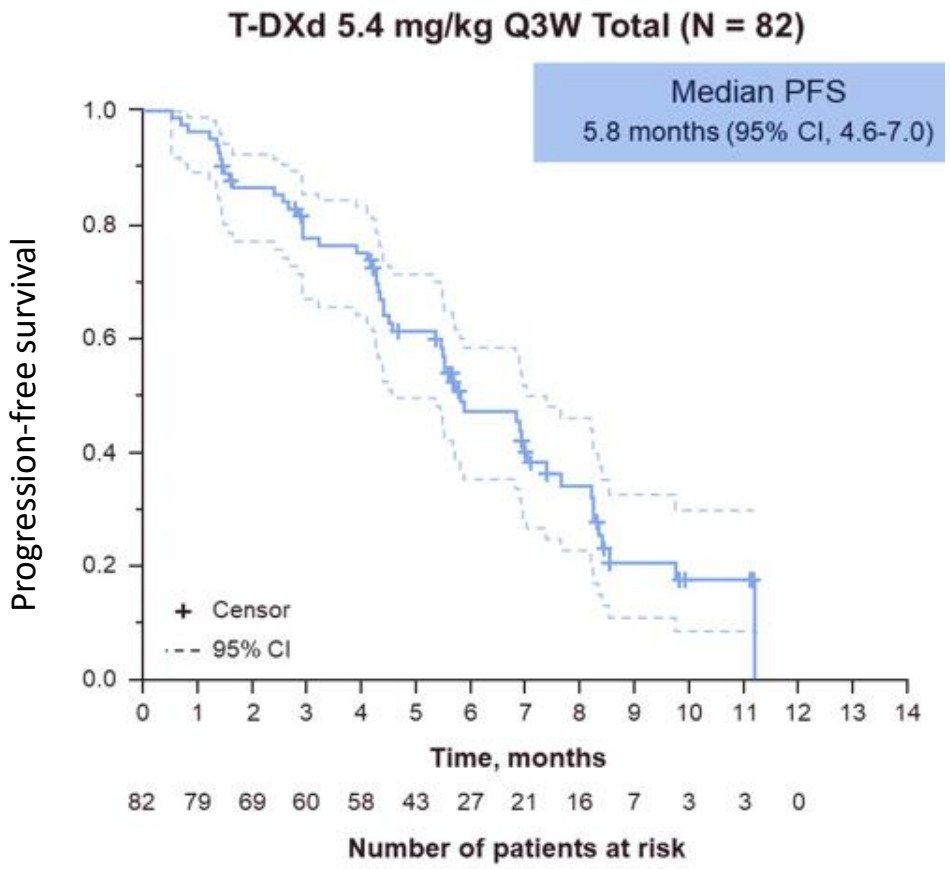
Efficacy

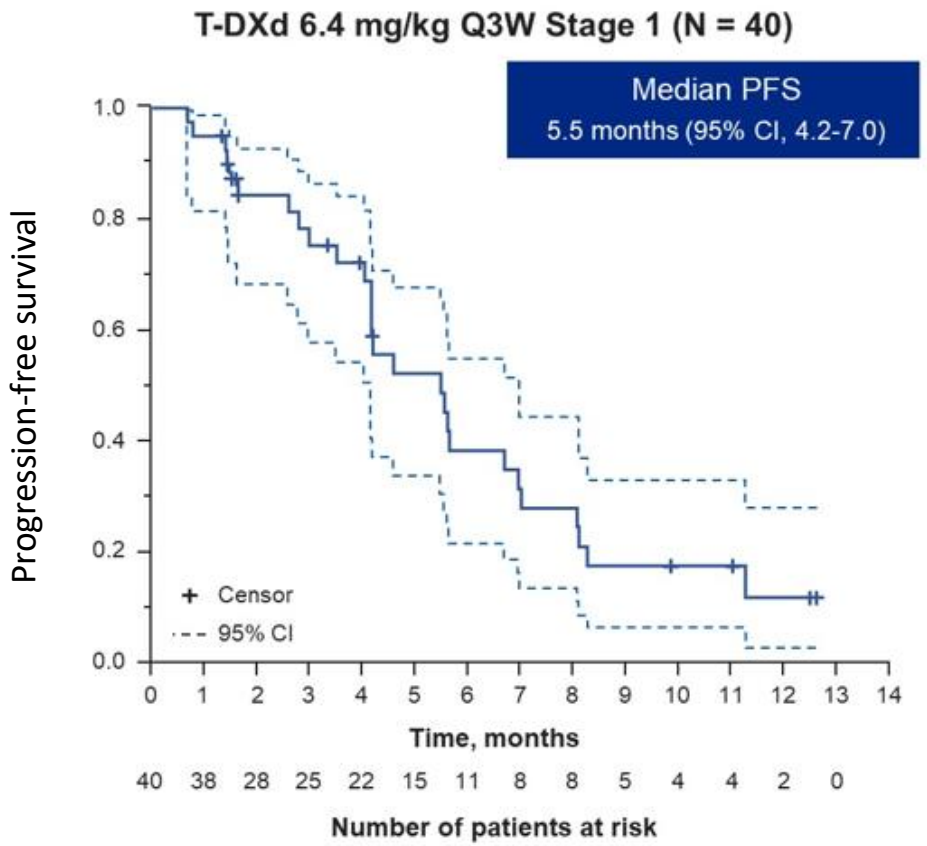
	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
cORR, n (%) [95% CI]	**18 (45.0) [29.3-61.5]**	**13 (31.0) [17.6-47.1]**	**31 (37.8) [27.3-49.2]**	**11 (27.5) [14.6-43.9]**
CR	0	0	0	0
PR	18 (45.0)	13 (31.0)	31 (37.8)	11 (27.5)
SD	20 (50.0)	20 (47.6)	40 (48.8)	23 (57.5)
PD	2 (5.0)	6 (14.3)	8 (9.8)	4 (10.0)
NE	0	3 (7.1)	3 (3.7)	2 (5.0)
Confirmed DCR, n (%) [95% CI]	38 (95.0) [83.1-99.4]	33 (78.6) [63.2-89.7]	71 (86.6) [77.3-93.1]	34 (85.0) [70.2-94.3]
Median DoR, mo (95% CI)	8.1 (4.2-NE)	4.6 (4.1-7.0)	5.5 (4.2-8.1)	5.5 (3.7-NE)
Median follow-up, mo (range)	10.6 (2.9-17.1)	7.7 (0.5-10.3)	8.9 (0.5-17.1)	10.3 (0.7-16.4)
Median treatment duration, mo (range)	5.5 (1.4-13.2)	4.8 (0.7-10.8)	5.5 (0.7-13.2)	4.9 (0.7-13.8)
Median total dose, mg/kg (range)	39.6 (10.5-96.8)	37.4 (5.4-81.3)	37.8 (5.4-96.8)	40.8 (6.4-128.4)
Median number of cycles initiated (range)	8.0 (2-19)	7.0 (1-15)	7.0 (1-19)	7.0 (1-20)

cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DoR, duration of response; mo, month; NE, not evaluable; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SD, stable disease; T-DXd, trastuzumab deruxtecan.

DESTINY-CRC02

Progression-Free Survival





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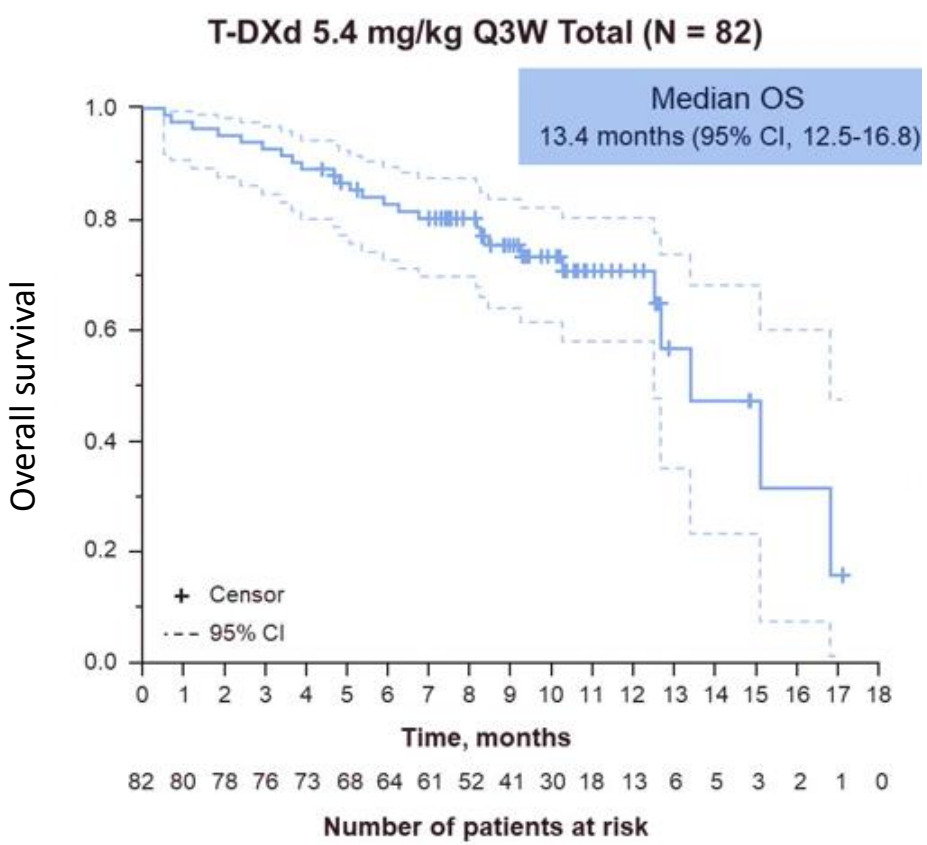
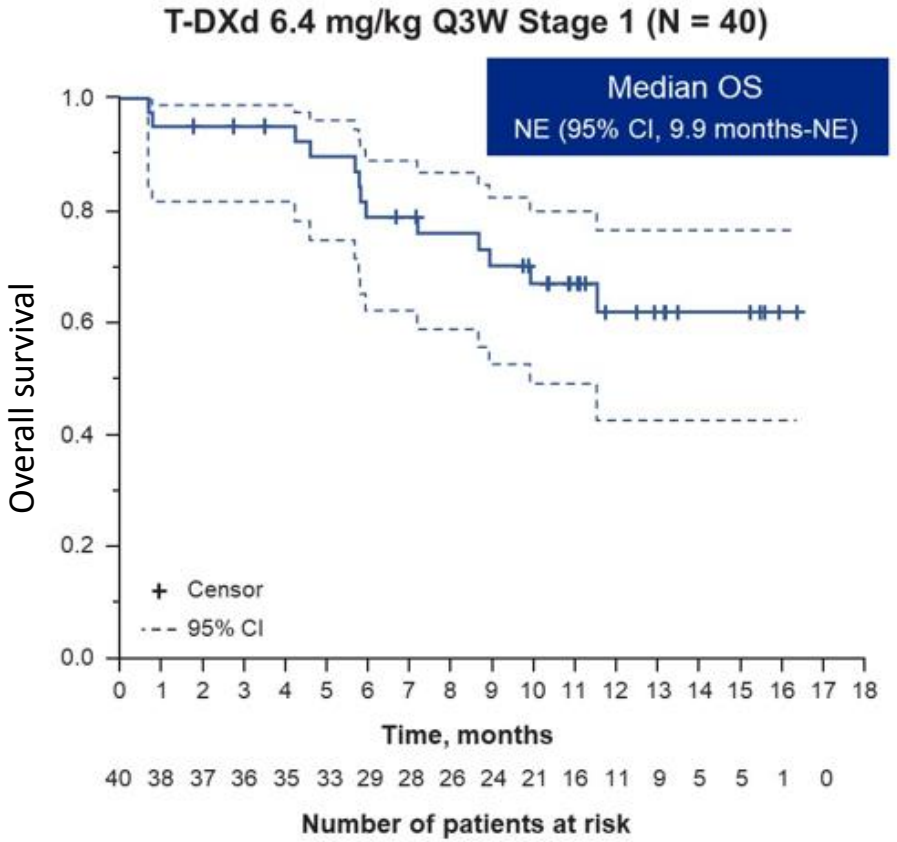
DESTINY-CRC02

Overall Survival

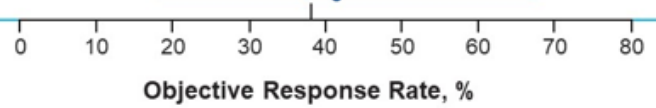




DESTINY-CRC02

Best Overall Response by BICR by subgroup with 5.4 mg/kg T-DXd

		ORR, % (n/N)	95% CI[a]
All patients (5.4 mg/kg)	**N = 82**	**37.8 (31/82)**	27.3-49.2
HER2 status	IHC 3+	**46.9 (30/64)**	34.3-59.8
	IHC 2+/ISH+	**5.6 (1/18)**	0.1-27.3
***RAS* status**	Wild-type	**39.7 (27/68)**	28.0-52.3
	Mutant[b]	**28.6 (4/14)**	8.4-58.1
ECOG PS	0	**39.1 (18/46)**	25.1-54.6
	1	**36.1 (13/36)**	20.8-53.8
Primary tumor site	Left colon[c]	**39.3 (24/61)**	27.1-52.7
	Right colon[d]	**33.3 (7/21)**	14.6-57.0
Prior anti-HER2 treatment	No	**36.9 (24/65)**	25.3-49.8
	Yes	**41.2 (7/17)**	18.4-67.1



[a]Based on the exact Clopper-Pearson method for binomial distribution. [b]All *RAS*m responders were IHC 3+. [c]Includes rectum, sigmoid, and descending. [d]Includes cecum, ascending, and transverse.

DESTINY-CRC02

Safety Summary

n (%)	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 41[a]	Stage 2 n = 42	Total N = 83	Stage 1 N = 39
TEAEs	**40 (97.6)**	**42 (100)**	**82 (98.8)**	**39 (100)**
Drug-related	38 (92.7)	38 (90.5)	76 (91.6)	37 (94.9)
TEAEs grade ≥3	**20 (48.8)**	**21 (50.0)**	**41 (49.4)**	**23 (59.0)**
Drug-related	16 (39.0)	18 (42.9)	34 (41.0)	19 (48.7)
Serious TEAEs	**8 (19.5)**	**12 (28.6)**	**20 (24.1)**	**12 (30.8)**
Drug-related	4 (9.8)	7 (16.7)	11 (13.3)	6 (15.4)
TEAEs associated with drug discontinuation	**3 (7.3)**	**5 (11.9)**	**8 (9.6)**	**3 (7.7)**
Drug-related	3 (7.3)	3 (7.1)	6 (7.2)	2 (5.1)
TEAEs associated with dose reduction	**9 (22.0)**	**6 (14.3)**	**15 (18.1)**	**10 (25.6)**
Drug-related	9 (22.0)	6 (14.3)	15 (18.1)	9 (23.1)
TEAEs associated with drug interruption	**19 (46.3)**	**20 (47.6)**	**39 (47.0)**	**19 (48.7)**
Drug-related	13 (31.7)	9 (21.4)	22 (26.5)	10 (25.6)
TEAEs associated with death	**1 (2.4)**	**3 (7.1)**	**4 (4.8)**	**3 (7.7)**
Drug-related	1 (2.4)[b]	0	1 (1.2)[b]	0[c]

[a]1 patient randomized to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and counted in the 5.4 mg/kg arm safety analysis set. [b]Patient experienced grade 5 hepatic failure. [c]There was 1 adjudicated, drug-related, grade 5 ILD/pneumonitis event, which was reported as respiratory failure, which was considered unrelated to study drug by investigator.

DESTINY-CRC02

Safety: Adjudicated Drug-Related ILD/Pneumonitis by Independent Adjudication Committee

Adjudicated as drug-related ILD/pneumonitis, n (%)	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 41[a]	Stage 2 n = 42	Total N = 83	Stage 1 N = 39
Any grade	4 (9.8)	3 (7.1)	7 (8.4)	5 (12.8)
Grade 1	1 (2.4)	0	1 (1.2)	2 (5.1)
Grade 2	3 (7.3)	3 (7.1)	6 (7.2)	2 (5.1)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	1 (2.6)[b]

[a]1 patient randomized to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and counted in the 5.4 mg/kg arm safety analysis set. [b]There was 1 adjudicated, drug-related, grade 5 ILD/pneumonitis event, which was reported as respiratory failure, which was considered unrelated to study drug by investigator.

SUMMARY

DESTINY-CRC02

- In patients with HER2+ metastatic CRC trastuzumab deruxtecan provided benefit
  - Among all patients who received a 5.4 mg/kg dosage of trastuzumab deruxtecan (n = 82), the cORR was 37.8% compared to 27.5% for those who received 6.4 mg/kg (n = 40)
  - The median DoR was similar, with both the 5.4 mg/kg and 6.4 mg/kg dose levels showing a DoR of 5.5 months
  - The disease control rate (DCR) was 86.6% in the group receiving a dosage of 5.4 mg/k, compared to 85.0% in the group receiving a dosage of 6.4 mg/kg
  - The median PFS was 5.8 months in the 5.4-mg/kg cohort, and the median OS was 13.4 months. In the 6.4-mg/kg cohort, the median PFS was 5.5 months, and the median OS was NE.
- Safety profile favors the 5.4 mg/kg dose

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DESTINY-CRC02

T-DXd monotherapy at the lower dose of 5.4mg/kg has the potential to benefit patients with HER2-overexpressing/amplified (HER2+) metastatic colorectal cancer

Identifying patients with HER2+ CRC will be important

More to come…

2023 ASCO Key Studies

Breast and Gynecological Cancer	GU/GI Cancer	Other Notable Studies
• NATALEE • PALLAS • PALMIRA • SONIA • MIRASOL	• PROSPECT* • DESTINY-CRC02 • PEACE-1 • NeoCol • CONTACT-03	• ADAURA* • INDIGO* • SWOG1826* • DESTINY-PanTumor02 • COMMANDS

* Plenary Session

CLINICAL QUESTION

PEACE-1

Does prostate irradiation provide benefit for men with *de novo*, low volume, metastatic castration-sensitive prostate cancer (mCSPC)?

KEY DATA

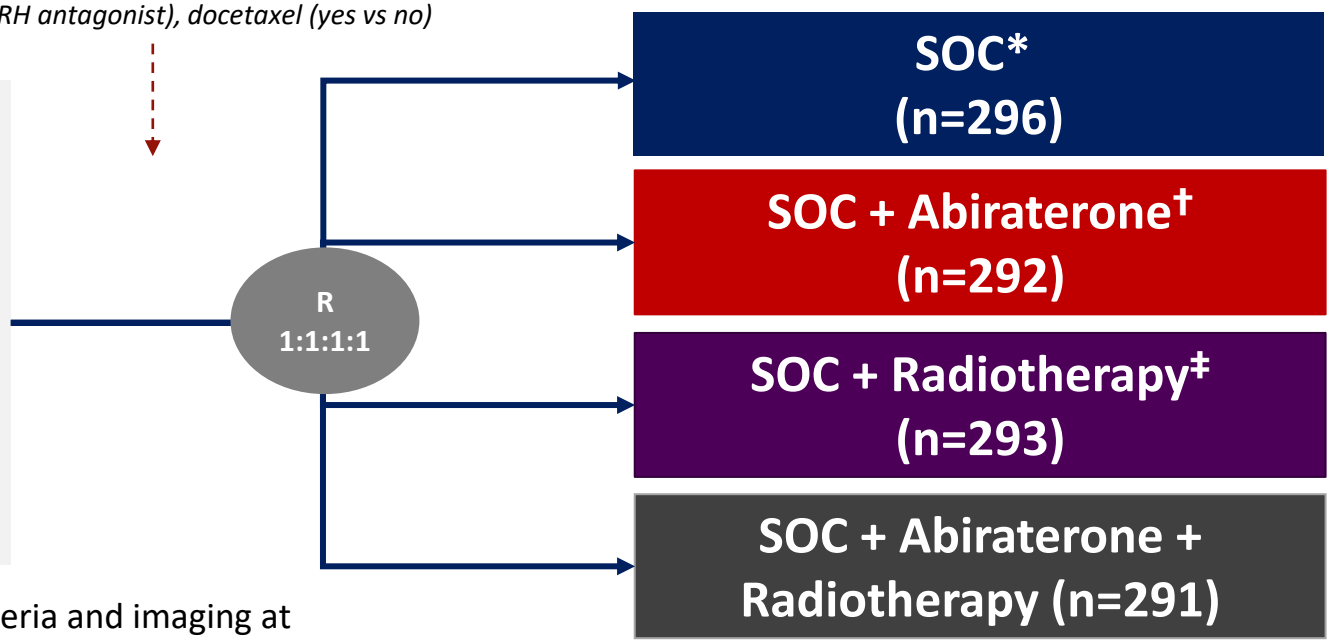
PEACE-1

Study Design: randomized, 2x2 design, phase 3 trial

- *De novo* mCSPC
- Distant metastatic disease: ≥1 lesion on bone scan oand /or CT scan
- ECOG PS 0-2
- On-study requirement of continuous ADT
- ADT ≤3 months permitted

(N=1172)

Stratified by ECOG PS (0 vs 1), metastatic sites (LN vs bone vs visceral), type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist), docetaxel (yes vs no)



Primary endpoint: radiographic PFS (rPFS; PCWG2 criteria and imaging at least q6m after PSA rise) and overall survival

Secondary endpoints: castration resistance-free survival, serious genitourinary EFS, PC specific survival, time to next skeletal-related event, PSA response rate, PSA at 8 mo after initiation of SOC, time to pain progression, time to chemo for CRPC, QoL, toxicity, changes in bone mineral density (BMD), biomarkers, outcomes for pts with NE differentiation

* SOC: androgen deprivation therapy (ADT) continuously (LHRH agonist/antagonist or bilateral orchiectomy) ± docetaxel 75 mg/m2/3w x 6 (G-CSF recommended)

†Abiratone 1000 mg/d + prednisone 5mg BID until disease progression or intolerance (concomitant to docetaxel)

‡Radiotherapy (RXT) of the prostate 74 Gy in 37 fractions (after docetaxel is completed)

