Applications for Community Oncology

ESMO Data Review

December 4, 2025

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2025 ESMO Key Studies

Breast Cancer

- *DESTINY-Breast11
- *DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*

- evERA BC
- VIKTORIA-1
  - *Polling Question*

GU GI

- *KEYNOTE-905/EV-303
- *IMvigor-011
  - *Polling Question*
- *PSMAddition
  - *Rapid Review*: CAPItello-281
- *Polling Question*
- *FORTITUDE-101
- *AGITG-DYNAMIC-III
  - *Polling Question*
- *RC48-C016
  - *Rapid Review*: POTOMAC

Lung Cancer and Other Notable Studies

- *HARMONI-6
- FLAURA2
  - *Polling Question*
- *OptiTROP-Lung04
  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

*ESMO Presidential Session

CLINICAL QUESTION

DESTINY-Breast11

HER2+ neoadjuvant

Comparison of neoadjuvant trastuzumab deruxtecan followed by paclitaxel + trastuzumab + pertuzumab (T-DXd-THP) vs anthracycline-cyclophosphamide ddAC-THP in patients with high-risk HER2+ primary breast cancer

Neoadjuvant T-DXd → THP vs ddAC → THP

KEY DATA

DESTINY-Breast11, neoadjuvant T-DXd → THP vs ddAC → THP

Study Design: Open-label, randomized phase III study

- HER2+ early breast cancer (eBC) considered high risk, defined as ≥cT3 and N0-3 or cT0-4 and N1-3 or with inflammatory BC
- (N = 927)

Stratified by HR status (ER and/or PR pos vs neg), HER2 status (IHC 3+ vs ISH+ without IHC 3+)

T-DXd, 5.4 mg/kg IV q3w (4 cycles) → **THP**† (4 cycles) (n = 321)

ddAC‡ (4 cycles) → **THP**§ (4 cycles) (n = 320)

T-DXd* (8 cycles) (n = 286)

SURGERY

Recommended post-neoadjuvant treatment per study protocol:

- **pCR**: radiotherapy and concomitant trastuzumab ± pertuzumab for up to 1 year
- **No pCR**: radiotherapy and T-DM1 for up to 14 cycles
- **HR-positive**: endocrine therapy

Primary endpoint: pCR (ypT0/is ypN0) by blinded central review
Secondary endpoints: pCR (ypT0 ypN0) by blinded central review, EFS, Safety, PK and immunogenicity, Invasive DFS, Overall survival, Health-related quality of life
Additional outcome measures: Residual cancer burden (RCB)

*T-DXd alone arm closed following IDMC recommendation. Reasons: lower pCR rate, low likelihood that T-DXd alone would be superior to ddAC-THP, surgery time

† Paclitaxel 80 mg/m^2 IV qw, trastuzumab 6 mg/kg IV q3w, pertuzumab 840 mg → 420 mg IV q3w. ‡Doxorubicin 60 mg/m^2 IV q2w, cyclophosphamide 600 mg/m^2 IV q2w. §Paclitaxel 80 mg/m^2 IV qw, trastuzumab 8 mg/kg → 6 mg/kg IV q3w, pertuzumab 840 mg → 420 mg IV q3w.

ESMO 2025. Abstr 291O. Harbeck. Ann Oncol. 2025 [Epub].

DESTINY-Breast11, neoadjuvant T-DXd → THP vs ddAC → THP

Baseline Characteristics

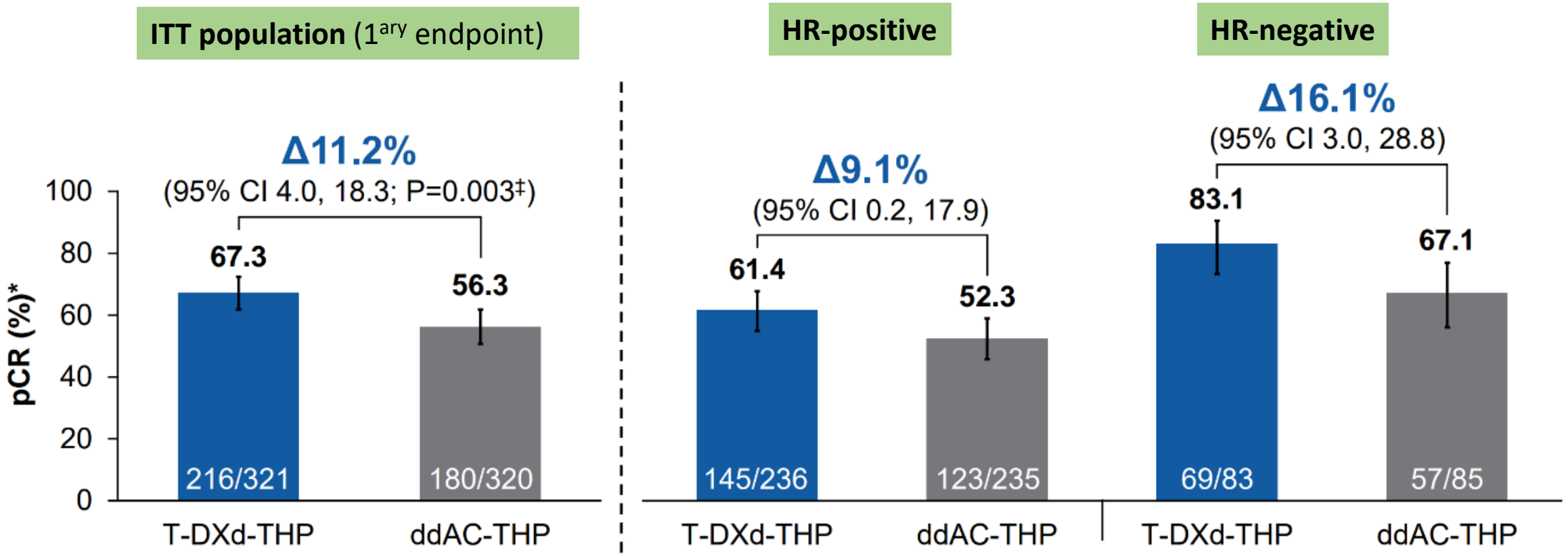
Characteristic	T-DXd–THP (n = 321)	ddAC-THP (n = 320)	T-DXd (n = 286)
Median age, yr (range)	50 (25-82)	50 (23-79)	50 (23-79)
Female, n (%)	321 (100)	320 (100)	286 (100)
Region, n (%)			
• Asia	152 (47.4)	152 (47.5)	124 (43.4)
• Western Europe	69 (21.5)	77 (24.1)	66 (23.1)
• North America	43 (13.4)	41 (12.8)	52 (18.2)
• Rest of world	57 (17.8)	50 (15.6)	44 (15.4)
Race, n (%)			
• Asian	160 (49.8)	157 (49.1)	127 (44.4)
• White	140 (43.6)	137 (42.8)	139 (48.6)
• Black	5 (1.6)	7 (2.2)	7 (2.4)
• Other	12 (3.7)	10 (3.1)	8 (2.8)

Characteristic, n (%)	T-DXd–THP (n = 321)	ddAC-THP (n = 320)	T-DXd (n = 286)
HER2 status			
• IHC 3+	280 (87.2)	283 (88.4)	254 (88.8)
• Other	40 (12.5)	36 (11.3)	32 (11.2)
HR+ status	236 (73.5)	235 (73.4)	205 (71.7)
Clinical tumor stage			
• cT0-2	176 (54.8)	188 (58.8)	157 (54.9)
• cT3-4	145 (45.2)	132 (41.3)	129 (45.1)
Nodal status			
• N0	26 (8.1)	35 (10.9)	20 (7.0)
• N+	287 (89.4)	281 (87.8)	254 (88.8)

KEY DATA

DESTINY-Breast11, neoadjuvant T-DXd → THP vs ddAC → THP

Primary Endpoint: pCR (ypT0/is ypN0) by blinded central review; in ITT and by HR status