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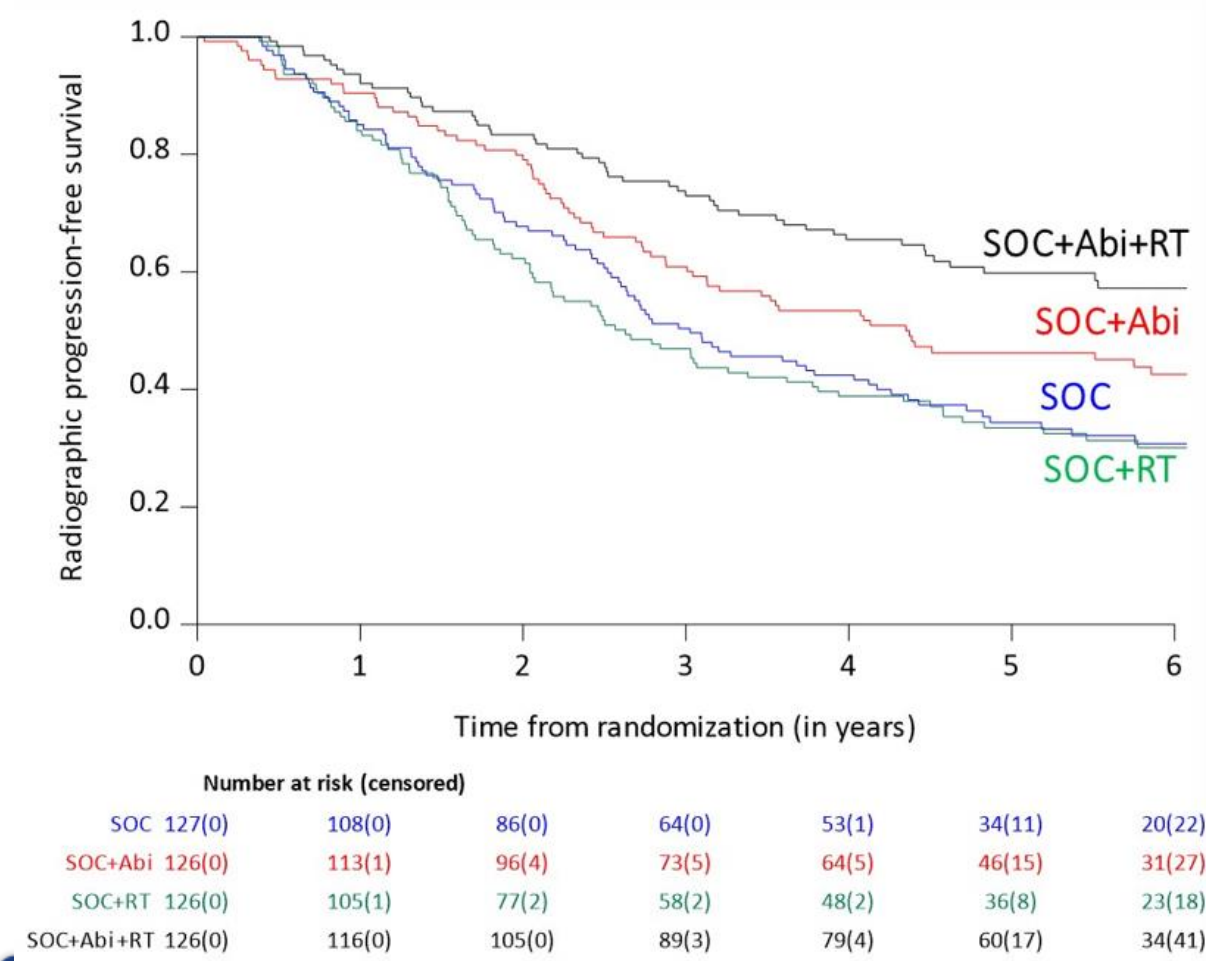
PEACE-1

Baseline Characteristics

		Overall population		Low volume population	
		SOC (± Abi) n=588	**SOC (± Abi + RT) n=584**	**SOC (± Abi) n=253**	**SOC (± Abi + RT) n=252**
Median age, year (range)		67 (43-88)	66 (37-94)	67 (43 – 86)	66 (46 – 84)
ECOG PS score, n (%)	0 1-2	411 (70) 177 (30)	413 (71) 171 (29)	180 (71) 73 (29)	194 (77) 58 (23)
Gleason score at diagnosis, n (%)	≤7 ≥8 Missing	142 (23) 429 (74) 17 (3)	136 (24) 441 (75) 7 (1)	71 (27) 173 (70) 9 (3)	66 (26) 184 (73) 2 (1)
Median time from diagnosis, month (IQR)		2.2 (1.5 – 3.1)	2.3 (1.5 – 3.2)	2.5 (1.8 – 3.4)	2.6 (1.7 – 3.5)
Metastatic sites, n (%)	LN only Bone only Visceral	51 (9) 474 (81) 63 (11)	48 (8) 473 (81) 63 (11)	47 (19) 206 (81) ---	41 (16) 211 (84) ---
Disease volume, n (%)	Low High	253 (43) 335 (57)	252 (43) 332 (37)	---	---
Median baseline PSA, ng/mL (IQR)		13.1 (3.5 – 57.1)	12.6 (3.0 – 62.4)	10.3 (3.3 – 31)	9 (2.3 – 39.1)
Docetaxel	Yes No	355 (60) 233 (40)	355 (61) 229 (39)	127 (50) 126 (50)	127 (50) 127 (50)

PEACE-1

Primary Endpoint: rPFS (low volume population)



	SOC (n=127)	SOC+RT (n=126)	SOC+Abi (n=126)	SOC+Abi+RT (n=126)
Median, ys. (99.9% CI)	3.0 (2.3-4.8)	2.6 (1.7-4.6)	4.4 (2.5-7.3)	7.5 (4,0-NE)
Events, n.	87	89	74	55
HR (99.9%CI)*	Ref	1.11 (0.67-1.84)	0.76 (0.45-1,28)	0.50 (0.28-0.88)
Global p-value	<0.0001			
HR (99.9% CI)*	Ref	1.08 (0.65-1.80)	Ref	0.65 (0.36-1.19)
P-values arms w/wo Abi	0.61		0.02	

* Adjusted on stratification factors (PS, type of castration, docetaxel)

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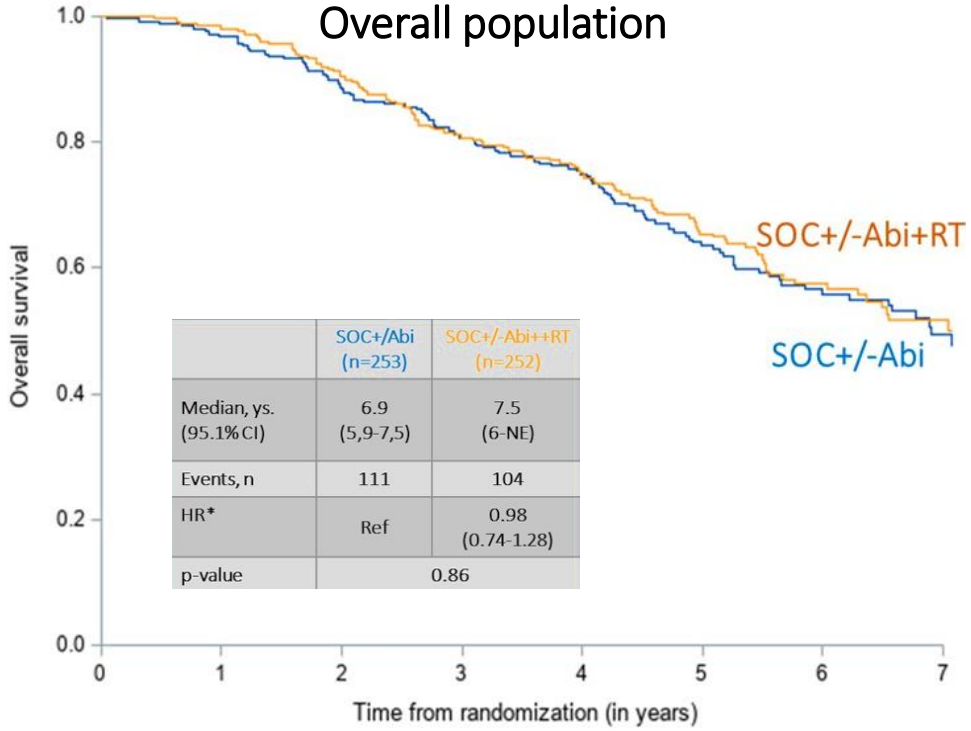
PEACE-1

Primary Endpoint: OS

Overall population

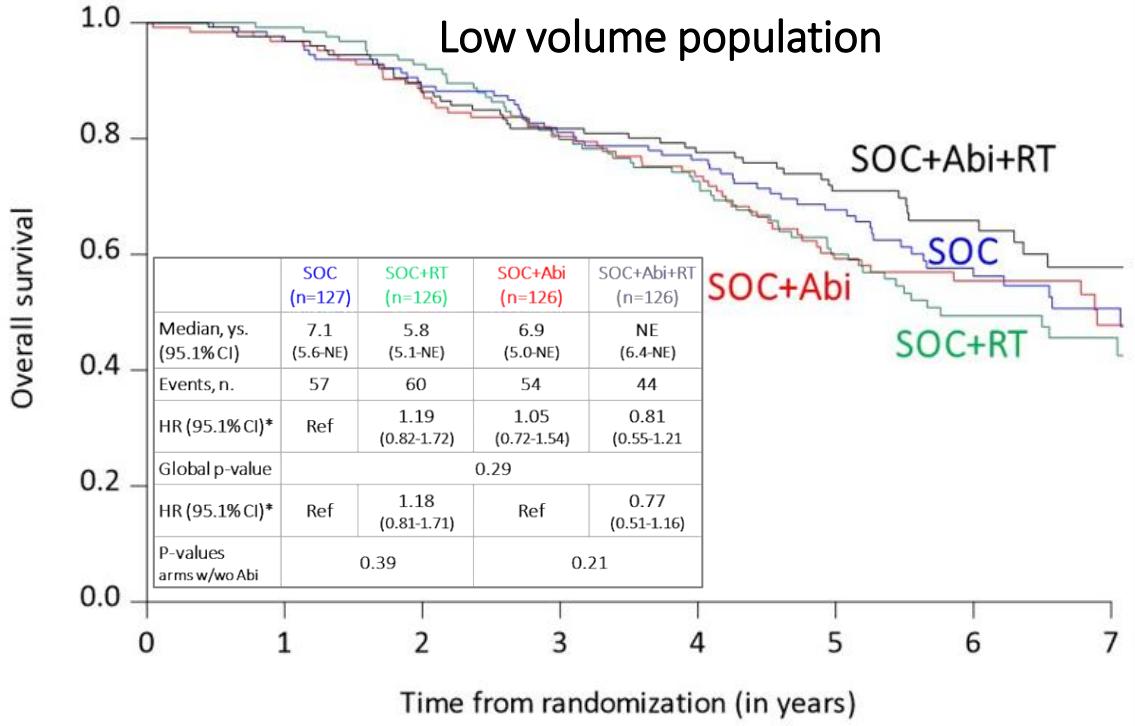


	SOC+/Abi (n=253)	SOC+/-Abi+RT (n=252)
Median, ys. (95.1% CI)	6.9 (5,9-7,5)	7.5 (6-NE)
Events, n	111	104
HR*	Ref	0.98 (0.74-1.28)
p-value	0.86	

Number at risk (censored)

SOC+/-Abi 253(0)	244(1)	219(5)	198(7)	182(9)	127(39)	75(78)	32(11
SOC+/-Abi+RT 252(0)	246(1)	226(2)	199(5)	184(6)	133(36)	71(85)	31(11

Low volume population



	SOC (n=127)	SOC+RT (n=126)	SOC+Abi (n=126)	SOC+Abi+RT (n=126)
Median, ys. (95.1% CI)	7.1 (5.6-NE)	5.8 (5.1-NE)	6.9 (5.0-NE)	NE (6.4-NE)
Events, n.	57	60	54	44
HR (95.1% CI)*	Ref	1.19 (0.82-1.72)	1.05 (0.72-1.54)	0.81 (0.55-1.21
Global p-value	0.29			
HR (95.1% CI)*	Ref	1.18 (0.81-1.71)	Ref	0.77 (0.51-1.16)
P-values arms w/wo Abi	0.39		0.21	

Number at risk (censored)

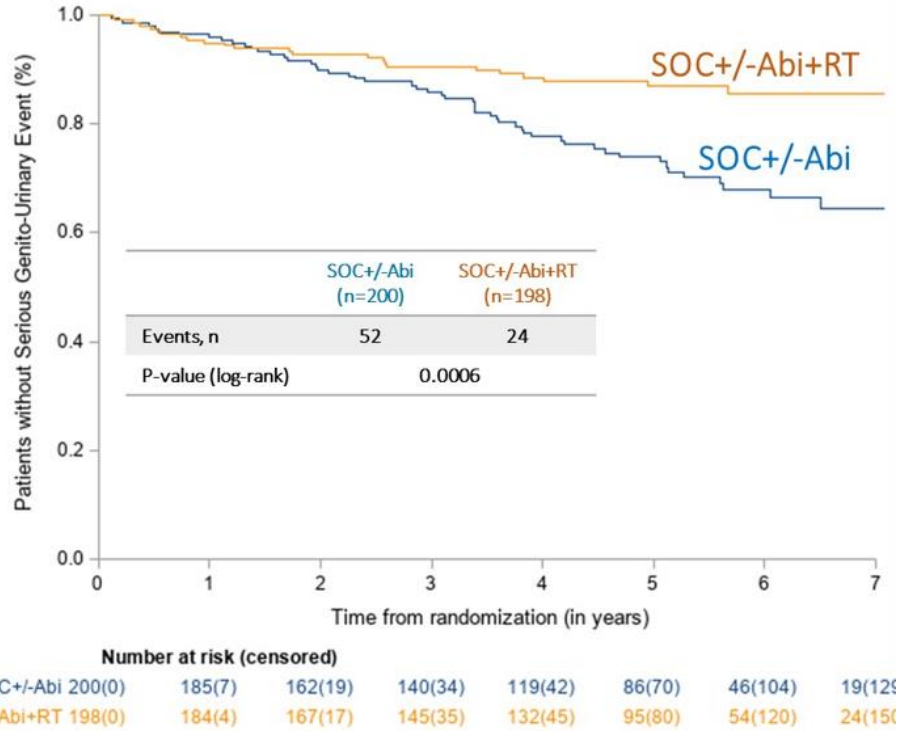
SOC 127(0)	123(0)	113(0)	103(0)	96(1)	70(17)	40(37)	17(57)
SOC+Abi 126(0)	121(1)	106(5)	95(7)	86(8)	57(22)	35(41)	15(58)
SOC+RT 126(0)	124(1)	115(2)	99(2)	90(2)	61(17)	33(36)	15(52)
SOC+Abi+RT 126(0)	122(0)	111(0)	100(3)	94(4)	72(19)	38(49)	16(67)

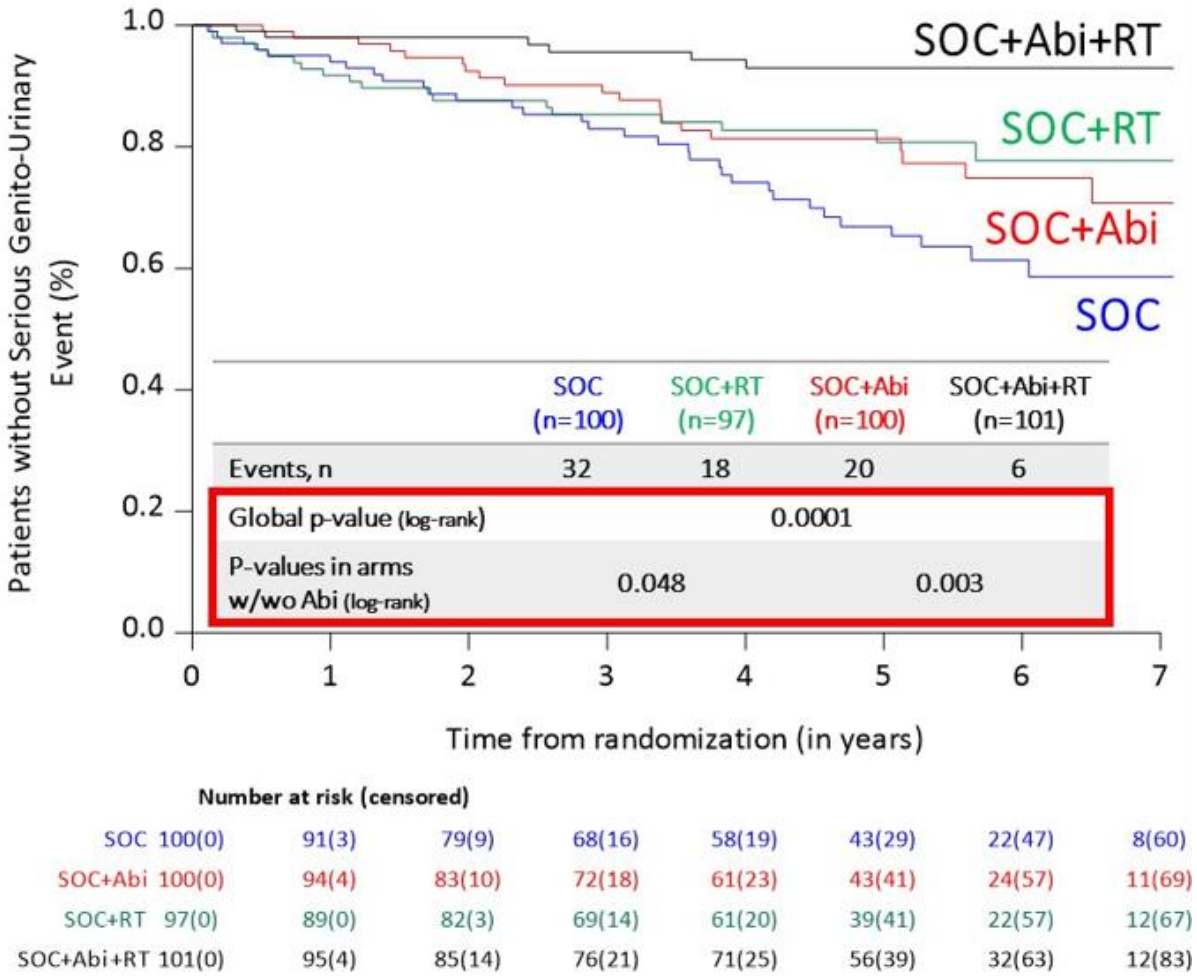
* Adjusted on abiraterone and stratification factors (PS, type of castration, docetaxel)

PEACE-1

Time to Serious Genitourinary events (low volume population)

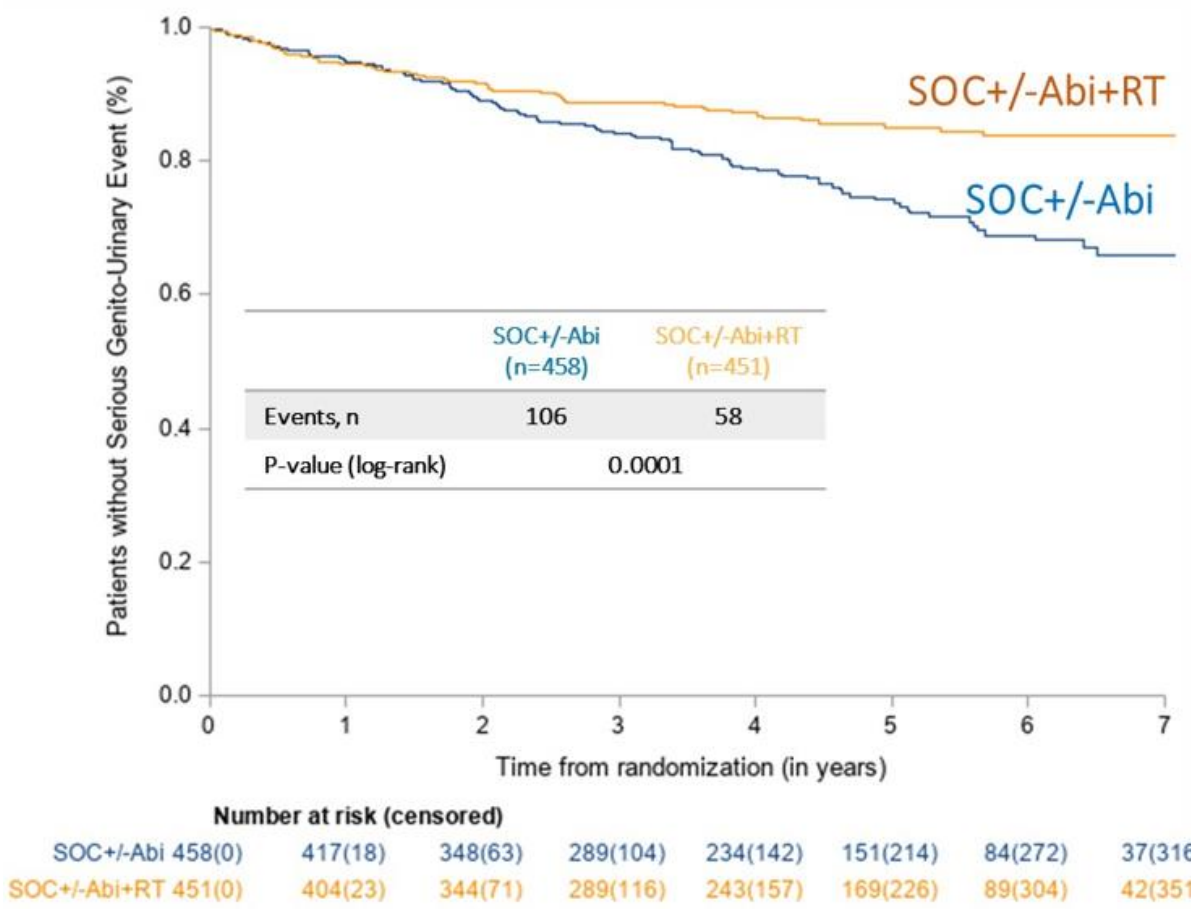
Serious Genitourinary events	No RT (n=200)	RT (n=198)
Urinary catheter	9	6
Double J Stent	13	12
Nephrostomy	2	1
Prostate RT or TURP	27	4 TURP (all RT)
Radical Prostatectomy	1	1

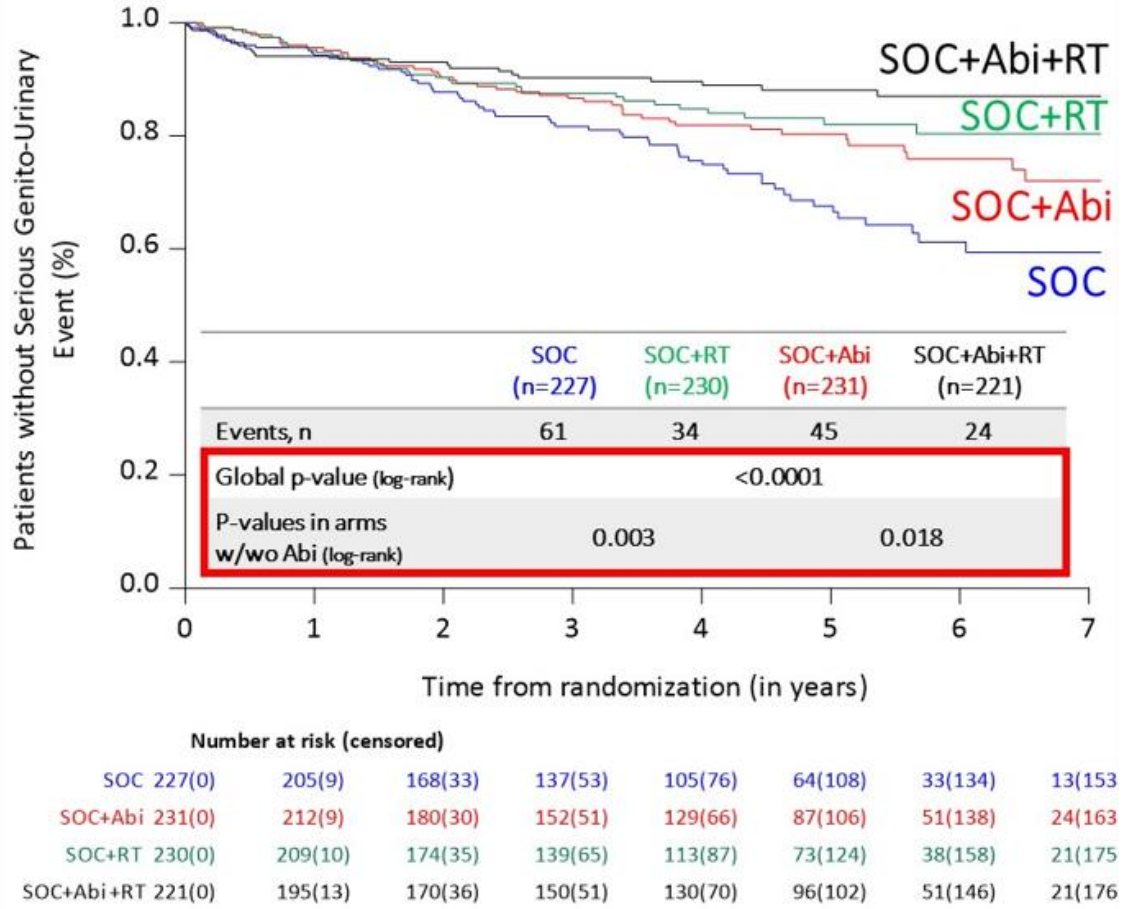




PEACE-1

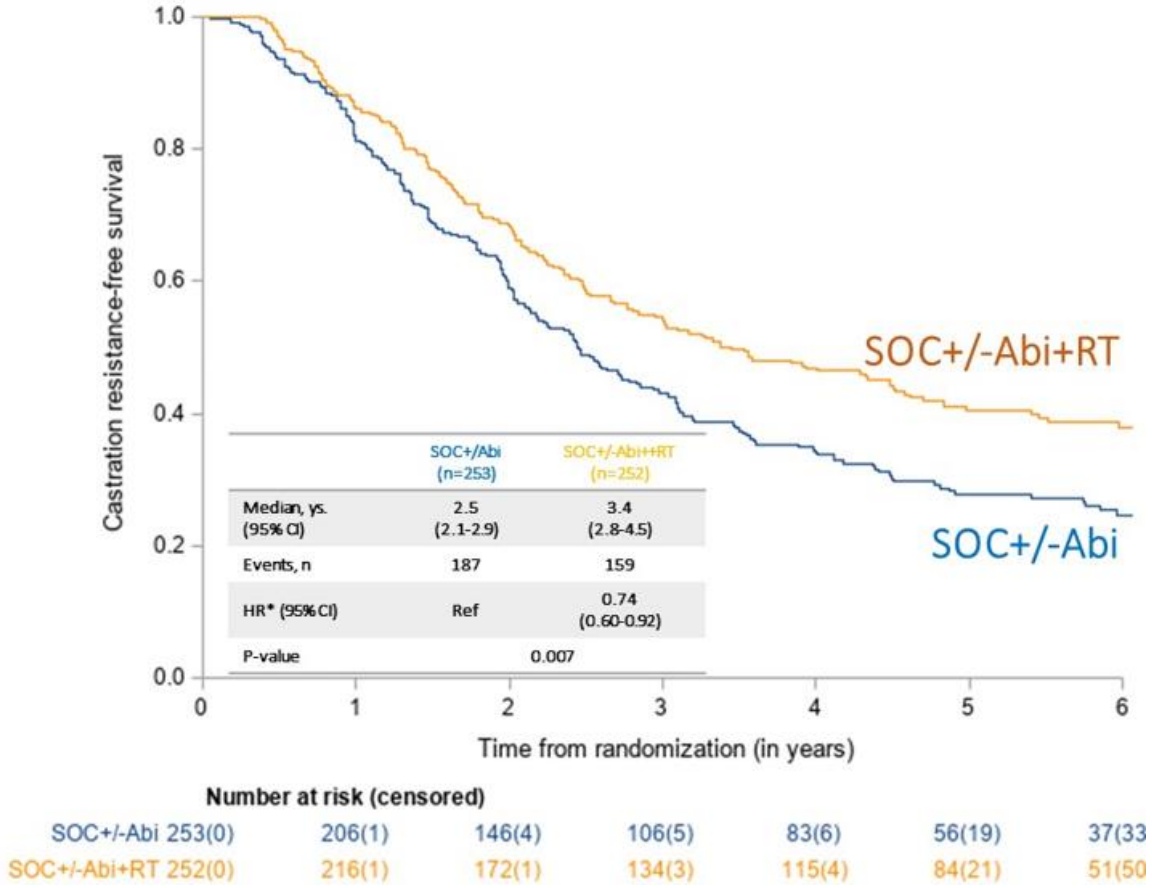
Time to Serious Genitourinary events (overall population)

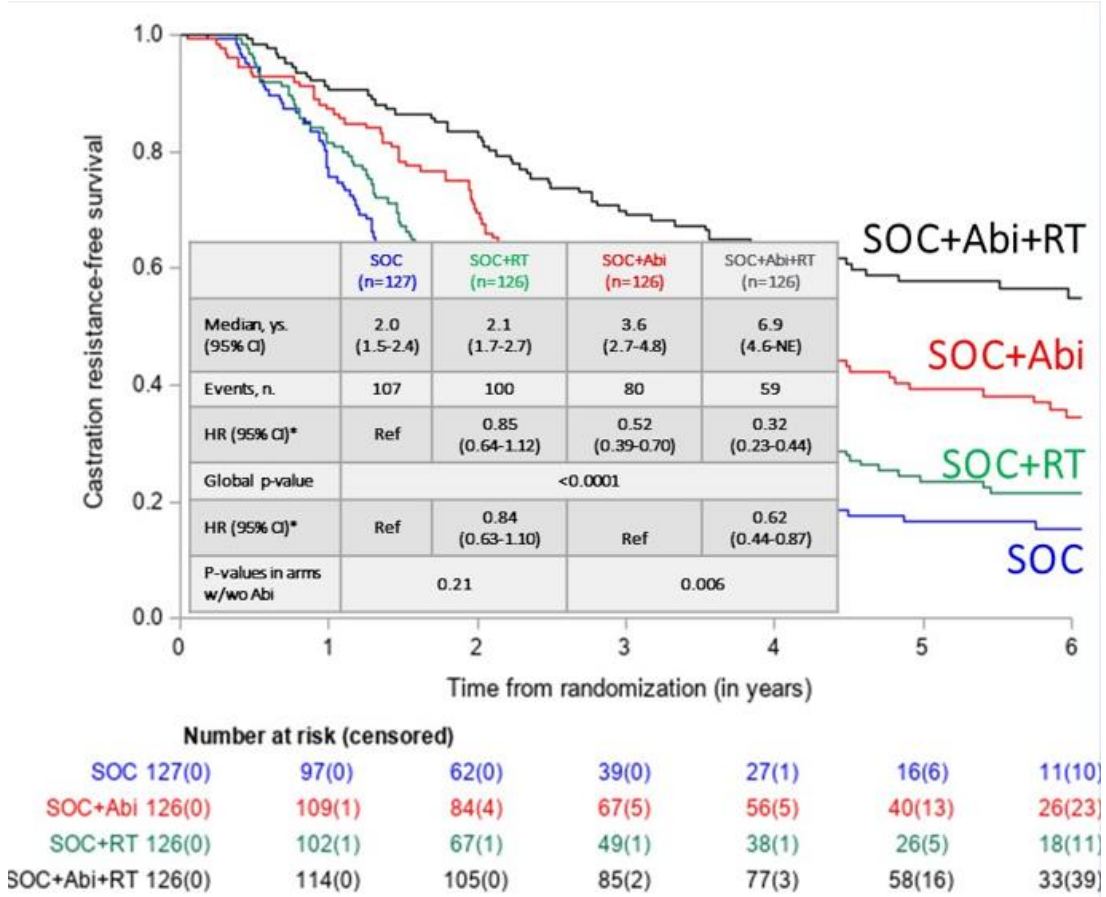




PEACE-1

Castration Resistance Free-survival (low volume population)

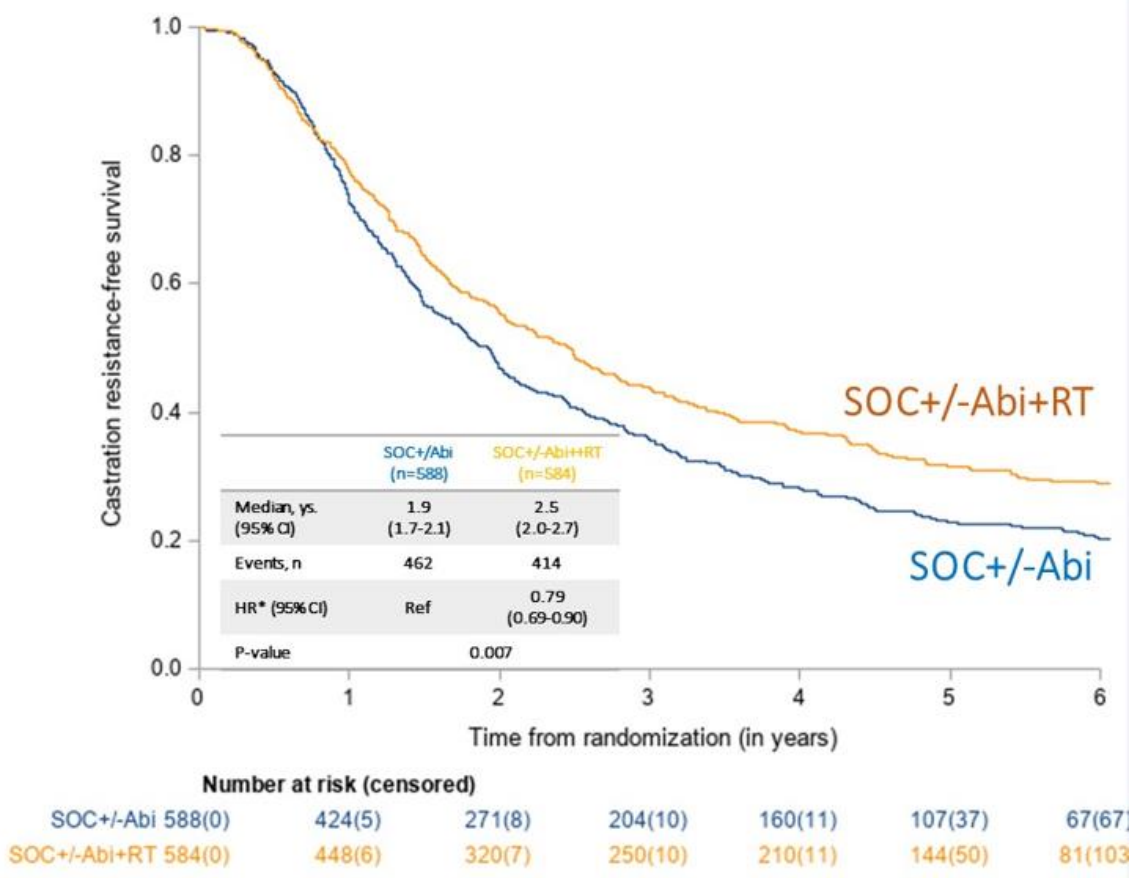


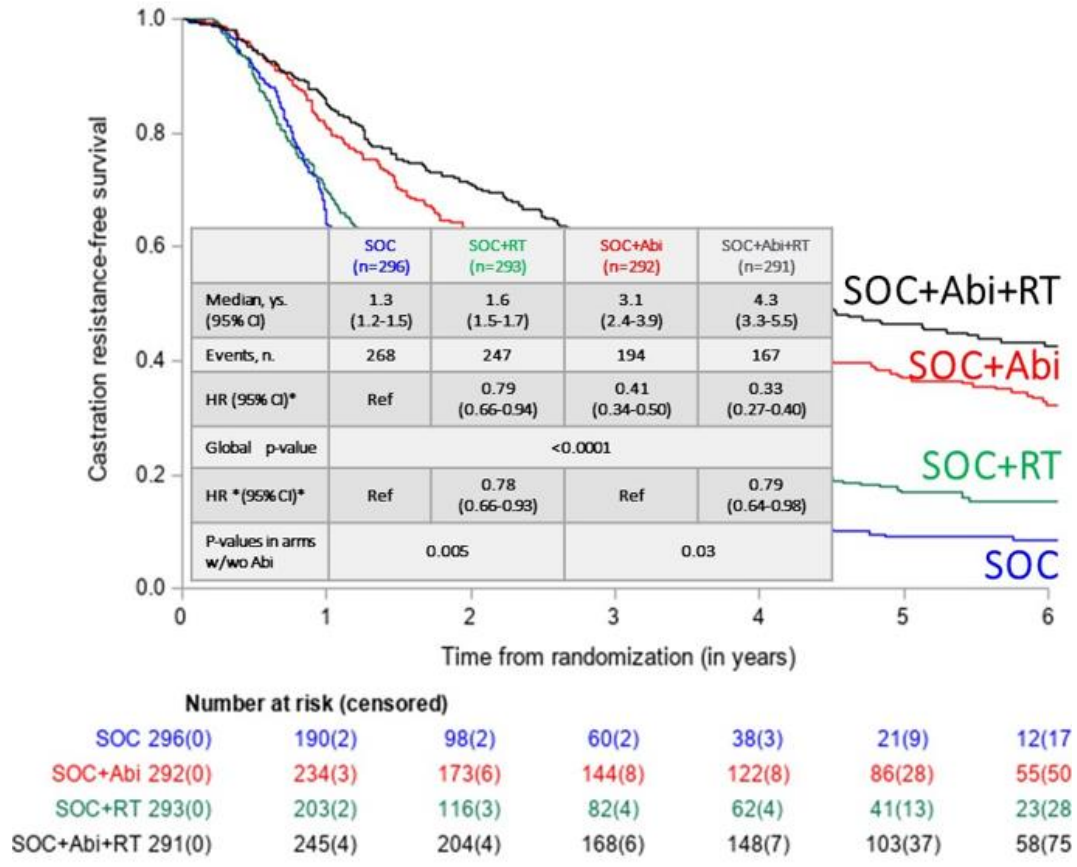


* Adjusted on stratification factors (PS, type of castration, docetaxel)

PEACE-1

Castration Resistance Free-survival (Overall population)





* Adjusted on stratification factors (PS, type of castration, docetaxel)

PEACE-1

Safety: Toxicity, Grade 3-5 (overall safety population)

n (%)	SOC ± ABI (n=604)	SOC ± ABI + RT* (n=560)
Hypertension	110 (18)	127 (23)
Neutropenia	40 (7)	29 (5)
Febrile neutropenia	20 (3)	19 (3)
Hepatotoxicity	22 (4)	18 (3)
Fatigue	17 (3)	12 (2)
Gastrointestinal disorders	29 (5)	17 (3)
Rectal hemorrhage	0 (0)	5 (1)

* Safety population: pts who received any part of study treatment, according to study treatments actually received

SUMMARY

PEACE-1

- Combining prostate radiotherapy with intensified systemic treatment (abiraterone +/- docetaxel) was associated with improved rPFS and CRPC free-survivals in men with low volume, *de novo* mCSPC
    - Prostate radiotherapy does not significantly improve OS
    - Prostate radiotherapy improves rates of serious GU events
- A similar toxicity profile was observed among patients receiving radiotherapy versus not

ASCO 2023. Abstr #3501.

PEACE-1

The addition of abiraterone plus prednisone to standard of care (ADT plus docetaxel) provides benefit for patients with de novo low burden mCSPC

The addition of RT to the regimen provides additional benefit

2023 ASCO Key Studies

Breast and Gynecological Cancer

- NATALEE
- PALLAS
- PALMIRA
- SONIA
- MIRASOL

GU/GI Cancer

- PROSPECT*
- DESTINY-CRC02
- PEACE-1
- NeoCol
- CONTACT-03

Other Notable Studies

- ADAURA*
- INDIGO*
- SWOG1826*
- DESTINY-PanTumor02
- COMMANDS

* Plenary Session

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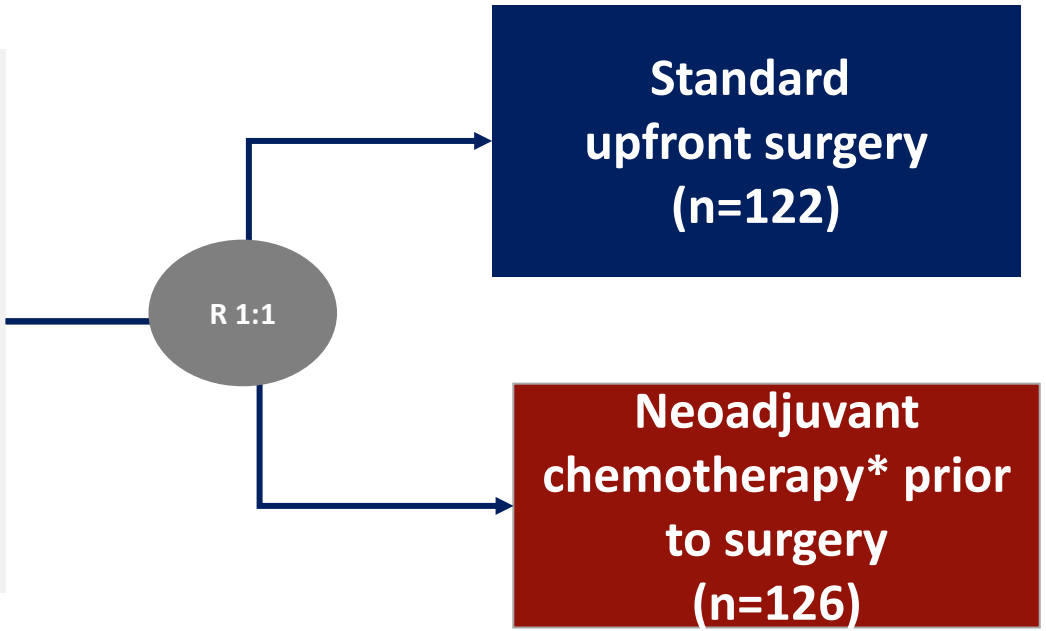
NeoCol

Does neoadjuvant chemotherapy provide benefit to patients with locally advanced colon cancer?

NeoCol

Study Design

- Histologically verified locally advanced T3 (ETI >5mm) to T4 colon cancer assessed by CT scan
- Age ≥18 years
- PS 0-2
- ANC ≥1.5x10^9/l
- Platelets ≥ 100x10^9/l
- Bilirubinemia ≤3 x upper normal level
- ALST ≤ 5 x upper normal value



Adjuvant chemotherapy in both arms not mandatory, chosen based on postoperative staging, and minus any neoadjuvant cycles

Primary endpoint: Disease free survival (DFS)

Secondary endpoints: Rate of patients fulfilling the criteria for adjuvant chemotherapy, overall survival, toxicity, QoL

* ***Preferred***: 3 cycles of CAPOX (3-week cycle, oxaliplatin 130 mg/m^2 and capecitabine 1000 mg/m^2 twice daily for 14 days)

Or: 4 cycles of FOLFOX (2-week cycle, oxaliplatin 85 mg/m^2, 5 FU 400mg/m^2 bolus and 2400 mg/m^2 over 46 hours)

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ASCO 2023. Abstr LBA3503.

NeoCol

Baseline Characteristics

n (%)	Upfront Surgery (standard) (n=122)	Neoadjuvant treatment prior to surgery (n=126)
Age, median (range)	69.4 (30.3 – 81.8)	63.8 (23.8 – 84.3)
Sex, (% female)	45 (37%)	66 (52%)
Localization of tumor		
• Right	52 (43%0	59 (47%)
• Left	70 (57%)	66 (52%)
• Not specified	---	1 (1%)
T-category at baseline CT scan		
• T3	89 (74%)	91 (72%)
• Medium extramural invasion (mm)	7 mm	8 mm
• T4	31 (25%)	33 (26%)
• Not specified	1 (1%)	2 (2%)
Performance status		
• 0	107 (88%)	115 (91%)
• 1	13 (10%)	8 (6%)
• 2	---	1 (1%)
• Not specified	2 (2%)	2 (2%)

Treatments administered	Upfront Surgery (standard) (n=82)	Neoadjuvant treatment prior to surgery (n=126)	*P*-value
Number of pre-operative cycles, mean ± SD	---	2.7 ± 0.7	---
Number of post-operative cycles, mean ± SD	5.9 ± 2.4	4.1 ± 1.3	<0.001
Total number of cycles, mean ± SD	**5.9 ± 2.4**	**4.8 ± 2.5**	0.06

Note: all CAPOX, no pt received FOLFOX

KEY DATA

NeoCol

Surgery

Surgery n (%)	Upfront Surgery (standard)	Neoadjuvant treatment prior to surgery
Surgery performed, Yes	121 (99%)	123 (98%)
• Time from randomization to surgery, median days (IQR)	7 (7)	74 (11)
Type of surgery		
• Laparotomy	39 (32%)	31 (25%)
• Laparoscopic	82 (68%)	92 (75%)
Procedure performed, sidedness		
• Right	51 (43%)	59 (48%)
• Left	67 (54%)	62 (50%)
• Other (colectomy, combined resections etc.)	3 (3%)	2 (2%)

Surgical complications n (%)	Upfront Surgery (standard)	Neoadjuvant treatment prior to surgery
Peri-operative complications		
• Intraoperative injury	8 (7%)	7 (6%)
• Blood transfusion	5 (4%)	9 (7%)
Post-operative complications		
• Hemorrhage	2 (2%)	4 (3%)
• Dehiscence	2(2%)	2 (2%)
• Ileus	10 (8%)	4 (3%)
• Intraabdominal abscess	2 (2%)	3 (2%)
• Anastomotic leakage	9 (8%)	3 (2%)
Length of stay, days, median (IQR)	5 (4)	5 (4)

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KEY DATA

NeoCol

Pathology

n (%)	Upfront Surgery (standard)	Neoadjuvant treatment prior to surgery
Involvement of resection margin		
• R1	10 (9%)	9 (7%)
• R0	109 (90%)	114 (93%)
• Unknown	2 (1%)	---
p/ypT-category at surgery*		
• 0	---	4 (3%)
• 1	2 (2%)	1 (1%)
• 2	3(2%)	7 (6%)
• 3	75 (62%)	76 (62%)
• 4	39 (32%)	35 (28%)
p/ypN-category at surgery		
• 0	57 (48%)	72 (59%)
• 1	43 (35%)	31 (25%)
• 2	20 (17%)	19 (16%)
Perineural invasion	21 (18%)	19 (15%)
Vascular invasion	**48 (39%)**	**30 (25%)**
Perforation	2 (2%)	3 (2%)

* Numbers may vary due to missing data

Adjuvant chemotherapy indication

n (%)	Upfront Surgery (standard)	Neoadjuvant treatment prior to surgery
Criteria for adjuvant chemotherapy fulfilled (according to national guidelines applied to p/ypTNM, investigator)	88 (73%)	72 (589%)
	P 0.03	