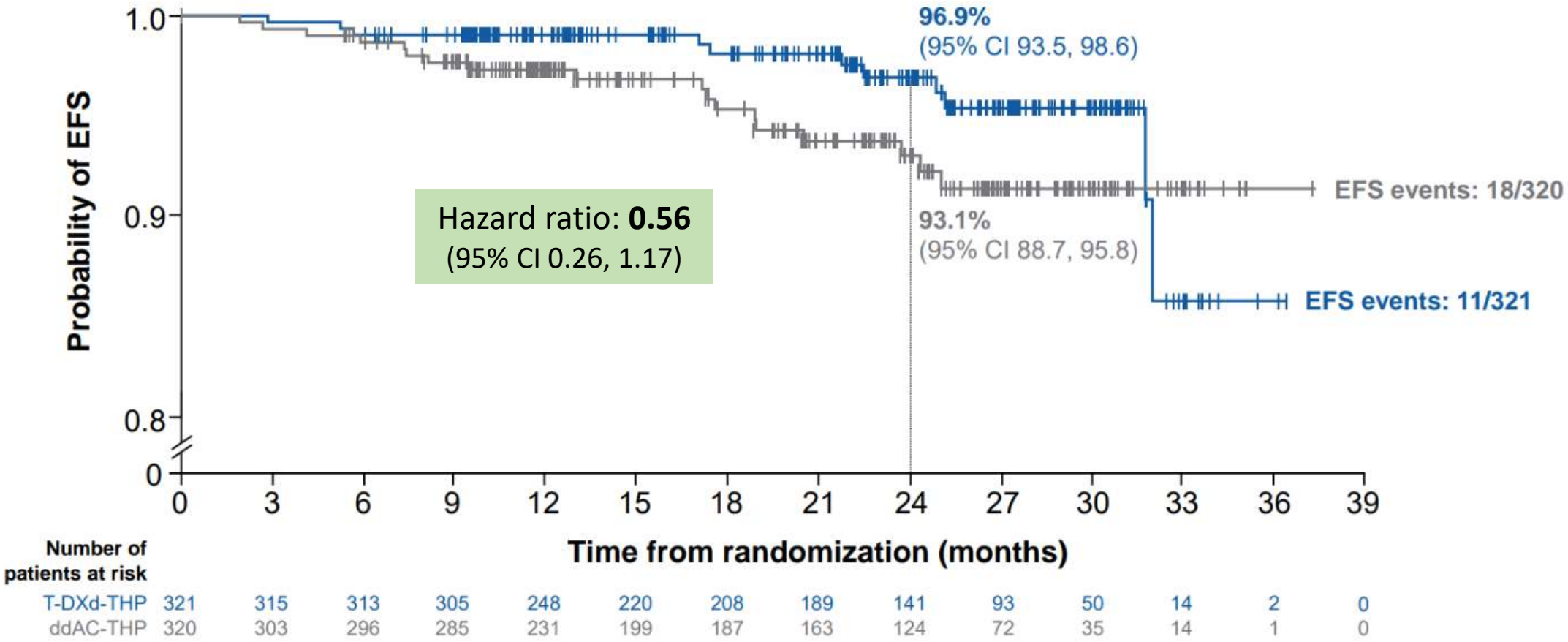
HR = hormone receptor

ESMO 2025. Abstr 291O. Harbeck. Ann Oncol. 2025 [Epub].

KEY DATA

DESTINY-Breast11, neoadjuvant T-DXd → THP vs ddAC → THP

Secondary Endpoint: Event free survival



At data cutoff (Mar 12, 2025), EFS event maturity was 4.5%; at final cutoff, maturity is predicted to be ~10%*

ESMO 2025. Abstr 291O. Harbeck. Ann Oncol. 2025 [Epub].

KEY DATA

DESTINY-Breast11, neoadjuvant T-DXd → THP vs ddAC → THP

Secondary Endpoint: Safety

AEs, n (%)	T-DXd–THP (n = 320)	ddAC-THP (n = 312)
Any	**314 (98.1)**	**308 (98.7)**
• Grade ≥3	120 (37.5)	174 (55.8)
Any serious	34 (10.6)	63 (20.2)
AE leading to adjustments		
• Any dose reduction	58 (18.1)	60 (19.2)
• Any dose interruption	121 (37.8)	170 (54.5)
• Any treatment discontinuation	45 (14.1)	31 (9.9)
Any AE with outcome of death	2 (0.6)	2 (0.6)
AEs of special interest		
• Drug-related adjudicated ILD/pneumonitis	14 (4.4)	16 (5.1)
– Grade ≥3	2 (0.6)	6 (1.9)
– Grade 5	1 (0.3)	1 (0.3)
• Left ventricular dysfunction	4 (1.3)	19 (6.1)
– Grade ≥3	1 (0.3)	6 (1.9)
– Grade 5	0	0
AE leading to surgical delay	11 (3.4)	8 (2.6)

ESMO 2025. Abstr 291O. Harbeck. Ann Oncol. 2025 [Epub].