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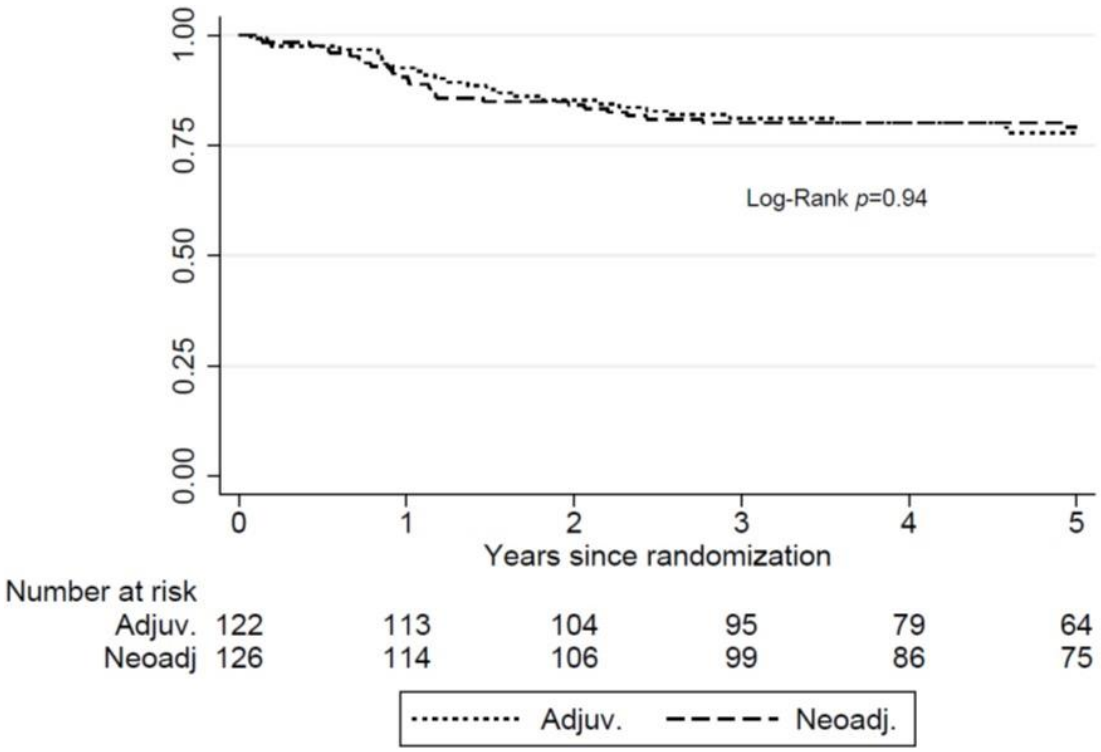
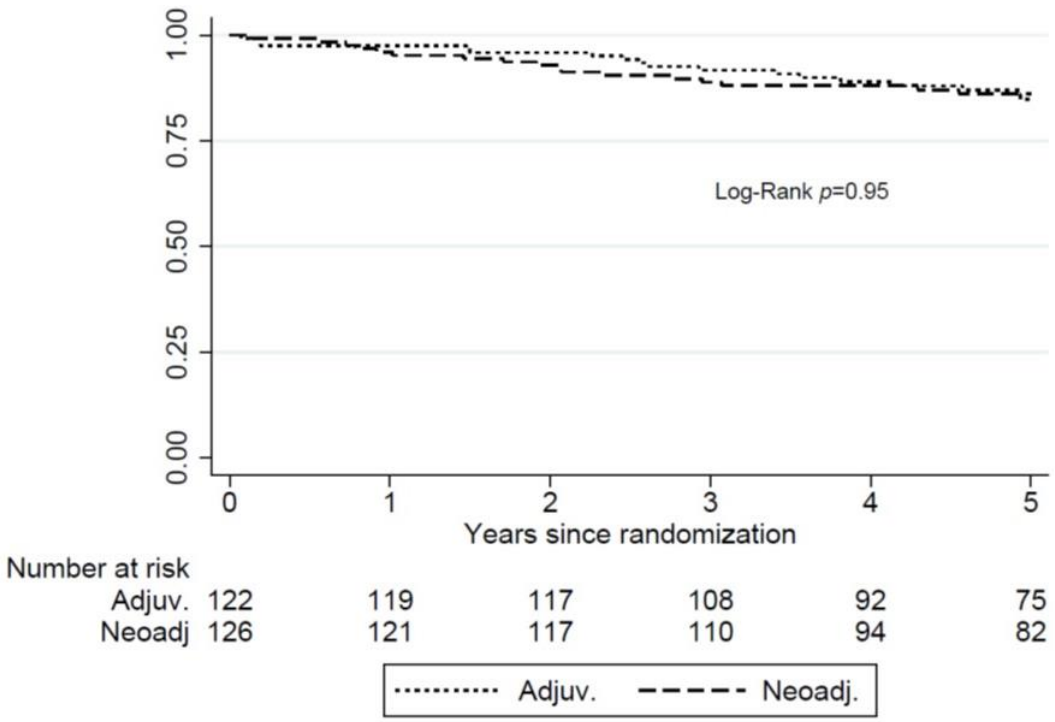
KEY DATA

NeoCol

Primary Endpoint: DFS



Secondary Endpoint: OS



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NeoCol

Safety

Toxicity grade 3-4, n (%)	Upfront Surgery (standard) n=82	Neoadjuvant treatment prior to surgery n=126
During Treatment		
• Nausea	3 (4%)	7 (7%)
• Vomiting	3 (4%)	3 (2%)
• Stomatitis	1 (1%)	---
• Diarrhea	11 (14%)	16 (13%)
• Sensory neuropathy	9 (11%)	9 (7%)
• Motor neuropathy	2 (2%)	2 (2%)
• Hand-foot syndrome	4 (5%)	---
• Obstipation	---	1 (1%)
• Pain	3 (4%)	3 (2%)
• Other	7 (7%)	12 (9%)
During follow-up		
• Sensory neuropathy	4 (5%)	2 (2%)
• Motor neuropathy	2 (3%)	1 (1%)
• Hand-foot syndrome	---	---
• Pain	2 (3%)	---

SUMMARY

NeoCol

- Neoadjuvant chemotherapy is not superior to standard upfront surgery for patients with locally advanced colon cancer
  - No difference in DFS or OS
- Neoadjuvant approach may be more favorable
  - Fewer total chemotherapy cycles
  - Timing of risk of adverse events from chemotherapy and post operative complications
  - Downsizing and downstaging

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ASCO 2023. Abstr LBA3503.

NeoCol

For locally advanced colon cancer neoadjuvant chemotherapy can be considered as a treatment option depending on patient preference for timing and risk of adverse events from chemotherapy and surgery

2023 ASCO Key Studies

Breast and Gynecological Cancer

- NATALEE
- PALLAS
- PALMIRA
- SONIA
- MIRASOL

GU/GI Cancer

- PROSPECT*
- DESTINY-CRC02
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- NeoCol
- CONTACT-03

Other Notable Studies

- ADAURA*
- INDIGO*
- SWOG1826*
- DESTINY-PanTumor02
- COMMANDS

* Plenary Session

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CLINICAL QUESTION

CONTACT-03

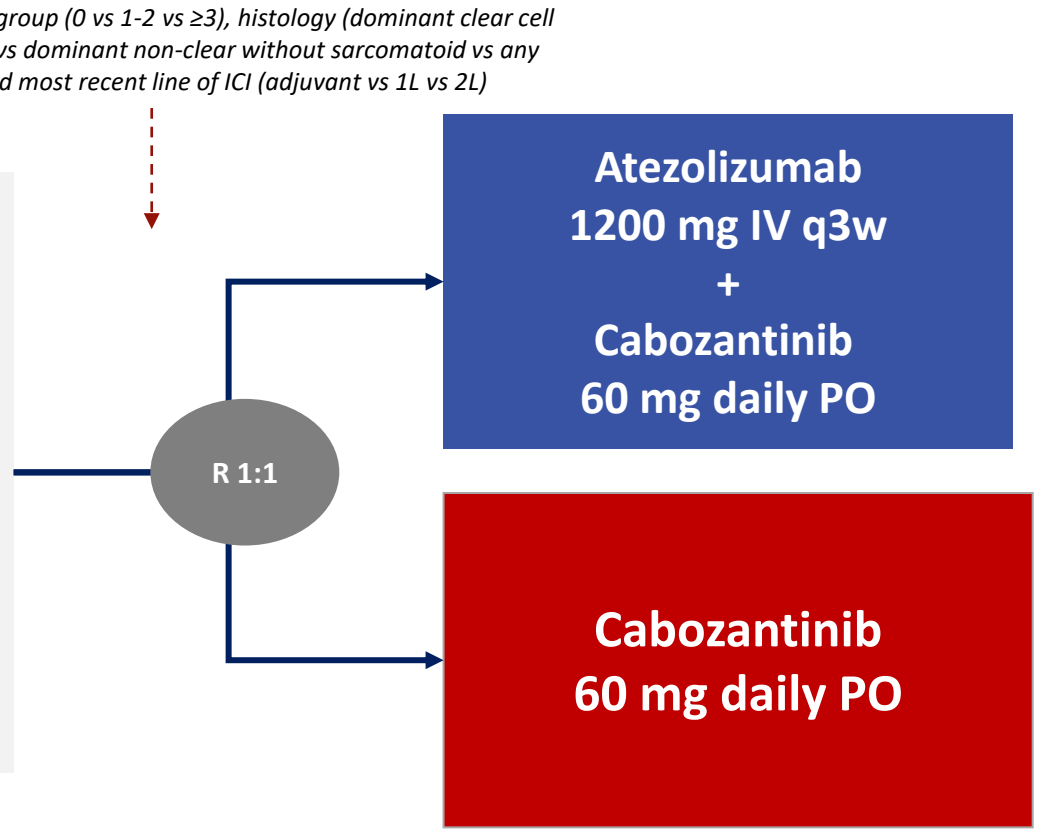
Does atezolizumab plus cabozantinib benefit patients with prior ICI treatment for metastatic renal cell carcinoma?

CONTACT-03

Study Design: Multicenter, randomized, open label, Phase III Study

- Advanced or metastatic clear cell or non-clear cell RCC with or without a sarcomatoid component
- Radiographic progression on or after prior ICI treatment
  - ICI as adjuvant, 1L or 2L (single agent or in combination with another permitted agent)
  - ICI in the immediately preceding line of therapy

N=522



Primary endpoint: Independent centrally assessed PFS (RECIST 1.1), OS

Secondary endpoints: Investigator-assessed PFS (RECIST 1.1), ORR and DoR (per central review and per investigator), safety

CONTACT-03

Baseline Characteristics

Characteristic	Atezo + Cabo (n=263)	Cabo (n=259)
Age, median (range), y	62 (20-85)	63 (18-89)
Male sex, n (%)	204 (77.6)	197 (76.1)
Race, n (%)		
White	219 (83.3)	213 (82.2)
Asian	33 (12.5)	23 (8.9)
Other	11 (4.2)	23 (8.9)
Most recent line of immune checkpoint inhibitor therapy, n (%)[a]		
Adjuvant	1 (0.4)	1 (0.4)
Locally advanced or metastatic; first line	144 (54.8)	132 (51.0)
Locally advanced or metastatic; second line	118 (44.9)	124 (47.9)
Histology, n (%)[b]		
Dominant clear cell without sarcomatoid	207 (78.7)	200 (77.2)
Dominant non-clear cell without sarcomatoid	30 (11.4)	31 (12.0)
Any sarcomatoid	25 (9.5)	28 (10.8)
IMDC score, n (%)[c]		
0	49 (18.6)	69 (26.6)
1-2	172 (65.4)	153 (59.1)
≥3	41 (15.6)	36 (13.9)
Prior VEGFR-TKI use, n (%)		
0	93 (35.4)	95 (36.7)
1	166 (63.1)	159 (61.4)
2	4 (1.5)	5 (1.9)

[a] In the Cabo arm, 2 patients had no most recent ICI. [b] In the Atezo + Cabo arm, 1 patient had missing histology. [c] In each arm, there was 1 patient with missing IMDC score.

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CONTACT-03

Prior Systemic Treatment

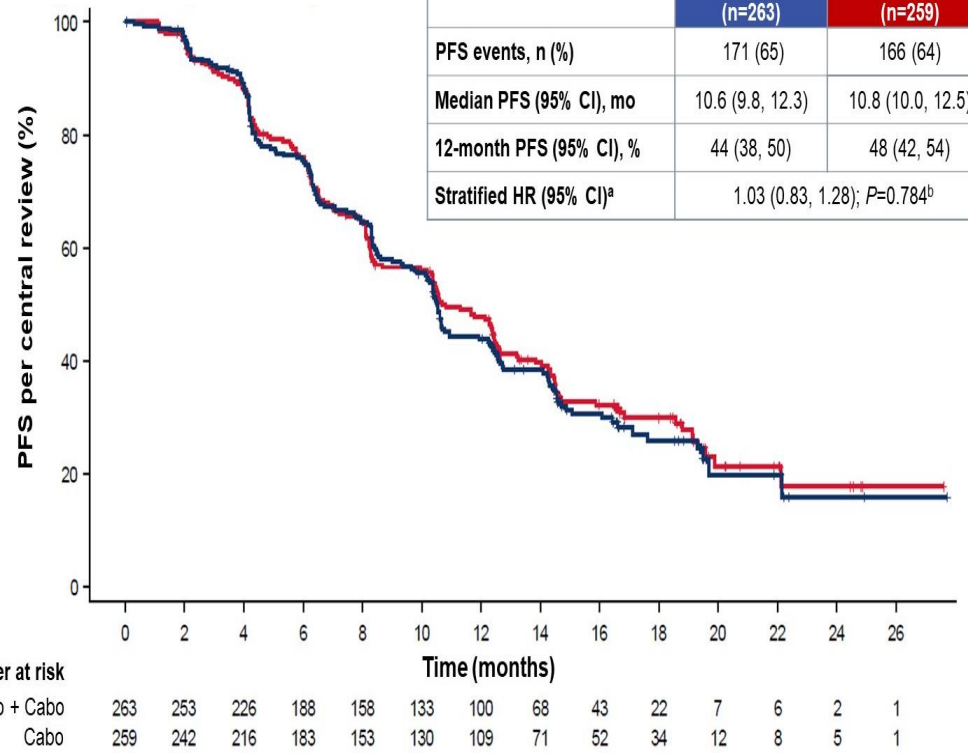
	Atezo + Cabo (n=263)	Cabo (n=259)
First-line treatment, n (%)[a,b]	**262 (99.6)**	**258 (99.6)**
Ipilimumab + nivolumab	80 (30.5)	70 (27.1)
Sunitinib	77 (29.4)	72 (27.9)
Pazopanib	36 (13.7)	43 (16.6)
Axitinib + pembrolizumab	36 (13.7)	28 (10.9)
Nivolumab	6 (2.3)	10 (3.9)
Avelumab + axitinib	7 (2.7)	6 (2.3)
Bempegaldesleukin + nivolumab	3 (1.1)	9 (3.5)
Lenvatinib + pembrolizumab	6 (2.3)	3 (1.2)
Sorafenib	3 (1.1)	1 (0.4)
Second-line treatment, n (%)[a,b]	**119 (45.2)**	**125 (48.3)**
Nivolumab	104 (87.4)	116 (92.8)
Ipilimumab + nivolumab	4 (3.4)	3 (2.4)
Axitinib + pembrolizumab	2 (1.7)	3 (2.4)
Adjuvant treatment, n (%)[a,b]	**8 (3.0)**	**4 (1.5)**
Sunitinib	2 (25)	2 (50)

Percentages for each regimen were calculated based on the total number of patients receiving the corresponding line of therapy.
[a] Treatments were mutually exclusive within each line of therapy, and patients could have received agents for >1 line of treatment. [b] Only regimens received by ≥4 patients are shown.

CONTACT-03

Primary Endpoint: PFS

	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	171 (65)	166 (64)
Median PFS (95% CI), mo	10.6 (9.8, 12.3)	10.8 (10.0, 12.5)
12-month PFS (95% CI), %	44 (38, 50)	48 (42, 54)
Stratified HR (95% CI)[a]	1.03 (0.83, 1.28); *P*=0.784[b]	

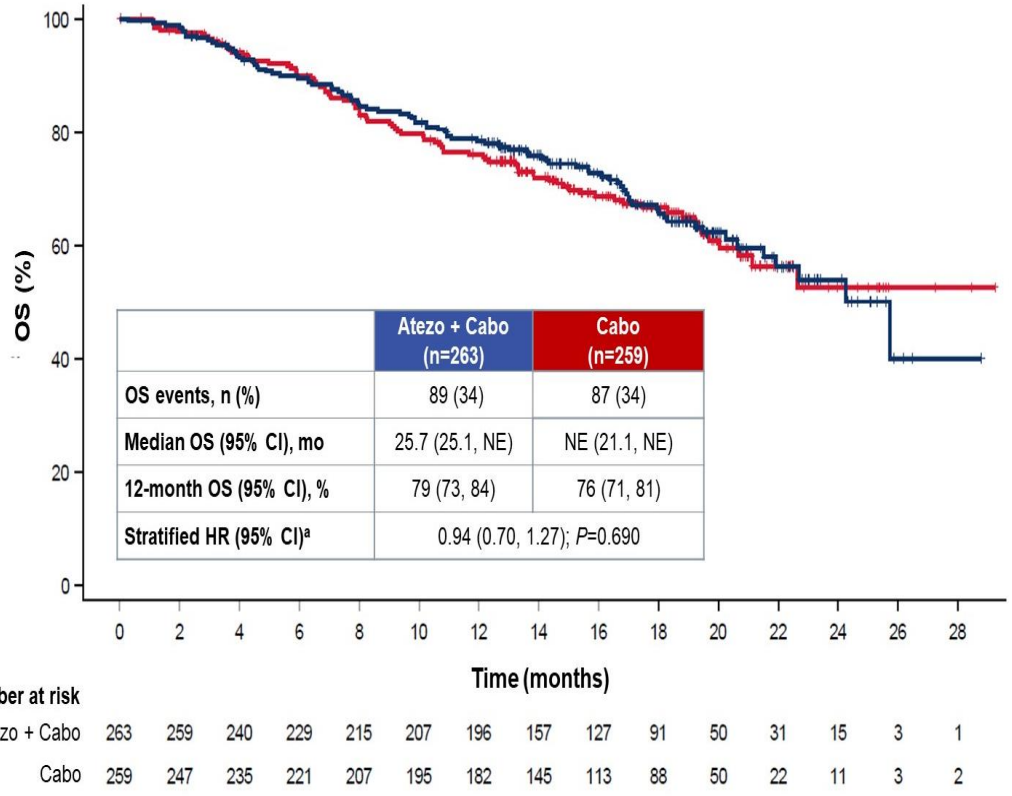


[a] Stratified for IMDC risk group. [b] Not significant at α=0.02.

- PFS subgroup analysis did not identify a subset of patients who may benefit from atezo + cabozantinib

Primary Endpoint: OS (interim analysis)

	Atezo + Cabo (n=263)	Cabo (n=259)
OS events, n (%)	89 (34)	87 (34)
Median OS (95% CI), mo	25.7 (25.1, NE)	NE (21.1, NE)
12-month OS (95% CI), %	79 (73, 84)	76 (71, 81)
Stratified HR (95% CI)[a]	0.94 (0.70, 1.27); *P*=0.690	



[a] Stratified for IMDC risk group.

CONTACT-03

Secondary Endpoints

	RECIST 1.1 per central review[a]		RECIST 1.1 per investigator[a]	
	Atezo + Cabo (n=259)	Cabo (n=254)	Atezo + Cabo (n=263)	Cabo (n=259)
Confirmed objective response, n, (%) [95% CI]	105 (40.5) [34.5, 46.8]	104 (40.9) [34.8, 47.3]	100 (38.0) [32.1, 44.2]	108 (41.7) [35.6, 48.0]
Complete response, n (%)	0	2 (0.8)	4 (1.5)	2 (0.8)
Partial response, n (%)	105 (40.5)	102 (40.2)	96 (36.5)	106 (40.9)
Stable disease, n (%)	131 (50.6)	121 (47.6)	127 (48.3)	120 (46.3)
Progressive disease, n (%)	11 (4.2)	13 (5.1)	24 (9.1)	17 (6.6)
Not evaluable or missing, n (%)	12 (4.6)	16 (6.3)	12 (4.6)	14 (5.4)
Ongoing response at data cutoff, n/N (%)[b]	53/105 (50.5)	55/104 (52.9)	58/100 (58.0)	48/108 (44.4)
Median duration of response (range), mo	12.7 (2.1+ to 22.9+)	14.8 (2.3+ to 25.6+)	NE (2.1+ to 23.2+)	12.2 (2.1+ to 25.6+)

[a] Included are patients who presented with measurable disease according to RECIST 1.1, as assessed by either a central review facility or by investigators. [b] Patients with complete or partial response who did not experience disease progression or death. The plus sign indicates a censored value.

CONTACT-03

Subsequent Systemic Treatment

	Atezo + Cabo (n=263)	Cabo (n=259)
TKI/VEGF inhibitor, n (%)[a,b]	**61 (23.2)**	**64 (24.7)**
Axitinib	26 (9.9)	20 (7.7)
Lenvatinib	20 (7.6)	24 (9.3)
Cabozantinib	9 (3.4)	15 (5.8)
Sunitinib	14 (5.3)	7 (2.7)
Pazopanib	6 (2.3)	3 (1.2)
Bevacizumab	2 (0.8)	4 (1.5)
mTOR inhibitor, n (%)[a,b]	**34 (12.9)**	**26 (10.0)**
Everolimus	33 (12.5)	26 (10.0)
Immunotherapy, n (%)[a,b]	**12 (4.6)**	**24 (9.3)**
Nivolumab	6 (2.3)	10 (3.9)
Pembrolizumab	3 (1.1)	11 (4.2)
Ipilimumab	2 (0.8)	4 (1.5)
Chemotherapy, n (%)[a,b]	**2 (0.8)**	**2 (0.8)**
Investigational or other agent, n (%)[a,b]	**1 (0.4)**	**3 (1.2)**

mTOR, mechanistic target of rapamycin kinase; VEGF, vascular endothelial growth factor.
[a] Treatments were not mutually exclusive, and patients could receive more than one agent. [b] Only regimens received by ≥5 patients are shown.

CONTACT-03

Safety

Adverse event, n (%)	Atezo + Cabo (n=262)	Cabo (n=256)
Any-cause AE	262 (100)	254 (99.2)
Any-cause treatment-related AE	252 (96.2)	249 (97.3)
Grade 3 or 4 AE	177 (67.6)	158 (61.7)
Grade 3 or 4 treatment-related AE	145 (55.3)	121 (47.3)
Death due to AE	17 (6.5)	9 (3.5)
Death due to treatment-related AE	3 (1.1)[a]	0
Serious AE	126 (48.1)	84 (32.8)
Serious treatment-related AE	63 (24.0)	30 (11.7)
AE leading to withdrawal from a trial drug	41 (15.6)	10 (3.9)
AE leading to withdrawal from atezo	29 (11.1)	–
AE leading to withdrawal from cabo	25 (9.5)	10 (3.9)
AE leading to interruption or reduction of a trial drug	240 (91.6)	223 (87.1)
AE leading to interruption of atezo[b]	159 (60.7)	–
AE leading to interruption or reduction of cabo	234 (89.3)	223 (87.1)

[a] Treatment-related AEs leading to death were immune-mediated enterocolitis and renal failure (both related to atezo) and intestinal perforation (related to cabo). [b] Dose reduction of atezo was not permitted.

CONTACT-03

Adverse Events

Adverse event, n (%)[a]	Atezo + Cabo (n=262)	Cabo (n=256)
Diarrhea	171 (65.3)	181 (70.7)
Palmar-plantar erythrodysesthesia syndrome	101 (38.5)	105 (41.0)
Decreased appetite	100 (38.2)	97 (37.9)
Hypothyroidism	95 (36.3)	97 (37.9)
Nausea	77 (29.4)	92 (35.9)
Asthenia	77 (29.4)	75 (29.3)
Hypertension	72 (27.5)	87 (34.0)
Fatigue	72 (27.5)	61 (23.8)
Increased alanine aminotransferase	62 (23.7)	57 (22.3)
Increased aspartate aminotransferase	60 (22.9)	61 (23.8)
Anemia	53 (20.2)	48 (18.8)
Decreased weight	46 (17.6)	64 (25.0)

[a] Adverse events occurring in ≥20% of pts in either arm

SUMMARY

CONTACT-03

- The addition of atezolizumab to cabozantinib did not improve PFS, OS, or response rates compared to cabozantinib alone for patients with mRCC who progressed on or after prior ICI treatment
  - mPFS: 10.6 mo vs 10.8 mo (HR 1.03; P = .784); 12-month PFS rate 44% vs 48%, respectively
  - mOS: 25.7 mo vs 21.1 mo (HR 0.94, *P* =0.690); 12-month OS rates 79% vs 76%, respective;y

- Increased toxicity was observed with the combination of atezolizumab plus cabozantinib compared to cabozantinib alone

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ASCO 2023. Abstr LBA4500.

CONTACT-03

Re-challenge with atezolizumab plus cabozantinib post-progression on a prior ICI therapy does not provide added benefit to patients with mRCC and should not be considered as an effective treatment strategy

2023 ASCO Key Studies

Breast and Gynecological Cancer	GU/GI Cancer	Other Notable Studies
• NATALEE • PALLAS • PALMIRA • SONIA • MIRASOL	• PROSPECT* • DESTINY-CRC02 • PEACE-1 • NeoCol • CONTACT-03	• ADAURA* • INDIGO* • SWOG S1826* • DESTINY-PanTumor02 • COMMANDS

* Plenary Session

ADAURA

Does adjuvant osimertinib after complete resection benefit patients with stage IB–IIIA EGFR-mutated NSCLC?

Overall Survival Analysis

* Plenary Session

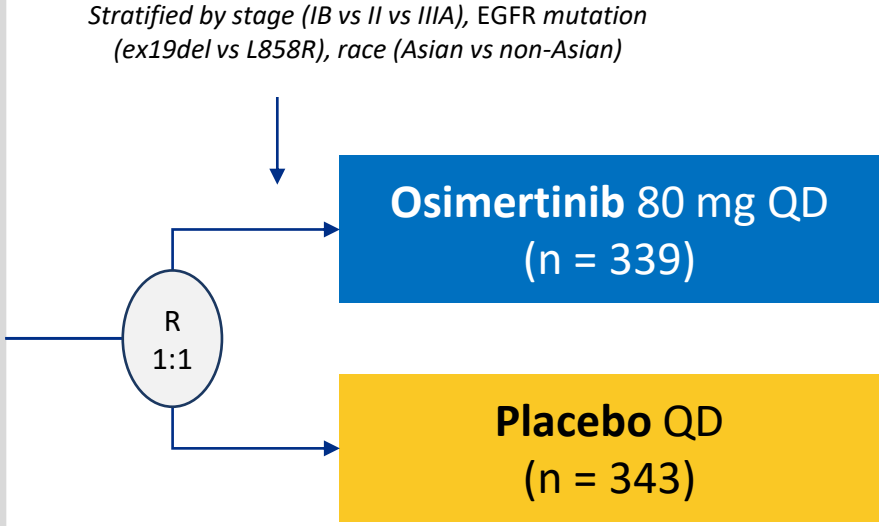
ADAURA

Study Design: Randomized, international double-blinded phase III

- Patients with completely resected stage IB/II/IIIA NSCLC with negative margins
- Confirmed primary nonsquamous NSCLC with *EGFR* ex19del or L858R*
- Aged ≥18 yr (≥20 yr in Japan/Taiwan)
- WHO PS 0/1
- Brain imaging done
- With or without adjuvant CT
- Maximum time between surgery and randomization:
  - 10 wk without adjuvant CT,
  - 26 wk with adjuvant CT

(N = 682)

*Confirmed centrally in tissue.



Planned treatment duration: 3 years

Treatment continues until:
Disease recurrence, treatment completed, or discontinuation criterion met

Follow-up:
Until recurrence: Wk 12 and 24, then Q24W to 5 yr, then yearly
After recurrence: Q24W for 5 yr, then yearly.

Primary endpoints: investigator-assessed DFS in patients with stage II/ IIIA disease designed to test superiority with assumed DFS HR of 0.70

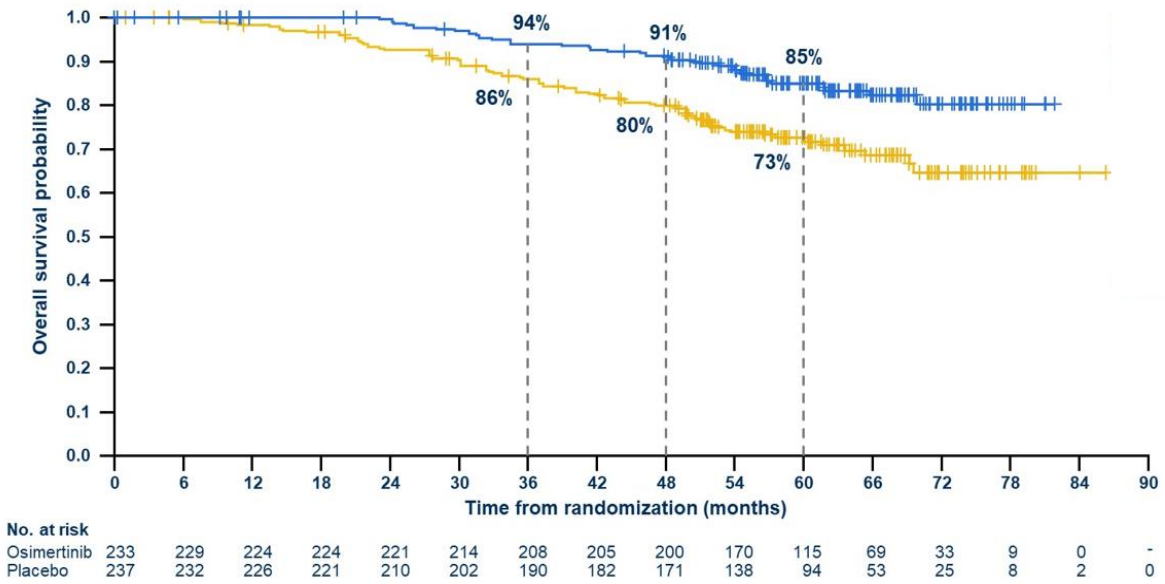
Key secondary endpoints: DFS in overall population, landmark DFS rates at 2, 3, 4, and 5 years, OS, HRQoL, safety

Exploratory endpoints: patterns of recurrence; time to CNS recurrence (CNS DFS)

Data cutoff for final OS analysis: 01/27/2023

ADAURA

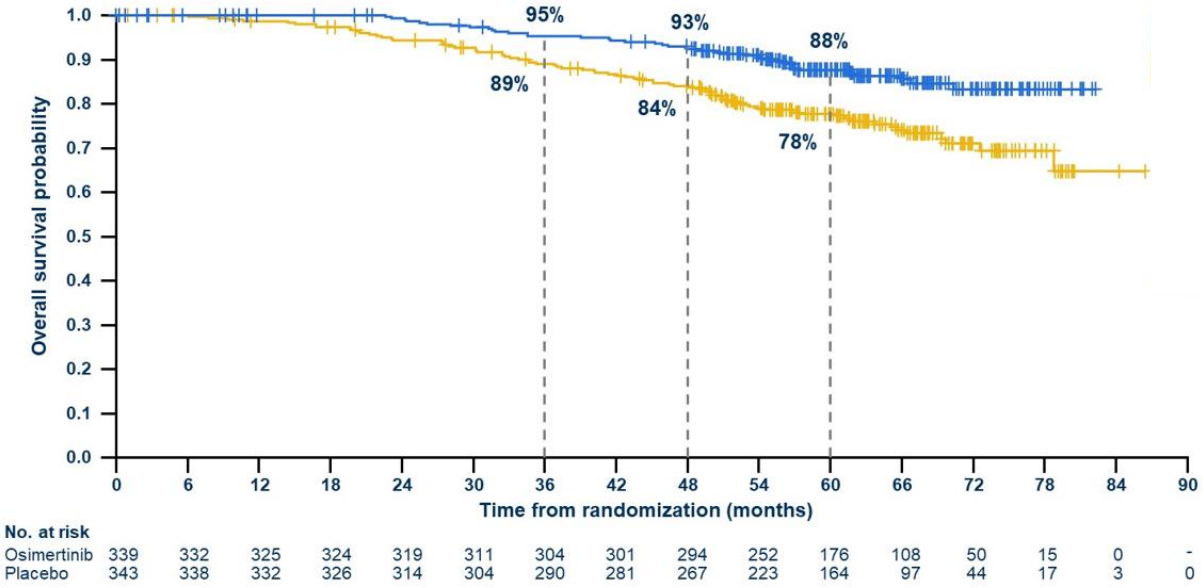
Overall Survival: Stage II / IIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=233)	85 (79 – 89)
Placebo (n=237)	73 (66 – 78)
Overall OS HR	**0.49** (0.33 – 0.73) P=0.0004

- Median follow-up for OS: 61.7 mo, placebo 60.4 mo
- Maturity 21%: (osimertinib 15%; placebo 27%)

Overall Survival: Stage IB / II / IIIA disease



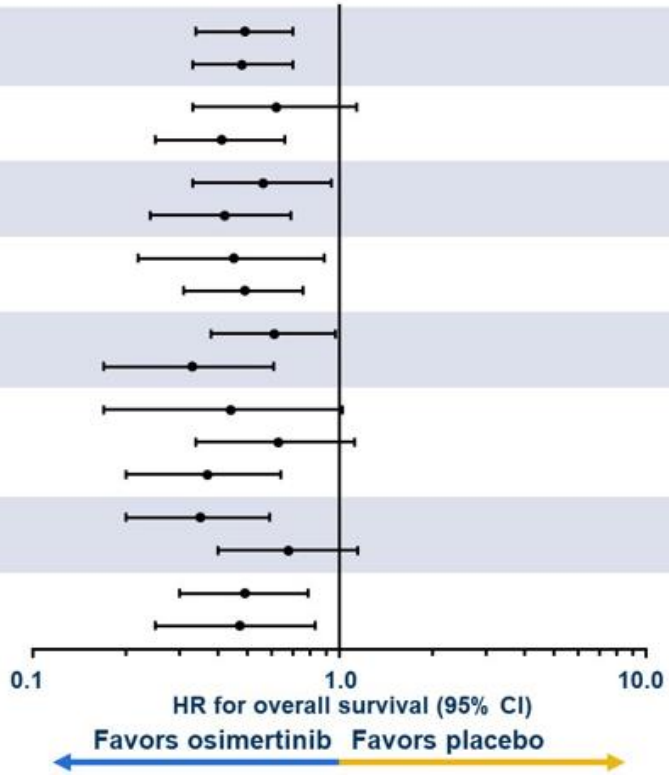
5-year OS rate, % (95% CI)	
Osimertinib (n=339)	88 (83 – 91)
Placebo (n=343)	78 (73 – 82)
Overall OS HR	**0.49** (0.34 – 0.70) P<0.0001

- Median follow-up for OS: 61.5 mo, placebo 61.5 mo
- Maturity 18%: (osimertinib 12%; placebo 24%)

ADAURA

Overall Survival by Subgroup: Stage IB/ II /IIIA disease

Subgroup		No. of events / patients	HR	95% CI
Overall (N=682)	Stratified log-rank	124 / 682	0.49	0.34, 0.70
	Unadjusted Cox PH	124 / 682	0.48	0.33, 0.70
Sex	Male	42 / 204	0.62	0.33, 1.13
	Female	82 / 478	0.41	0.25, 0.66
Age	<65 years	60 / 380	0.56	0.33, 0.94
	≥65 years	64 / 302	0.42	0.24, 0.69
Smoking history	Yes	34 / 194	0.45	0.22, 0.89
	No	90 / 488	0.49	0.31, 0.76
Race	Asian	73 / 434	0.61	0.38, 0.97
	Non-Asian	51 / 248	0.33	0.17, 0.61
Stage*	IB	24 / 212	0.44	0.17, 1.02
	II	46 / 236	0.63	0.34, 1.12
	IIIA	54 / 234	0.37	0.20, 0.64
EGFR mutation	Ex19del	65 / 378	0.35	0.20, 0.59
	L858R	59 / 304	0.68	0.40, 1.14
Adjuvant chemotherapy	Yes	74 / 410	0.49	0.30, 0.79
	No	50 / 272	0.47	0.25, 0.83



ADAURA

Subsequent Treatments

Subsequent Treatment, n (%)	Osimertinib (n = 76)	Placebo (n = 184)
EGFR TKI	58 (76)	162 (88)
• Osimertinib	31 (41)	79 (43)
• Other EGFR TKI	29 (38)*	114 (62)†
Chemotherapy		
• Platinum	20 (26)	43 (23)
• Pemetrexed	13 (17)	27 (15)
• Taxanes	8 (11)	20 (11)
• Other‡	7 (9)	20 (11)
Radiotherapy	30 (39)	53 (29)
Other anticancer therapy	14 (18)	38 (21)

At data cutoff for OS analysis, 76/339 (22%) patients in osimertinib arm and 184/343 (54%) in placebo arm had received ≥1 subsequent anticancer therapy

*Includes gefitinib (n = 13), afatinib (n = 7), erlotinib (n = 6), icotinib (n = 2), aumolertinib mesylate (n = 1).
†Includes gefitinib (n = 55), afatinib (n = 30), erlotinib (n = 24), icotinib (n = 15), and aumolertinib mesylate, aumolertinib, dacomitinib, epitinib, furmonertinib, and other EGFR TKI (n = 1 each).
‡Includes pyrimidine analogues, vinca alkaloids/analogues, etoposide, anthracyclines, irinotecan, and cyclophosphamide.

SUMMAY

ADAURA

- Statistically significant OS benefit with adjuvant osimertinib among patients with stage IB-IIIA EGFR-mutated NSCLC following complete resection
  - Stage II-IIIA NSCLC: 51% reduction in risk of death (HR: 0.49; 95.03% CI: 0.33-0.73; P <.001)
  - Overall population: 51% reduction in risk of death (HR: 0.49; 95.03% CI: 0.34-0.70; P <.001)
  - OS benefit was consistent across subgroups, including disease stage, and regardless of prior adjuvant CT use
- No new safety signals were observed with extended follow-up
  - Patients with AEs occurring >28 days after treatment discontinuation (n = 15) at OS data cutoff (1/27/2023)
    - Osimertinib arm (n = 10)
    - Placebo arm (n = 5)
  - At OS data cutoff, 1 additional serious AE was reported (COVID-19 pneumonia)
    - Occurred >28 days after treatment discontinuation; deemed unrelated to treatment, and patient made full recovery

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ADAURA

Osimertinib should be standard of care in the adjuvant setting for patients with stage IB/II/IIIA EGFR-mutated NSCLC following complete resection

2023 ASCO Key Studies

Breast and Gynecological Cancer

- NATALEE
- PALLAS
- PALMIRA
- SONIA
- MIRASOL

GU/GI Cancer

- PROSPECT*
- DESTINY-CRC02
- PEACE-1
- NeoCol
- CONTACT-03

Other Notable Studies

- ADAURA*
- INDIGO*
- SWOG S1826*
- DESTINY-PanTumor02
- COMMANDS

* Plenary Session

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INDIGO

Does vorasidenib benefit patients with residual or recurrent grade 2 glioma with an IDH1/2 mutation?

* Plenary Session

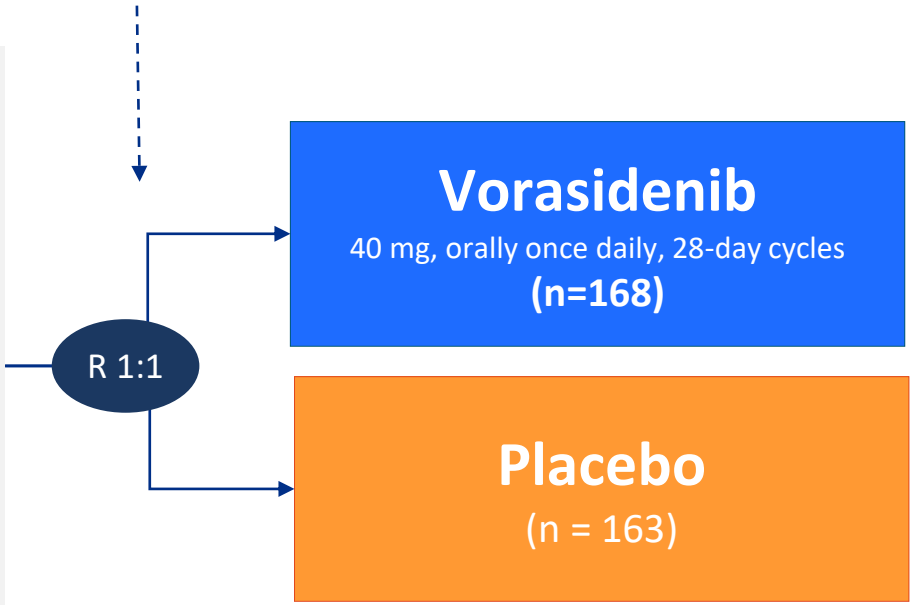
INDIGO

Study Design: International randomized open-label phase III trial

- Patients ≥12 yr of age
- IDH1/2-mutated* grade 2 oligodendroglioma or astrocytoma per WHO 2016 guidelines
- Prior surgery
- Measurable non-enhancing disease (≥1 target lesions measuring at least 1 cm x 1 cm, confirmed by blinded review
- Not in need of immediate chemotherapy or radiotherapy per investigator assessment

(N = 331)

*Centrally confirmed using an investigational clinical trail assay based on the Oncomine Dx Target Test and developed in partnership with Thermo Fisher Scientific Inc.



Centrally confirmed progressive disease permitted unblinding and crossover†

(†real-time single BIRC reader)

- Data cut off: Sept 2022
- Safety, other clinical data, as well as efficacy data following prespecified interim analyses regularly reviewed by an independent data monitoring committee (IDMC)
- *Study unblinded in March 2023 following IDMC recommendation based on early efficacy, majority placebo crossed over to vorasidenib*

Primary endpoint: PFS, from randomization to the first imaging-based disease progression as assessed by BIRC or death due to any cause (MRI every 3 months for 3 years, then every 6 months

Secondary endpoints: TTNI, from randomization to the initiation of first subsequent anticancer therapy or death due to any cause; safety, tumor growth rate by volume, ORR, OS, HRQoL, seizure activity and neuro-cognitive function

INDIGO

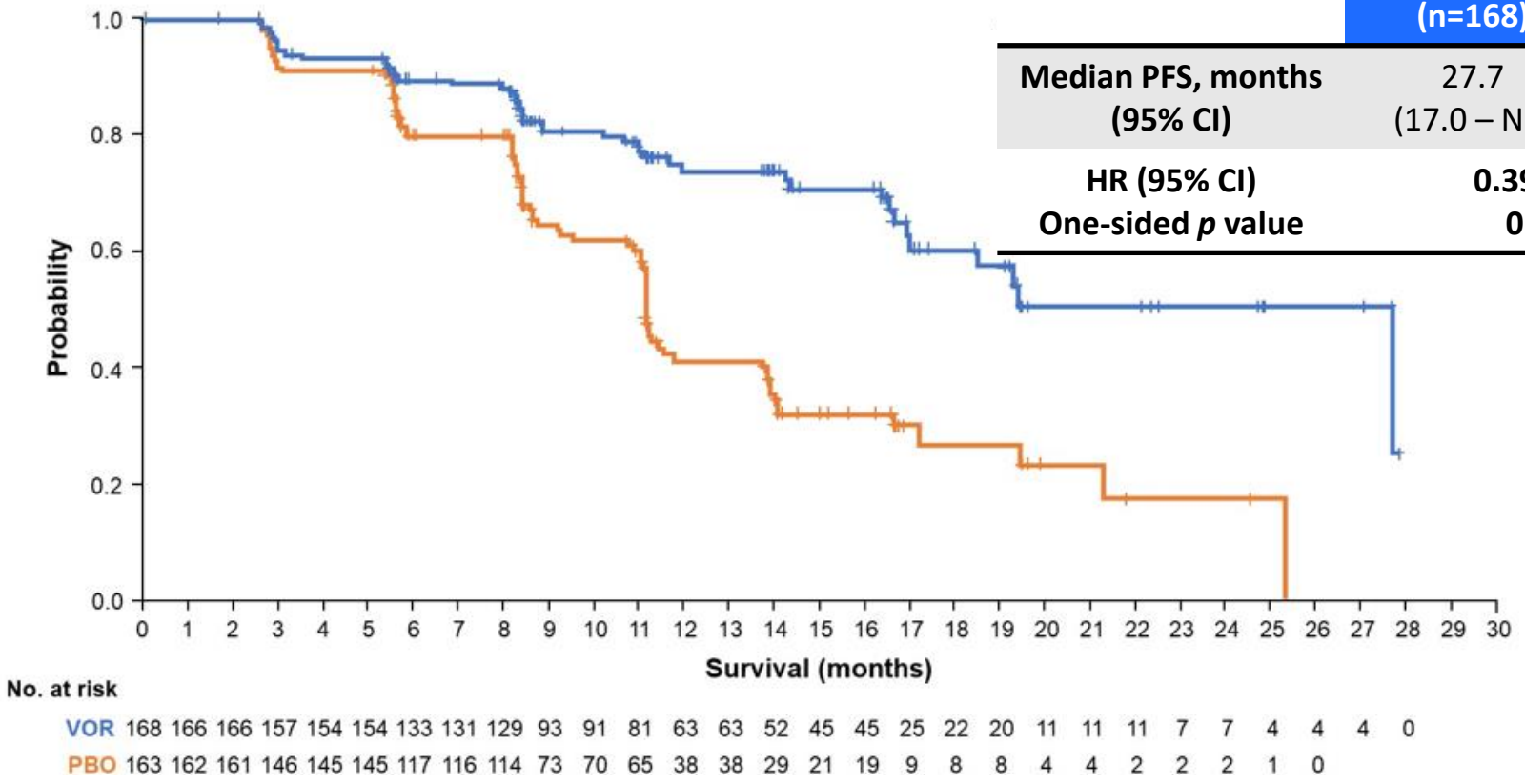
Baseline Characteristics

	Vorasidenib (N=168)	Placebo (N=163)
Median age (range) – year	40.5 (21–71)	39.0 (16–65)
Sex – n (%)		
Male/female	101/67 (60.1/39.9)	86/77 (52.8/47.2)
Karnofsky performance score – n (%)		
100	90 (53.6)	87 (53.4)
90–80*	77 (45.8)	76 (46.6)
Time from last surgery for glioma to randomization – year		
Median (range)	2.5 (0.2–5.2)†	2.2 (0.9–5.0)
Chromosome 1p19q codeletion status – n (%)‡		
Codeleted/non-codeleted	88/80 (52.4/47.6)	84/79 (51.5/48.5)
Tumor size at baseline – n (%)‡		
Longest diameter of ≥2 cm/<2 cm	139/29 (82.7/17.3)	137/26 (84.0/16.0)

*One additional patient (0.6%) met eligibility criteria during screening but then has score of 70 on Day 1 of the first cycle
†One patient had a biopsy during prescreening to obtain tumor tissue for IDH mutation status testing, which was allowed per protocol
‡ Data are reported as collected by electronic case report forms