SUMMARY

DESTINY-Breast11

- Neoadjuvant T-DXd → THP demonstrated improved clinical and statistical pCR rates of 67.3% vs 56.3% with ddAC→ THP (*P* = 0.003), with benefit regardless of HR status and clinical stage
  - Similar low rate of ILD between the 2 arms
- T-DXd alone arm closed by the IDMC; data pending
- *Perspective: recent multicenter retrospective study: pCR rates did not significantly differ between anthracycline and non-anthracycline regimens*
  - *48.7% TCHP vs. 53.2% THP-AC, p = 0.659*

Breast Cancer Res Treat. 2025 Nov;214(1):69-77.

IMPACT

Trastuzumab deruxtecan followed by THP is a new potential neoadjuvant treatment option for patients with high risk HER2+ early breast cancer

Data support becoming a new standard of care ----not yet FDA approved

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*ESMO Presidential Session

CLINICAL QUESTION

DESTINY-Breast05

HER2+ post-neoadjuvant

Comparison of trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients with high-risk HER2+ primary breast cancer with residual invasive disease after neoadjuvant therapy

post-neoadjuvant T-DXd vs T-DM1

KEY DATA

DESTINY-Breast05, post-neoadjuvant T-DXd vs T-DM1

Study Design: Open-label, randomized phase III

- Residual invasive disease in breast and/or axillary LNs after neoadjuvant chemo with HER2-directed therapy (NAT*)
- High-risk defined as presentation prior to NAT with
  - inoperable early BC (cT4, N0-3, M0 or cT1-3, N2-3, M0) OR
  - operable early BC (cT1-3, N0-1, M0) with axillary node-positive disease (ypN1-3) after NAT
- HER2+ (IHC 3+ or ISH+) early BC
- ECOG PS 0-1

*NAT (neoadjuvant therapy): ≥16 wks NAT with ≥9 wks trastuzumab ± pertuzumab and ≥9 wks taxane-based chemotherapy

T-DXd 5.4 mg/kg IV q3w for 14 cycles N ≅ 800

T-DM1 3.6 mg/kg IV q3w for 14 cycles N ≅ 800

Concomitant adjuvant endocrine therapy (ET) allowed. RT could be initiated concurrent or completed prior to initiation of study therapy per investigator.

40-day safety follow-up

Stratified by extent of disease at presentation (inoperable vs operable), HER2-targeted NAT (single vs dual), HR status (pos vs neg), post-NAT pathologic nodal status (pos vs neg)

Primary endpoint:

- Invasive disease–free survival (IDFS)

Secondary endpoints:

- Disease-free survival (DFS)
- Overall survival (OS)
- Distant recurrence–free interval (DRFI)
- Brain metastasis–free interval (BMFI)
- Safety

Interim analysis timeline
Data Cutoff: 2 July 2025
Median study duration: 29.9 mo (range, 0.3-53.4 mo) with T-DXd and 29.7 mo (range, 0.1-54.4 mo) with T-DM1