INDIGO

Primary Endpoint: PFS by BIRC

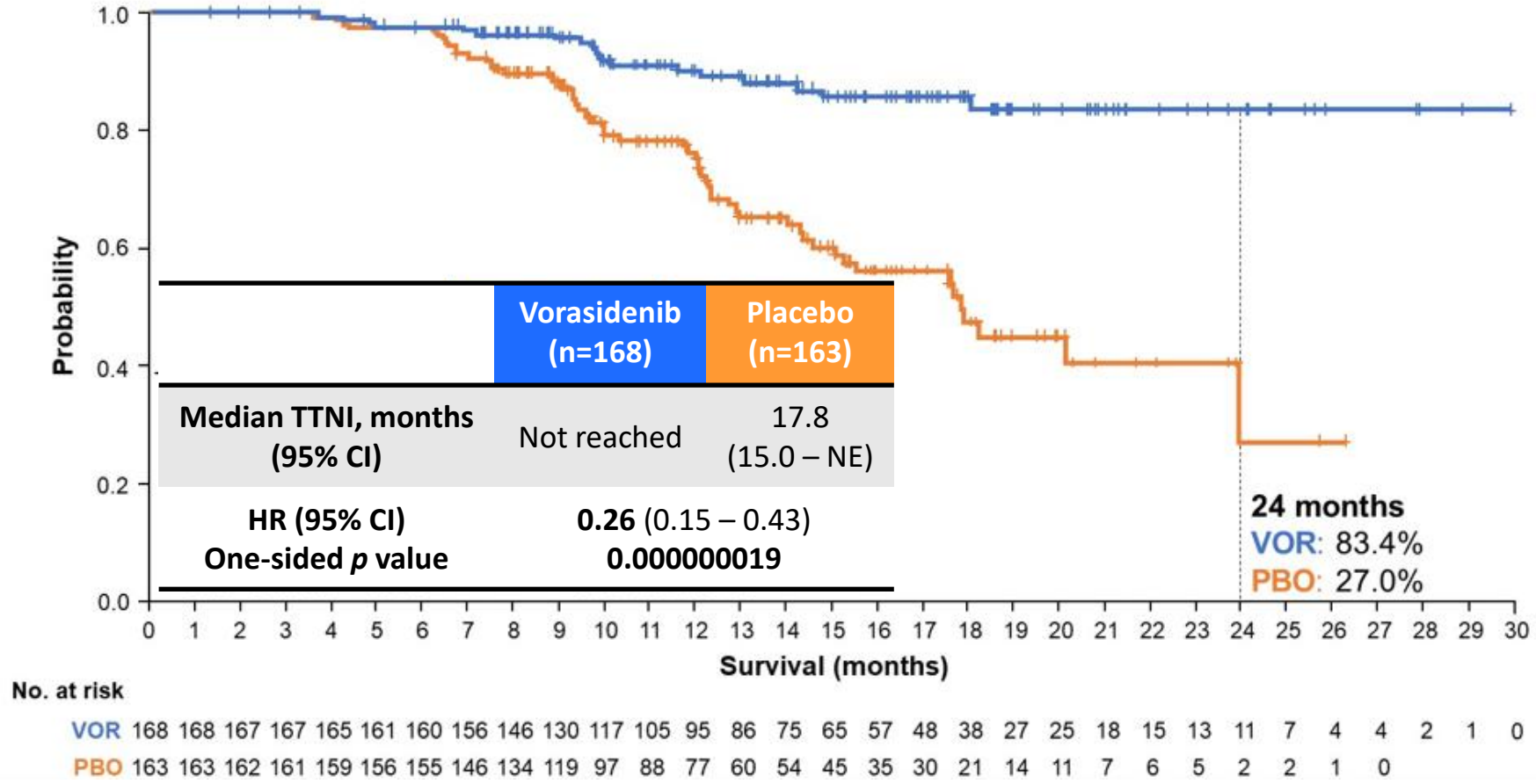


	Vorasidenib (n=168)	Placebo (n=163)
Median PFS, months (95% CI)	27.7 (17.0 – NE)	11.1 (11.0 – 13.7)
HR (95% CI)	**0.39** (0.27 – 0.56)	
One-sided *p* value	**0.000000067**	

NE: not estimable

INDIGO

Secondary Endpoint: Time To Next Intervention (TTNI)



	Vorasidenib (n=168)	Placebo (n=163)
Median TTNI, months (95% CI)	Not reached	17.8 (15.0 – NE)
HR (95% CI)	**0.26** (0.15 – 0.43)	
One-sided *p* value	**0.000000019**	

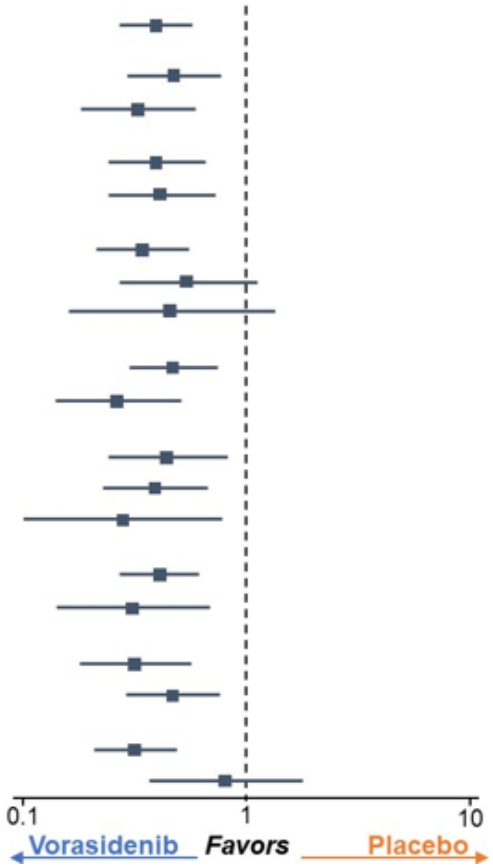
No. at risk

VOR	168	168	167	167	165	161	160	156	146	130	117	105	95	86	75	65	57	48	38	27	25	18	15	13	11	7	4	4	2	1	0
PBO	163	163	162	161	159	156	155	146	134	119	97	88	77	60	54	45	35	30	21	14	11	7	6	5	2	2	1	0			

INDIGO

PFS by Subgroups (BIRC)

Subgroup	Events/N (%)	HR (95% CI)
Overall	135/331 (40.8)	0.39 (0.27–0.56)
18–<40 years	80/163 (49.1)	0.47 (0.29–0.75)
40–<65 years	53/164 (32.3)	0.32 (0.18–0.58)
Male	72/187 (38.5)	0.39 (0.24–0.64)
Female	63/144 (43.8)	0.41 (0.24–0.70)
North America	89/193 (46.1)	0.34 (0.21–0.54)
Western Europe	31/97 (32.0)	0.54 (0.27–1.10)
Rest of the World	15/41 (36.6)	0.45 (0.16–1.31)
Frontal tumor at initial diagnosis	92/222 (41.4)	0.47 (0.30–0.73)
Non-frontal tumor at initial diagnosis	43/109 (39.4)	0.26 (0.14–0.50)
<2 years from last surgery to randomization	51/130 (39.2)	0.44 (0.24–0.82)
2–<4 years from last surgery to randomization	59/145 (40.7)	0.39 (0.23–0.66)
≥4 years from last surgery to randomization	25/56 (44.6)	0.28 (0.10–0.76)
1 prior surgery	106/260 (40.8)	0.41 (0.27–0.61)
≥2 prior surgeries	29/71 (40.8)	0.31 (0.14–0.68)
Codeleted chromosome 1p19q*	59/172 (34.3)	0.32 (0.18–0.57)
Non-codeleted chromosome 1p19q	76/159 (47.8)	0.47 (0.29–0.75)
Longest tumor diameter of ≥2 cm at baseline*	109/269 (40.5)	0.32 (0.21–0.48)
Longest diameter of <2 cm at baseline	26/62 (41.9)	0.81 (0.37–1.77)



*Data are reported as collected by the interactive web response system.

INDIGO

Safety

n (%)	Vorasidenib (n=167)	Placebo (n=163)
Any grade ≥3 A	38 (22.8)	22 (13.5)
Increased alanine aminotransferase	16 (9.6)	0
Increased aspartate aminotransferase	7 (4.2)	0
Seizure	7 (4.2)	4 (2.5)
Increased gamma-glutamyltransferase	5 (3.0)	2 (1.2)
Syncope	3 (1.8)	1 (0.6)
Hypertension	2 (1.2)	3 (1.8)
Decreased neutrophil count	2 (1.2)	0

n (%)	Vorasidenib (n=167)	Placebo (n=163)
Treatment interruption due to TEAE	50 (29.9)	37 (22.7)
Dose reduction due to TEAE	18 (10.8)	5 (3.1)
Discontinuation due to TEAE	6 (3.6)	2 (1.2%)

Note: no fatal TEAE

SUMMARY

INDIGO

- INDIGO is the first randomized phase 3 study of a targeted therapy in grade 2 IDH1/2-mutated glioma
- Vorasidenib led to a 61% reduction in the risk of tumor progression or death
  - Median PFS 27.7 months (HR 0.39)
- Vorasidenib significantly delayed the need for more toxic therapy when compared with placebo
  - TTNI not reached for vorasidenib
- Manageable safety profile

Vorasidenib monotherapy has received fast track designation from the FDA for the treatment of patients with IDH-mutant gliomas

cornerstone specialty network™

INDIGO

Vorasidenib provides benefit to patients with low grade gliomas with IDH1/2 mutation who are not in need of immediate chemotherapy or radiotherapy and delays the use of more aggressive therapies

More to come…

2023 ASCO Key Studies

Breast and Gynecological Cancer

- NATALEE
- PALLAS
- PALMIRA
- SONIA
- MIRASOL

GU/GI Cancer

- PROSPECT*
- DESTINY-CRC02
- PEACE-1
- NeoCol
- CONTACT-03

Other Notable Studies

- ADAURA*
- INDIGO*
- SWOG S1826*
- DESTINY-PanTumor02
- COMMANDS

* Plenary Session

cornerstone specialty network™

CLINICAL QUESTION

SWOG S1826

Does nivolumab plus AVD benefit patients with newly diagnosed advanced stage classic Hodgkin Lymphoma (cHL)?

Planned 2nd Interim Analysis

* Plenary Session

cornerstone specialty network™

SWOG S1826

Study Design: International randomized open-label phase III trial

Stratified by age (12-17, 18-60, or >60yr), IPS (0-3 or 4-7), EOT RT intended (yes or no)

- Patients ≥12 yr of age with newly diagnosed stage III-IV cHL
- CrCl ≥30 mL/min
- LVEF ≥50% (or SF ≥27%)
- Tbili ≤2 x ULN
- AST and ALT ≤3 x ULN
- No ILD/pneumonitis, active autoimmune disease, peripheral neuropathy grade ≥2
- ECOG PS 0-2[†]

(N = 994)

R 1:1

Nivolumab* 240 mg Days 1, 15 + **AVD** D1, 15 x 6 28-day cycles (G-CSF optional) (n =496)

BV 1.2 mg/kg Days 1, 15 + **AVD** Days 1, 15 x 6 28-day cycles (G-CSF required) (n = 498)

Optional EOT RT at physician discretion (if residual FDG-avid lesions)

*For ages ≤17 yr, 3 mg/kg, max 240 mg.

[†]Pediatric: Lansky score vs ECOG; CrCl/GFR ≥70 mL/min or SCr ≤1.5 ULN.

Primary endpoint: PFS

Secondary endpoints: OS, EFS, safety

Data cutoff: December 15, 2022

Nivolumab (N); Brentuximab vedotin (Bv); Doxorubicin, Vinblastine, Dacarbazine (AVD)

SWOG S1826

Baseline Characteristics

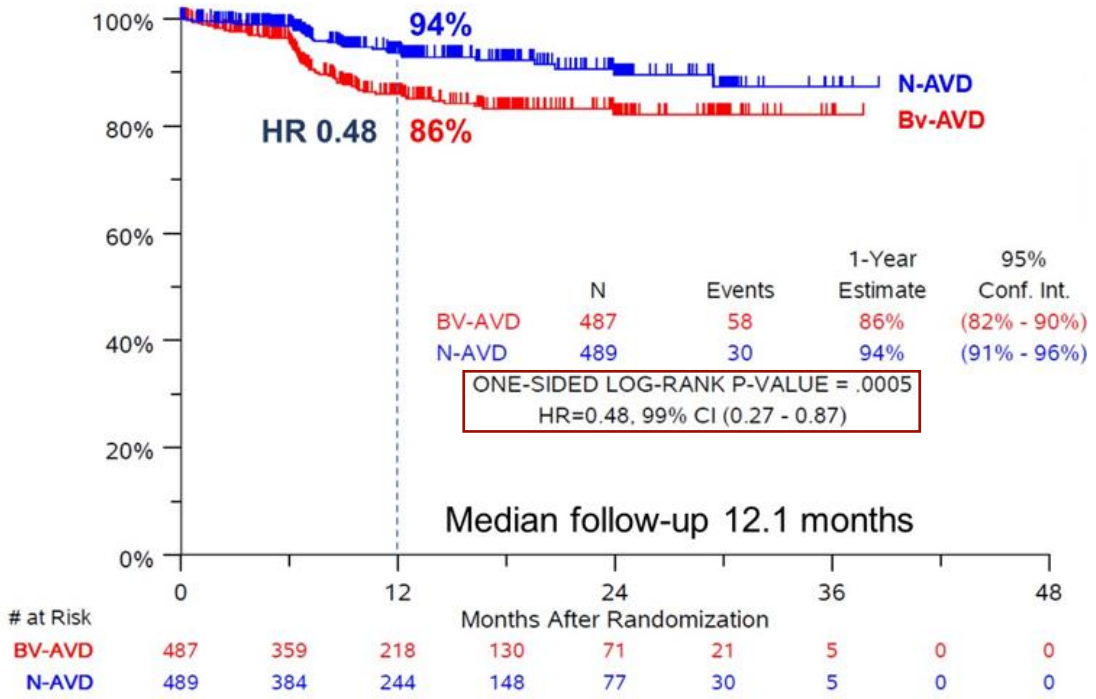
Parameter	N-AVD (n = 489)	BV-AVD (n = 487)
Age, median (range), yr	27 (12-83)	26 (12-81)
• 12-17 yr, n (%)	120 (25)	117 (24)
• 18-60 yr, n (%)	323 (66)	323 (66)
• ≥61 yr, n (%)	46 (9)	47 (10)
Female, n (%)	218 (45)	213 (44)
Race, n (%)		
• White	375 (77)	364 (75)
• Black	57 (12)	56 (11)
• Asian	11 (2)	17 (3)
• Other/unknown	46 (9)	50 (10)
Hispanic, n (%)	68 (14)	59 (12)
Stage, n (%)		
• III	187 (38)	167 (34)
• IV	301 (62)	317 (65)
• Not reported	1 (<1)	3 (1)

Parameter	N-AVD (n = 489)	BV-AVD (n = 487)
B symptoms present, n (%)	286 (58)	274 (56)
IPS, n (%)		
• 0-3	331 (68)	330 (68)
• 4-7	158 (32)	157 (32)
Bulky disease >10 cm, n (%)	155 (32)	131 (27)
HIV positive, n (%)	10 (2)	5 (1)

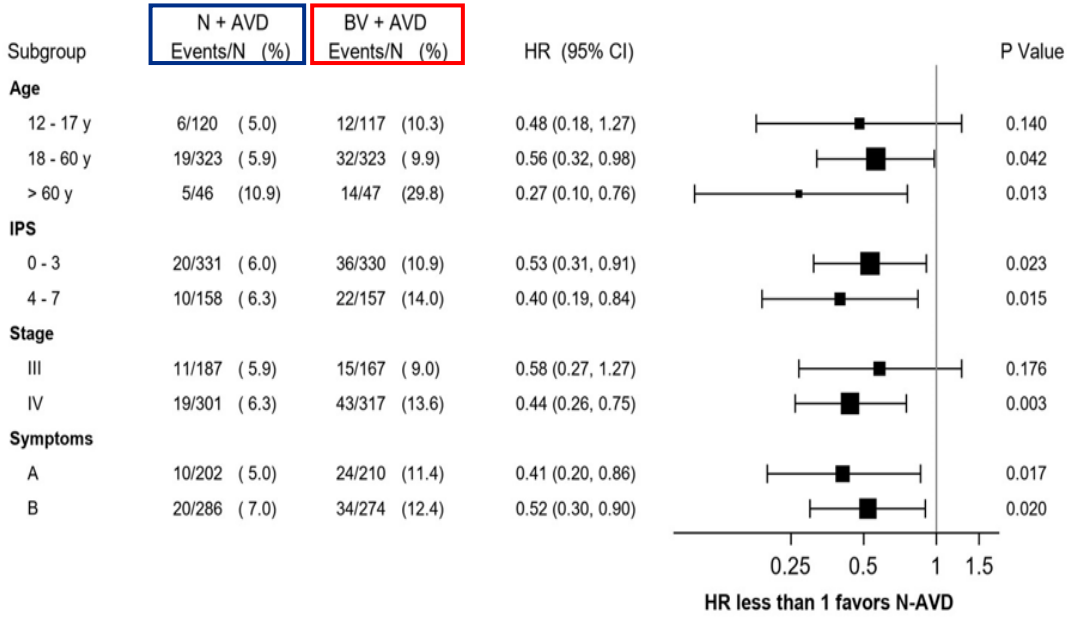
Nivolumab (N); Brentuximab vedotin (Bv); Doxorubicin, Vinblastine, Dacarbazine (AVD)

SWOG S1826

Primary Endpoint: Progression-Free Survival



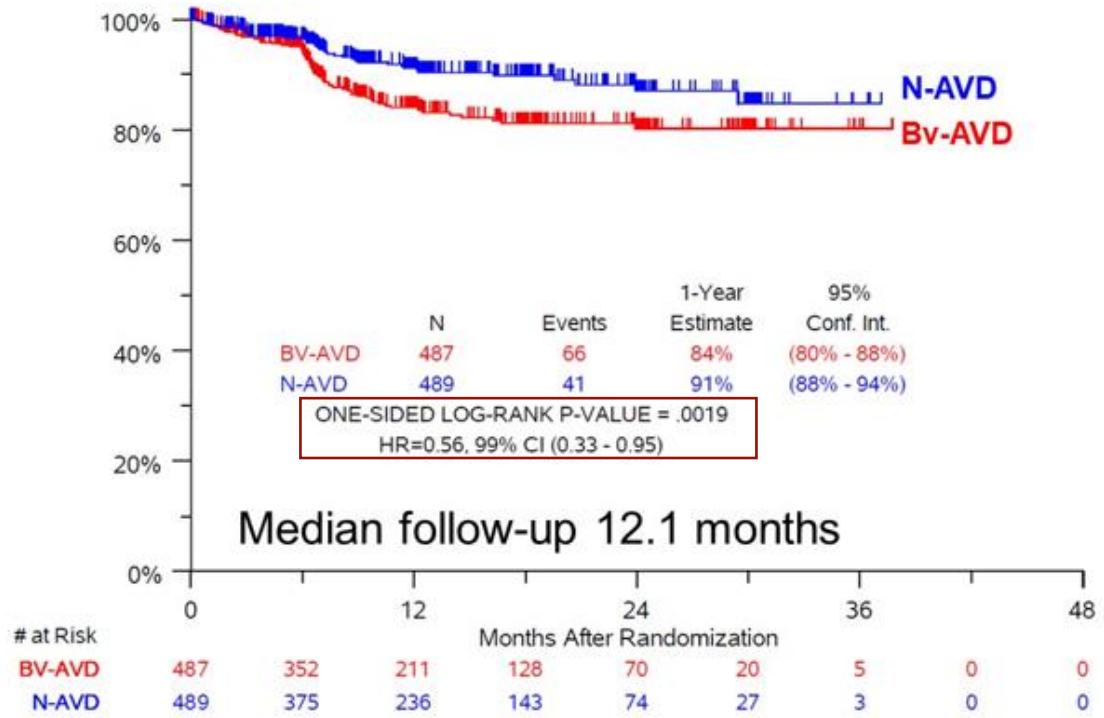
PFS by Subgroups



Nivolumab (N); Brentuximab vedotin (Bv); Doxorubicin, Vinblastine, Dacarbazine (AVD)

SWOG S1826

Event-Free Survival



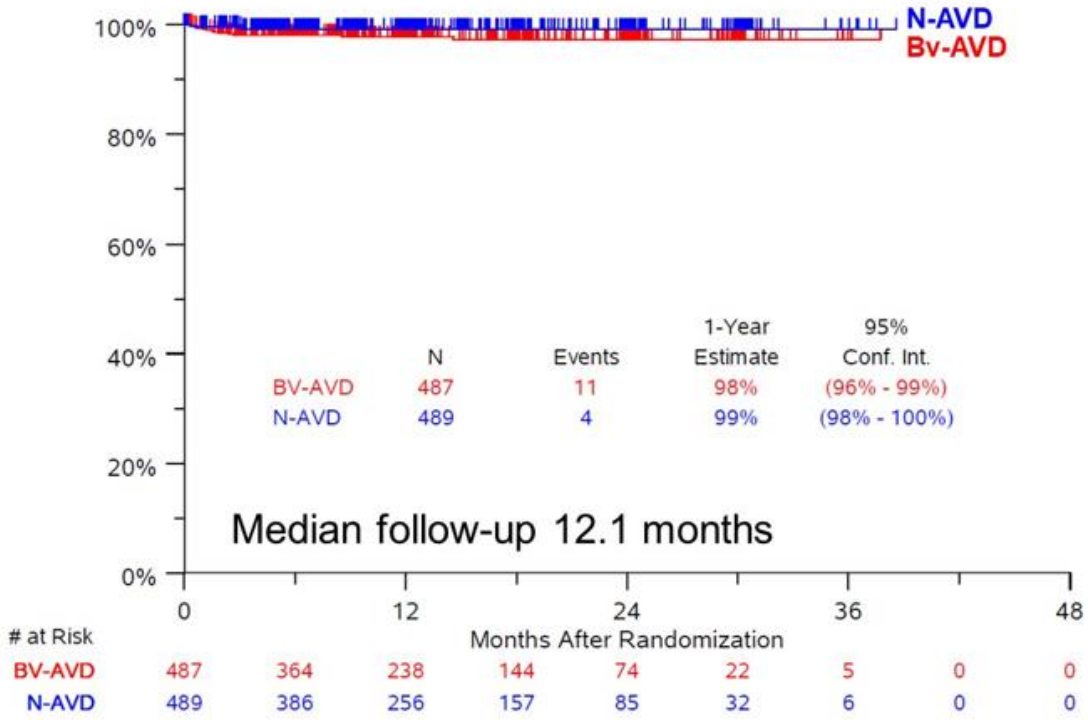
EFS Event, n	N-AVD (n = 489)	BV-AVD (n = 487)
Total EFS events	41	66
Nonprotocol CT before PD	9	6
Nonprotocol IO before PD	1	0
Nonprotocol RT before PD	1*	3†
Progression/relapse	26	47
Death without progression	4	10

*Intended for RT, EOT DS = 3, received RT anyway.
†Intended for RT: 1 patient with EOT DS=2 and off tx due to AE then received RT, 2 patients with EOT DS=2 and received RT anyway.

Nivolumab (N); Brentuximab vedotin (Bv); Doxorubicin, Vinblastine, Dacarbazine (AVD)

SWOG S1826

Overall Survival



Cause of Death, n	N-AVD (n = 489)	BV-AVD (n = 487)
Total deaths	**4**	**11**
Infection	2	4
Sepsis	1	2*
Cardiac arrest	0	1
Pneumonitis	0	1
Dehydration, vomiting, cHL	0	1
cHL	1†	0
Unknown	1	2

*COVID-19/sepsis.
†Ineligible at start date and never received treatment.

Nivolumab (N); Brentuximab vedotin (Bv); Doxorubicin, Vinblastine, Dacarbazine (AVD)

SWOG S1826

Safety

AEs of Interest, n (%)	N-AVD (n = 483)		BV-AVD (n = 473)	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3
Infectious				
• Febrile neutropenia	26 (5)	--	32 (7)	--
• Sepsis	9 (2)	--	16 (3)	--
• Infections/infestations	22 (5)	--	36 (8)	--
Immune/other				
• ALT increased	156 (32)	22 (5)	194 (41)	22 (5)
• AST increased	120 (25)	12 (2)	153 (32)	13 (3)
• Rash maculopapular	51 (11)	4 (1)	58 (12)	0
• Hypothyroidism	33 (7)	1 (0)	3 (1)	0
• Rash acneiform	18 (4)	0	12 (3)	0
• Pneumonitis	10 (2)	2 (0)	15 (3)	10 (2)
• Gastritis	10 (2)	3 (1)	8 (2)	0
• Hyperthyroidism	14 (3)	0	0	0
• Colitis	5 (1)	1(0)	6 (1)	4 (1)
Peripheral neuropathy				
• Sensory	138 (29)	6 (1)	262 (55)	37 (8)
• Motor	20 (4)	1 (0)	35 (7)	6 (1)

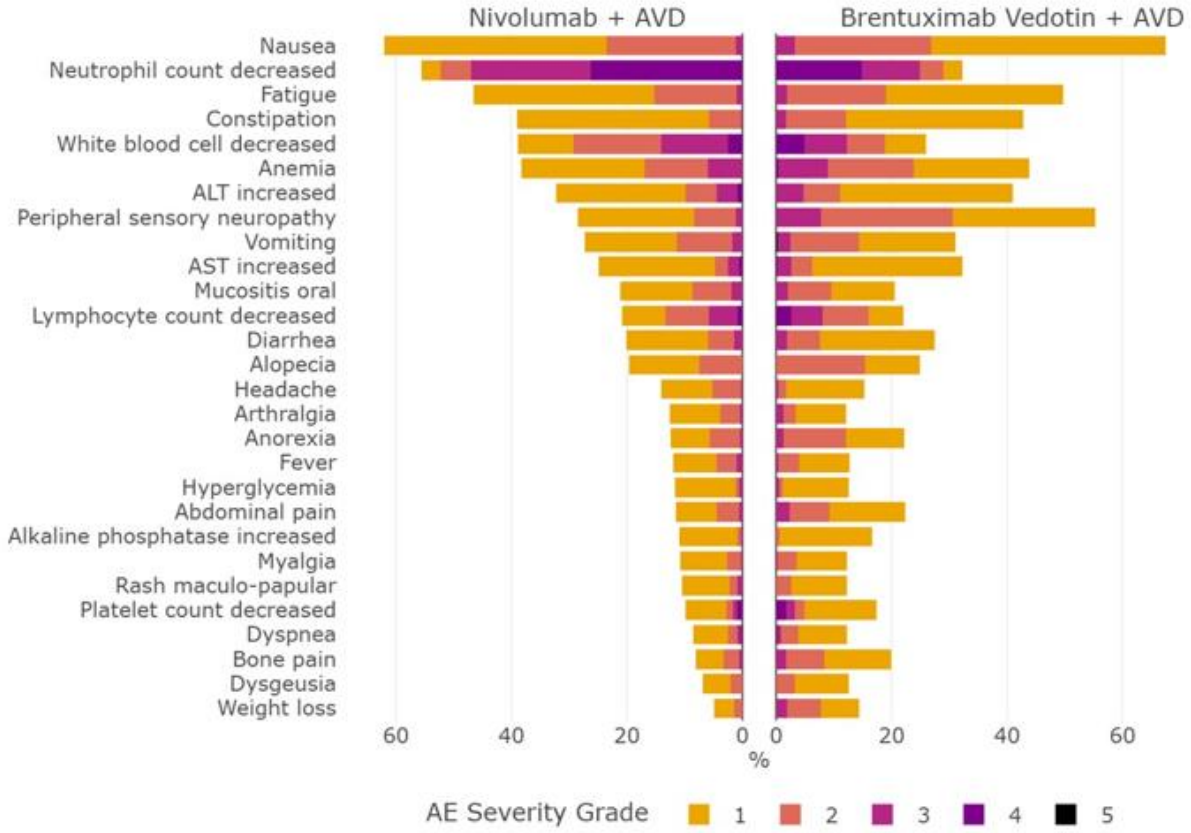
AEs of Interest, n (%)	N-AVD (n = 483)		BV-AVD (n = 473)	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3
Hematologic				
• Neutropenia	268 (55)	227 (47)	152 (32)	118 (25)
• Anemia	185 (38)	29 (6)	207 (44)	42 (9)
• Thrombocytopenia	48 (10)	8 (2)	82 (17)	15 (3)
• Received G-CSF	265 (54)	-	463 (95)	-
• Bone pain	39 (8)	-	92 (20)	-

Nivolumab (N); Brentuximab vedotin (Bv); Doxorubicin, Vinblastine, Dacarbazine (AVD)

SWOG S1826

Safety

Adverse Events in ≥10% patients



Patients, n (%)	N-AVD (n = 483)	BV-AVD (n = 473)
Treatment Ongoing	22	30
Completed treatment	428	400
Discontinued all treatment	39 (8)	57 (12)
• AE	22 (4)	18 (4)
• Patient refusal unrelated to AE	10 (2)	14 (3)
• Progression/relapse	0	7 (1.4)
• Death	2 (<1)	8 (1.6)
• Other	5 (1)	10 (2)
Discontinued BV or Nivo	53 (11)	109 (22)
Received RT	2 (<1)	4 (<1)

Nivolumab (N); Brentuximab vedotin (Bv); Doxorubicin, Vinblastine, Dacarbazine (AVD)

SUMMARY

SWOG S1826

- Nivo-AVD significantly improved PFS (HR: 0.48) and EFS (HR: 0.56) compared with BV-AVD
  - 1-yr PFS: 94% vs 86%; 1-yr EFS: 91% vs 84%
  - <1% of patients received consolidative RT
  - Subgroup analysis supports use of Nivo-AVD across all age groups
- Nivo-AVD was well tolerated with few immune-related AEs
- Ongoing follow-up will assess long-term PFS, safety, OS, and PROs

IMPACT

SWOG S1826

Nivolumab plus AVD provides another treatment option for advanced stage classic Hodgkin lymphoma for pediatric and adult patients

2023 ASCO Key Studies

Breast and Gynecological Cancer

- NATALEE
- PALLAS
- PALMIRA
- SONIA
- MIRASOL

GU/GI Cancer

- PROSPECT*
- DESTINY-CRC02
- PEACE-1
- NeoCol
- CONTACT-03

Other Notable Studies

- ADAURA*
- INDIGO*
- SWOG S1826*
- DESTINY-PanTumor02
- COMMANDS

* Plenary Session

CLINICAL QUESTION

DESTINY-PanTumor02

Does trastuzumab deruxtecan provide benefit for patients with HER2-expressing solid tumors?

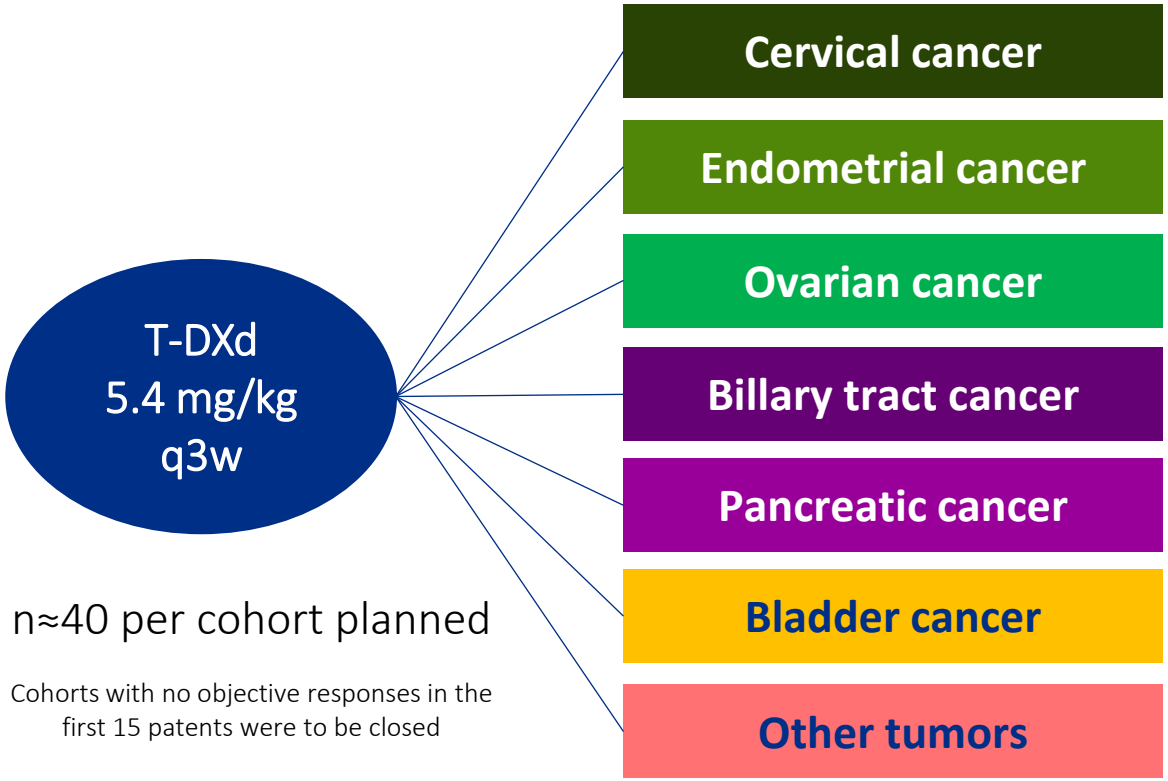
Interim Results

DESTINY-PanTumor02

Study Design: Open-label, multicenter, Phase II study

- Patients with advanced solid tumor not eligible for curative therapy
- 2L + patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by Hercep test if local test not feasible (ASCO/CAP gastric cancer guidelines)*
- Prior HER2-targeting therapy allowed
- ECOG / WHO PS 0-1

*All patients centrally confirmed



n≈40 per cohort planned

Cohorts with no objective responses in the first 15 patents were to be closed

Primary endpoints: Confirmed ORR (investigator)
Secondary endpoints: DOR, DCR, PFS, OS, Safety

Data cutoff : Nov 16, 2022

DESTINY-PanTumor02

Patient Disposition

	Cervical	Endometrial	Ovarian	BTC	Pancreatic	Bladder	Other[a]	All patients
Patients treated, n	40	40	40	41	25	41	40	267
Ongoing treatment at DCO, n (%)	**10 (25.0)**	**14 (35.0)**	**6 (15.0)**	**3 (7.3)**	**1 (4.0)**	**5 (12.2)**	**5 (12.5)**	**44 (16.5)**
Discontinued treatment, n (%)	30 (75.0)	26 (65.0)	34 (85.0)	38 (92.7)	24 (96.0)	36 (87.8)	35 (87.5)	223 (83.5)
Disease progression	21 (52.5)	18 (45.0)	29 (72.5)	22 (53.7)	17 (68.0)	26 (63.4)	23 (57.5)	156 (58.4)
Adverse event	4 (10.0)	2 (5.0)	3 (7.5)	8 (19.5)	3 (12.0)	4 (9.8)	6 (15.0)	30 (11.2)
Other[b]	5 (12.5)	6 (15.0)	2 (5.0)	8 (19.5)	4 (16.0)	6 (14.6)	6 (15.0)	37 (13.9)
Median follow up at DCO, months (range)	7.2 (0.9–23.0)	14.6 (0.8–24.2)	12.7 (0.7–23.7)	6.0 (0.7–20.0)	4.9 (1.1–19.8)	12.0 (0.4–21.2)	12.0 (0.7–23.9)	9.7 (0.4–24.2)
Median duration of treatment at DCO, months (range)	5.5 (0.7–19.8)	9.0 (0.7–24.4)	5.9 (0.7–23.0)	3.5 (0.7–20.1)	2.1 (0.7–11.0)	6.2 (0.4–18.0)	6.9 (0.7–19.9)	5.5 (0.4–24.4)

[a]Includes salivary gland cancer (n=19), malignant neoplasm of unknown primary site (n=5), extramammary Paget's disease (n=3), melanoma (n=2), oropharyngeal neoplasm (n=2), adenoid cystic carcinoma, adenocarcinoid tumor of the appendix, head and neck, intestinal adenocarcinoma, lip and/or oral cavity, oesophageal adenocarcinoma, oesophageal squamous cell carcinoma, testis and vulva (all n=1).
[b]Includes patients who were lost to follow-up (n=1) and patients who discontinued for unknown reasons (n=3), patient decision (n=10), investigator decision (n=5), and other reasons (n=22; n=16 of which died while on treatment).
BTC, biliary tract cancer; DCO, data cut-off (Nov 16, 2022).

DESTINY-PanTumor02

Baseline Characteristics

Characteristic			All patients (N=267)
Age, median (range), years			62 (23–85)
Female, n (%)			178 (66.7)
Race, n (%)	White		163 (61.0)
	Asian		87 (32.6)
	Other		6 (2.25)
	Not reported		5 (1.9)
Prior lines of therapy	Median (range)		2 (0–13)
	n (%)	0	3 (1.1)
		1	70 (26.2)
		2	84 (31.5)
		≥3	107 (40.1)
		Unknown	3 (1.1)
Prior HER2 therapy, n (%)	Monoclonal antibody		34 (12.7)
	Tyrosine kinase inhibitor		1 (0.4)
ECOG PS, n (%)	0		127 (47.6)
	1		139 (52.1)
	2		1 (0.4)

		All patients (N=267)
HER2 testing for eligibility, n (%)[a]	Local	205 (76.8)
	Central	61 (22.8)
	Unknown[b]	1 (0.4)
HER2-expression for eligibility, n (%)[a]	IHC 3+	108 (40.4)
	IHC 2+	153 (57.3)
	IHC 1+[c]	5 (1.9)
	Unknown[b]	1 (0.4)
Centrally confirmed HER2 status for efficacy evaluation, n (%)	IHC 3+	75 (28.1)
	IHC 2+	125 (46.8)
	IHC 1+	25 (9.4)
	IHC 0	30 (11.2)
	Unknown[d]	12 (4.5)

[a]HER2 expression for eligibility was based on local assessment, based on any HER2 test, where available. [b]Patient had missing IHC status (pancreatic cancer cohort) at data cut-off but was confirmed IHC3+ by local testing post-data cut-off. [c]In the cervical cohort, 5 patients with IHC 1+ status were included per protocol. [d]Includes patients whose samples were not evaluable and may have included patients who did not provide a sample for central testing.
ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

DESTINY-PanTumor02

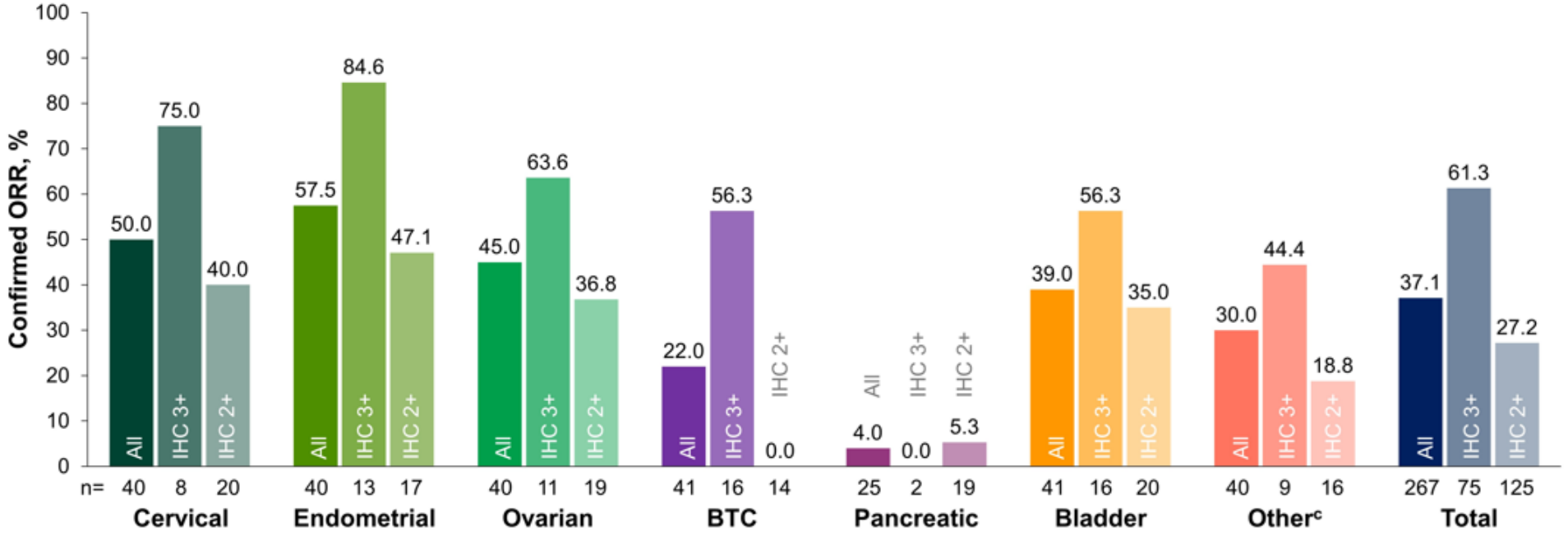
Primary Endpoint: ORR
Secondary Endpoints: DCR and DOR

		Cervical (n=40)	Endometrial (n=40)	Ovarian (n=40)	BTC (n=41)	Pancreatic (n=25)	Bladder (n=41)	Other (n=40)	All patients (N=267)
Investigator assessment									
ORR, n (%)		**20 (50.0)**	**23 (57.5)**	**18 (45.0)**	**9 (22.0)**	**1 (4.0)**	**16 (39.0)**	**12 (30.0)**	**99 (37.1)**
Best overall response, n (%)	Complete response	2 (5.0)	7 (17.5)	4 (10.0)	1 (2.4)	0	1 (2.4)	0	15 (5.6)
	Partial response	18 (45.0)	16 (40.0)	14 (35.0)	8 (19.5)	1 (4.0)	15 (36.6)	12 (30.0)	84 (31.5)
	Stable disease	12 (30.0)	13 (32.5)	14 (35.0)	25 (61.0)	17 (68.0)	18 (43.9)	24 (60.0)	123 (46.1)
	PD	7 (17.5)	4 (10.0)	7 (17.5)	7 (17.1)	7 (28.0)	7 (17.1)	3 (7.5)	42 (15.7)
	Not evaluable	1 (2.5)	0	1 (2.5)	0	0	0	1 (2.5)	3 (1.1)
DCR[a] at 12 weeks, n (%)		27 (67.5)	32 (80.0)	28 (70.0)	27 (65.9)	9 (36.0)	29 (70.7)	30 (75.0)	182 (68.2)
Median DOR, months (95% CI)		9.8 (4.2–NE)	NR (9.9–NE)	11.3 (4.1–NE)	8.6 (2.1–NE)	NR	8.7 (4.3–11.8)	NR (4.1–NE)	11.8 (9.8–NE)
Independent central review: ORR, n (%)		16 (40.0)	21 (52.5)	17 (42.5)	11 (26.8)	3 (12.0)	17 (41.5)	13 (32.5)	98 (36.7)

Analysis of response and DCR was performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd (n=99).
[a]Confirmed complete response, confirmed partial response or stable disease.
BTC, biliary tract cancer; CI, confidence interval; DCR, disease control rate; DOR, duration of response; NE, not estimable; NR, not reached; ORR, objective response rate; PD, progressive disease.

DESTINY-PanTumor02

ORR by HER2 Status

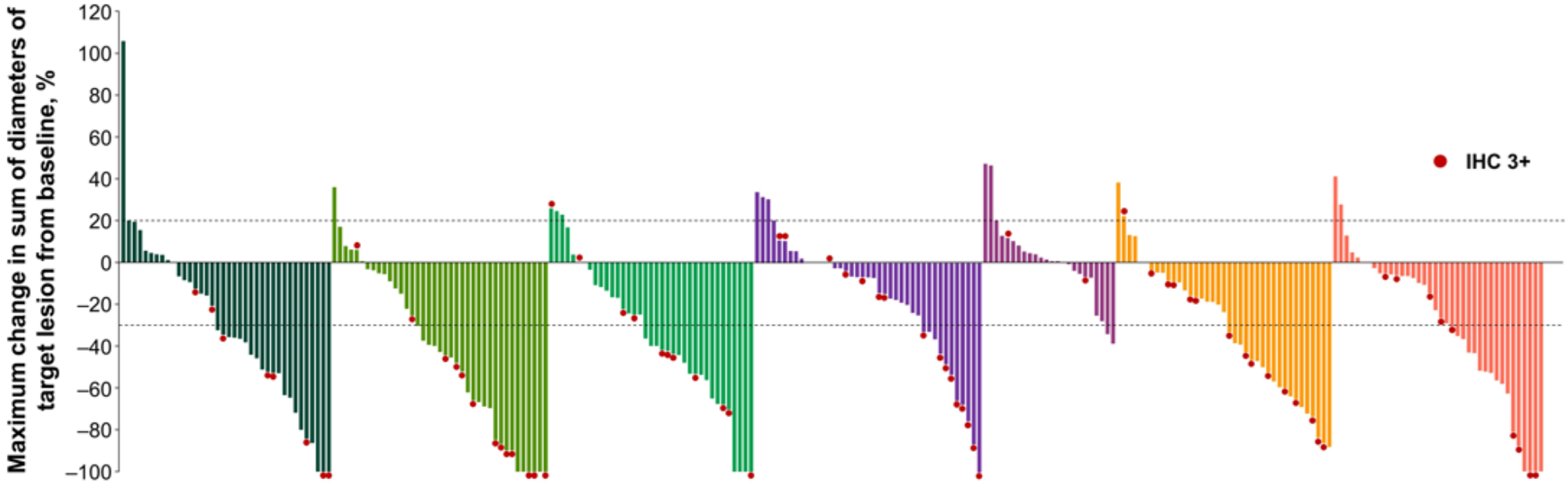


	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [c]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NE, non-estimable; ORR, objective response rate.

DESTINY-PanTumor02

Best Percentage Change in Target Lesion from Baseline

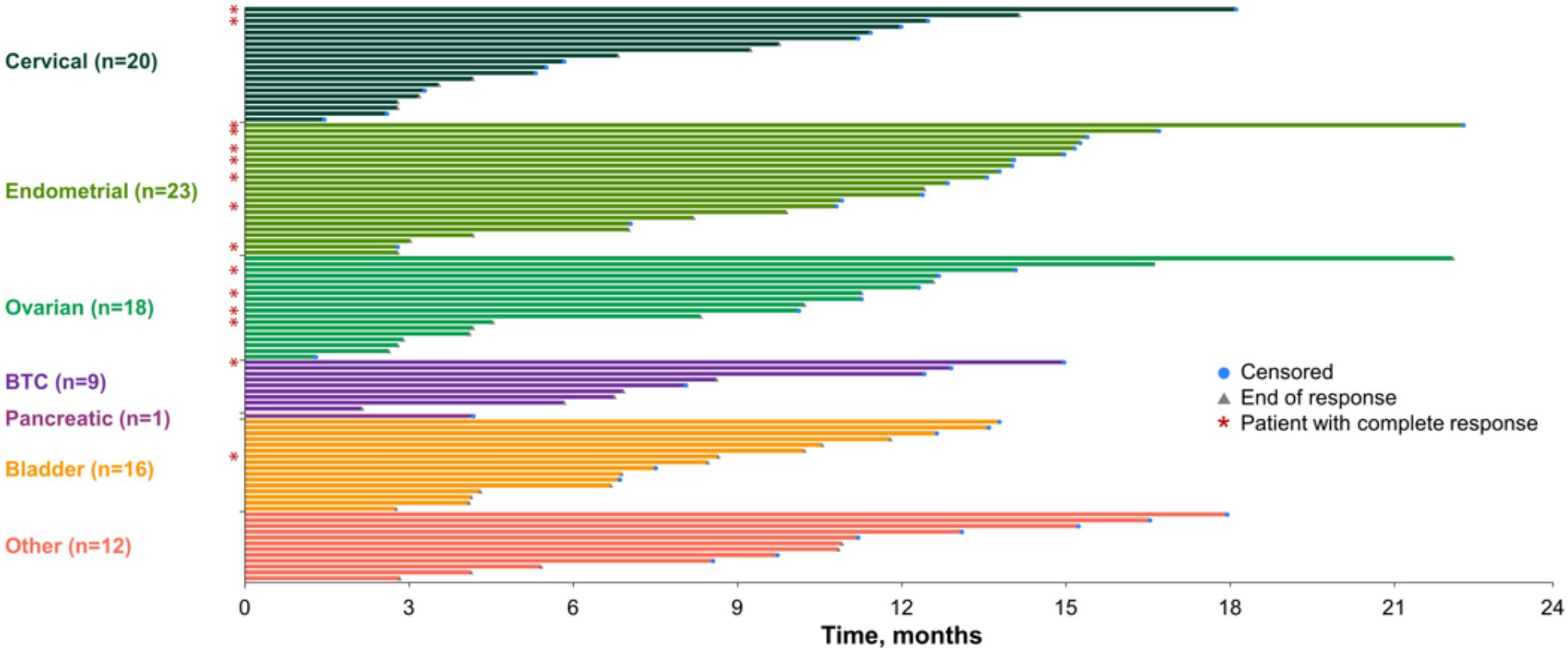


ORR in IHC 3+ n (%)	Cervical (n=8)	Endometrial (n=13)	Ovarian (n=11)	BTC (n=16)	Pancreatic (n=2)	Bladder (n=16)	Other[a] (n=9)
	6 (75.0)	11 (84.6)	7 (63.6)	9 (56.3)	0	9 (56.3)	4 (44.4)

Analyses were performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of ORR in IHC 3+ was performed in patients with centrally confirmed HER2 status (n=75).
[a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; IHC, immunohistochemistry; ORR, objective response rate.

DESTINY-PanTumor02

Duration of Objective Response



Kaplan-Meier estimate of response at 12 months (%)	Cervical	Endometrial	Ovarian	BTC	Pancreatic	Bladder	Other	All
	47.6	72.3	45.8	41.7	0	23.2	53.6	49.6

Analyses were performed in patients with objective response who received ≥1 dose of T-DXd (n=99). At data cut-off, 44 patients (16.5%) are still ongoing treatment, and 128 patients (47.9%) remain in the study. BTC, biliary tract cancer.

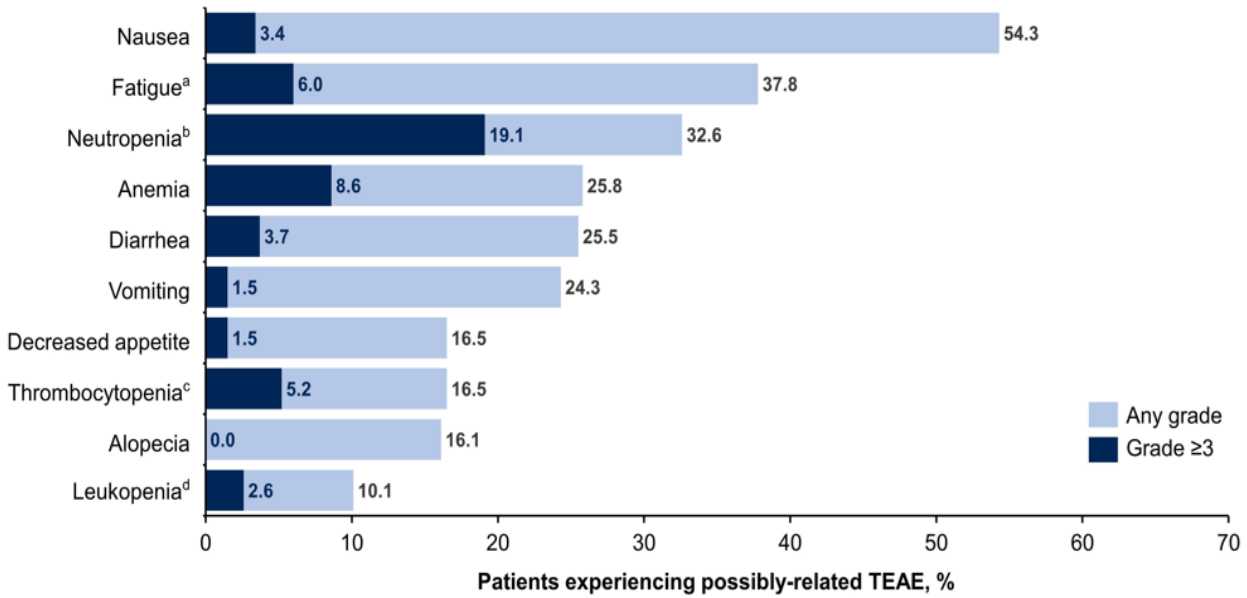
DESTINY-PanTumor02

Safety

n (%)	All patients (N=267)
Any drug-related TEAs	225 (84.3)
Drug-related TEAEs Grade ≥3	103 (38.6)
Serious drug-related TEAEs	32 (12.0)
Drug-related TEAEs associated with dose discontinuations	22 (8.2)
Drug-related TEAEs associated with dose interruptions	49 (18.4)
Drug-related TEAEs associated with dose reductions	50 (18.7)
Drug-related TEAEs associated with death	2 (0.7)*

Analyses were performed in patients who received ≥1 dose of T-DXd (n=267)
* Included neutropenic sepsis (n=1) and pneumonia (n=1)

Drug-Related TEAEs in ≥10% of Patients



DESTINY-PanTumor02

Safety: Adverse Events of Special Interest

ILD/pneumonitis adjudicated as T-DXd–related

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
All patients (N=267)	6 (2.2)	12 (4.5)	1 (0.4)	0	1 (0.4)	20 (7.5)

Left ventricular dysfunction[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Ejection fraction decreased						
All patients (N=267)	1 (0.4)	4 (1.5)	1 (0.4)	0	0	7 (2.6)[b]
Cardiac failure						
All patients (N=267)	0	0	1 (0.4)	0	0	1 (0.4)

Analyses were performed in patients who received ≥1 dose of T-DXd (n=267).
[a]Left ventricular dysfunction was reported in a total of 12 (4.5%) patients, of which 8 (3.0%) were considered possibly T-DXd–related. [b]One patient had unknown grade of ejection fraction decrease.
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.

SUMMARY

DESTINY-PanTumor02

- Trastuzumab deruxtecan resulted in encouraging activity across all tumor types investigated
  - ORR 37.1% in all patients, with greatest activity in IHC3+ expressing tumors
  - Median DOR 11.8 months in all patients, and 22.1 months in patients with IHC3+ expressing tumors
- No new safety concerns
- OS and PFS data to come…

DESTINY-PanTumor02

Trastuzumab deruxtecan has the potential to benefit patients with multiple HER2-expressing tumor types

Testing will be critical for patient identification

More to come…

2023 ASCO Key Studies

Breast and Gynecological Cancer	GU/GI Cancer	Other Notable Studies
• NATALEE • PALLAS • PALMIRA • SONIA • MIRASOL	• PROSPECT* • DESTINY-CRC02 • PEACE-1 • NeoCol • CONTACT-03	• ADAURA* • INDIGO* • SWOG S1826* • DESTINY-PanTumor02 • COMMANDS

* Plenary Session

COMMANDS

Does luspatercept benefit erythropoiesis-stimulating agent-naïve, transfusion-dependent patients with lower-risk myelodysplastic syndromes?

Prespecified interim analysis when primary endpoint data 85% mature

COMMANDS

Study Design: Global, randomized, open-label phase III trial

- Patients ≥18 yr of age
- Very low–, low-, or intermediate-risk MDS (IPSS-R) and <5% BM blasts
- ESA-naive
- sEPO <500 U/L
- RBC transfusion dependent*
- ECOG PS 0-2

(N = 356)

*2-6 RBC U/8 wk for ≥8 wk prior.

Stratified by baseline sEPO, baseline RBC transfusion burden, RS status

R 1:1

Luspatercept
1.0 mg/kg SC Q3W;
titration up to 1.75 mg/kg max
(n=178)

Epoetin alfa
450 IU/kg SC QW;
titration up to 1050 IU/kg
(n=178)

MDS disease status assessment
Day 169, Q24W thereafter

Until PD, death, unacceptable toxicity, patient/physician decision, or withdrawal

<u>Post-treatment safety follow-up:</u>

- Monitoring for other malignancies, HR-MDS or AML progression, subsequent therapies, survival
- For 5 years from first dose or 3 years from last dose, whichever is later

Primary endpoint: RBC-TI ≥12 wk with concurrent mean Hgb increase ≥1.5 g/dL

Secondary endpoints: HI-E ≥8 wk per IWG criteria, RBC-TI for 24 wk, RBC-TI ≥12 wk, time to first RBC transfusion, safety

Prespecified interim analysis when primary endpoint data 85% mature

COMMANDS

Baseline Characteristics

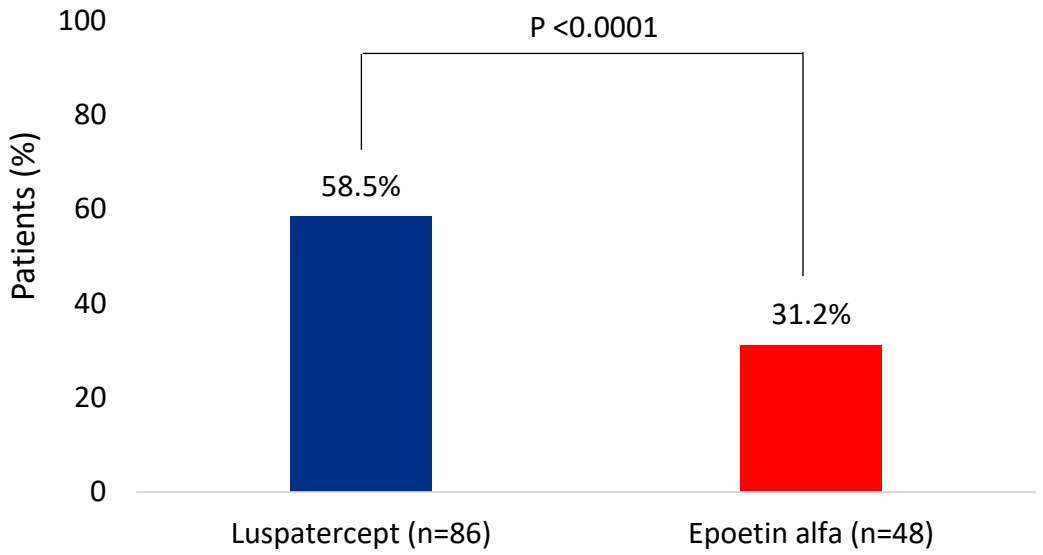
Characteristic, n (%)	Luspatercept (n = 178)	Epoetin alfa (n = 178)
Median age, yr (range)	74.0 (46.0-93.0)	75.0 (33.0-91.0)
Female sex, n (%)	71 (39.9)	87 (48.9)
Median time since MDS diagnosis, mo (range)	8.02 (-0.4 to 243.1)	5.17 (-0.3 to 171.6)
Baseline RBC transfusion burden, n (%)		
• 2 pRBC U/8 wk	80 (44.9)	79 (44.4)
• <4 U/8 wk	114 (64.0)	109 (61.2)
• ≥4 U/8 wk	64 (36.0)	69 (38.8)
Baseline IPSS-R risk, n (%)		
• Very low	16 (9.0)	17 (9.6)
• Low	126 (70.8)	131 (73.6)
• Intermediate	34 (19.1)	28 (15.7)
• High*	1 (0.6)	0
• Missing	1 (0.6)	2 (1.1)

Characteristic	Luspatercept (n = 178)	Epoetin alfa (n = 178)
SF3B1 mutation status, n (%)		
• Mutated	111 (62.4)	99 (55.6)
• Wild type	65 (36.5)	72 (40.4)
• Missing	2 (1.1)	7 (3.9)
RS status, n (%)		
• RS+	130 (73.0)	128 (71.9)
• RS-	48 (27.0)	49 (27.5)
• Missing	0	1 (0.6)
Median Hb, g/dL (range)	7.8 (4.7-9.2)	7.8 (4.5-10.2)
Median sEPO, U/L (range)	78.7 (7.8-495.8)	85.9 (4.6-462.5)
Median platelet count x 10^9/L (range)	230.0 (38-770)	234.5 (47-715)
Median absolute neutrophil count, x 10^9/L (range)	2.390 (0.39-9.1)	2.295 (0.50-13.3)
Median serum ferritin, µg/L (range)	626.20 (12.4-3170.0)	651.30 (39.4-6960.5)

COMMANDS

Primary Endpoint: Efficacy in ITT

RBC-TI ≥12 wk with concurrent Hb increase ≥1.5 g/dL, weeks 1-24



By Subgroups (%)	Luspatercept (n = 147)	Epoetin alfa (n = 154)
Baseline sEPO level		
• ≤200 U/L	62.7	36.4
• >200-500 U/L	41.4	12.1
RS status		
• RS+	64.8	25.9
• RS-	41.0	46.3
Baseline RBC transfusion burden		
• <4 U/8 wk	66.3	38.9
• ≥4 U/8 wk	45.5	20.3
SF3B1 mutation status		
• Mutated	69.6	30.7
• Wild type	41.5	32.3

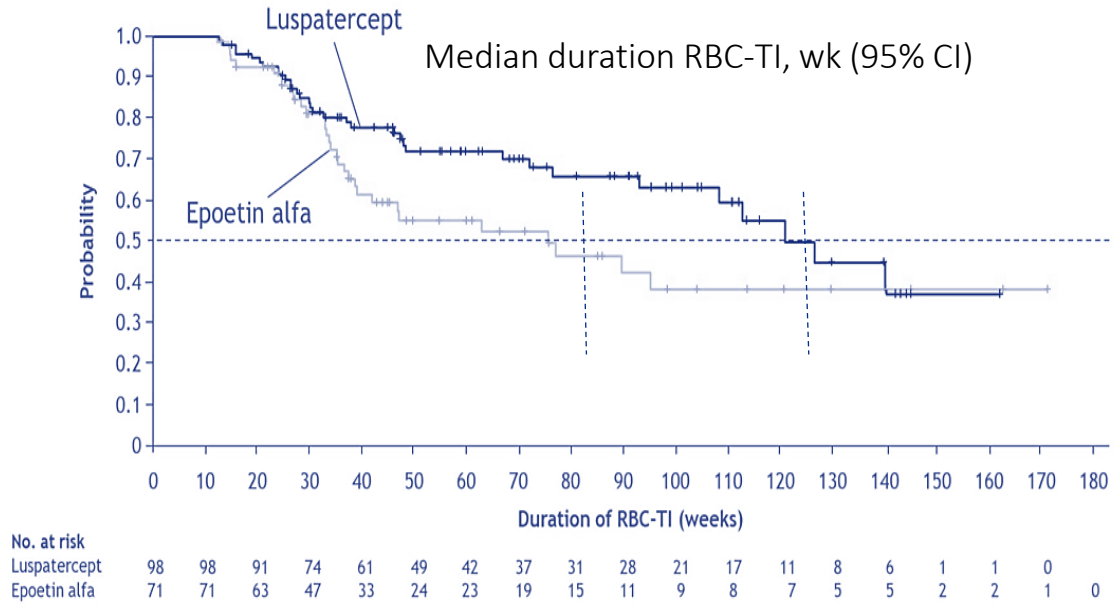
- Of 301 patients included in the efficacy analysis, 86 (58.5%) patients receiving luspatercept and 48 (31.2%) receiving epoetin alfa achieved the primary endpoint

COMMANDS

Secondary Endpoint: HI-E ≥8 wk per IWG criteria, RBC-TI for 24 wk, RBC-TI ≥12 wk, time to first RBC transfusion

Endpoint	Luspatercept (n = 147)	Epoetin alfa (n = 154)
Received transfusion during tx, n	93	116
Median time to first RBC transfusion, days (range)	**168.0** (64.0-323.0)	**42.0** (22.0-55.0)
RBC-TI ≥12 wk, n (%)	98 (66.7)	71 (46.1)
	P = 0.0002	
RBC-TI 24 wk, n (%)	70 (47.6)	45 (29.2)
	P = 0.0006	
HI-E ≥8 wk, n (%)	109 (74.1)	79 (51.3)
	P <0.0001	

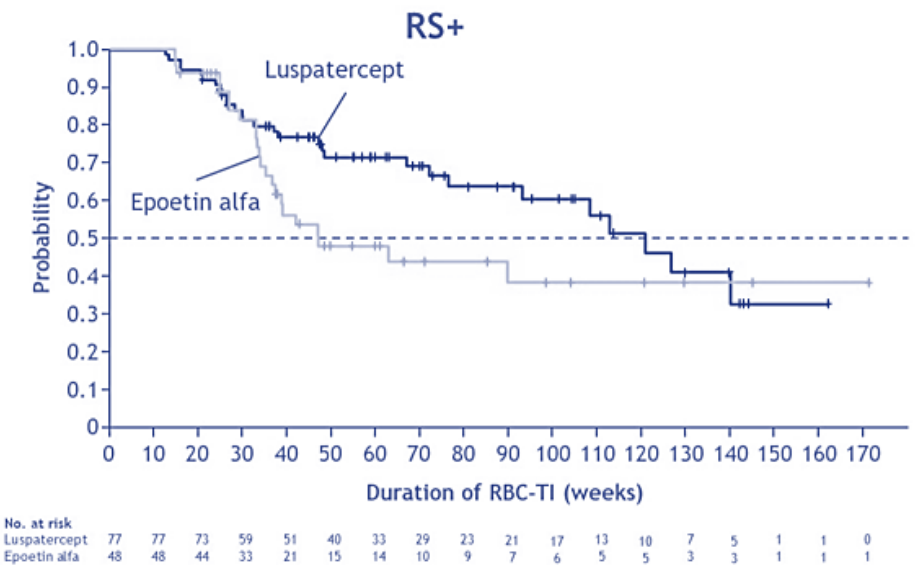
Endpoint	Luspatercept (n = 147)	Epoetin alfa (n = 154)
Median duration RBC-TI, wk (95% CI)	**126.6** (108.3-NE)	**77.0** (39.0-NE)
	HR: **0.456** (95% CI: 0.260-0.798)	

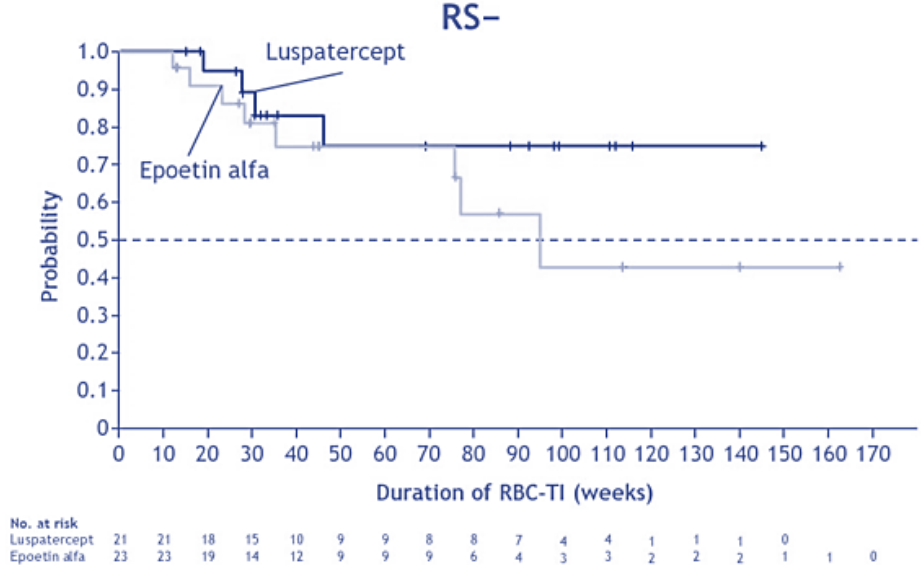


COMMANDS

RBC-TI ≥12 wk in RS+ and RS- luspatercept and epoetin alfa patients

Median duration RBC-TI, wk (95% CI)	Luspatercept (n = 147)	Epoetin alfa (n = 154)
RS+	**120.9** (76.4-NE)	**47.0** (36.6-NE)
	HR: **0.626** (95% CI: 0.361-1.085)	
RS-	NE (46.0-NE)	95.1 (35.3-NE)
	HR: 0.492 (95% CI: 0.148-1.638)	





COMMANDS

Safety

Patients, n (%)	Luspatercept (n = 178)		Epoetin alfa (n = 176)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic TEAEs				
• Anemia	17 (9.6)	13 (7.3)	17 (9.7)	12 (6.8)
• Thrombocytopenia	11 (6.2)	7 (3.9)	3 (1.7)	1 (0.6)
• Neutropenia	9 (5.1)	7 (3.9)	13 (7.4)	10 (5.7)
• Leukocytopenia	2 (1.1)	0	3 (1.7)	0
TEAEs of interest				
• Fatigue	26 (14.6)	1 (0.6)	12 (6.8)	1 (0.6)
• Diarrhea	26 (14.6)	2 (1.1)	20 (11.4)	1 (0.6)
• Peripheral edema	23 (12.9)	0	12 (6.8)	0
• Asthenia	22 (12.4)	0	25 (14.2)	1 (0.6)
• Nausea	21 (11.8)	0	13 (7.4)	0
• Dyspnea	21 (11.8)	7 (3.9)	13 (7.4)	2 (1.1)
• Thromboembolic event	8 (4.5)	5 (2.8)	5 (2.8)	1 (0.6)
Progression to HR-MDS	5 (2.8)		7 (4.0)	
Progression to AML	4 (2.2)		5 (2.8)	

TEAEs of any grade:

- 92.1% (n=164) luspatercept
- 85.2% (n=150) epoetin alfa

Treatment discontinuation:

- 43.8% (n=78) with luspatercept
- 59.7% (n=105) with epoetin alfa

Most common reason was lack of efficacy:

- 15.7% (n=28) with luspatercept
- 32.4% (n=57) with epoetin alfa
- Rates of discontinuation for disease progression (n=7 vs 7), adverse event (n=8 vs 4), or death (n=11 vs 11) were similar between treatment arms, respectively

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SUMMARY

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- For ESA-naïve patients with transfusion-dependent lower-risk MDS, luspatercept resulted in improved efficacy over epoetin alfa in a head-to-head study
  - Primary endpoint of RBC-TI ≥12 wk + mean Hb increase ≥1.5 g/dL achieved by **58.5%** of patients treated with luspatercept vs **31.2%** treated with epoetin alfa
  - Median time to the first RBC transfusion was **168 days** for patients treated with luspatercept versus **42 days** for patients treated with epoetin alfa
  - Median duration of RBC-TI: **126.6 wk** for luspatercept vs **77.0 wk** for epoetin alfa
  - Benefit with luspatercept observed across patient subgroups
- Safety profile was manageable and consistent with previous reports
- Dosing and dosing schedule is better
  - Need to dose titrate up to see response (start at 1 mg/kg increase to 1.33 mg/kg to 1.75 mg/kg)

Based on results from Phase 3 COMMANDS study in which first-in-class Reblozyl demonstrated a highly statistically significant and clinically meaningful improvement compared to an erythropoiesis-stimulating agent in patients with very low/low/intermediate-risk MDS, the FDA has assigned a target action date of August 28, 2023

ASCO 2023. Abstr 7003

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Luspatercept improves anemia and delays transfusion for patients ***with*** *lower-risk myelodysplastic syndromes in the 1L setting and could be consider as a new standard of care with a* ***PUDFA date of August 28th***