DESTINY-Breast05, post-neoadjuvant T-DXd vs T-DM1

Baseline Characteristics

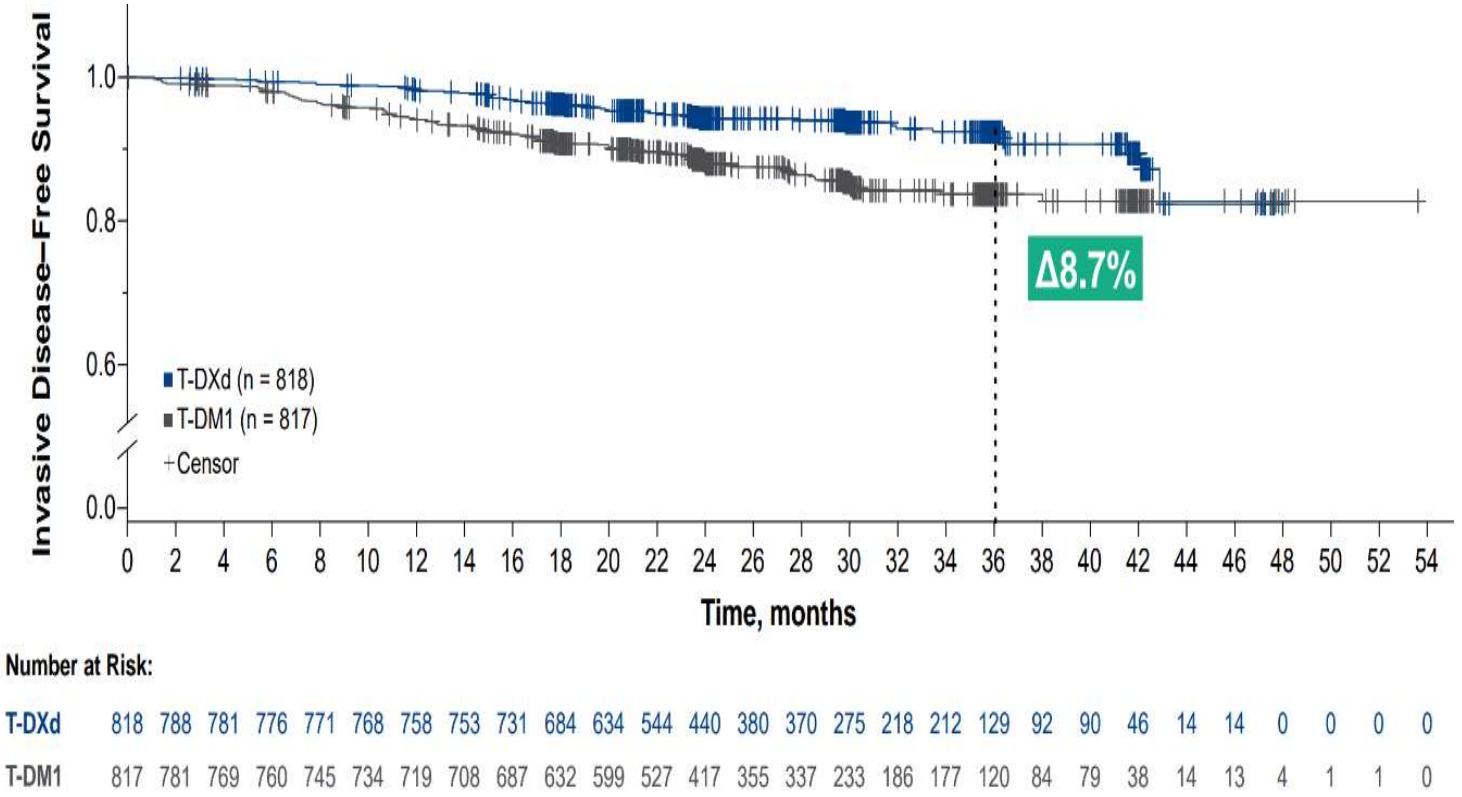
Characteristic	T-DXd (n = 818)	T-DM1 (n = 817)
Median age, yr (range)	50.3 (24-78)	50.6 (21-83)
• <65	735 (89.9)	736 (90.1)
• ≥65	83 (10.1)	81 (9.9)
Female sex, n (%)	814 (99.5)	814 (99.6)
Race, n (%)		
• White	301 (36.8)	333 (40.8)
• Black or African American	22 (2.7)	13 (1.6)
• Asian	399 (48.8)	386 (47.2)
• Other	96 (11.7)	85 (10.4)
Region, n (%)		
• Asia	392 (47.9)	380 (46.5)
• Europe	222 (27.1)	223 (27.3)
• North America + Australia	57 (7.0)	72 (8.8)
• Rest of world	147 (18.0)	142 (17.4)
HER2 status, n (%)		
• IHC 3+	676 (82.6)	670 (82.0)
• IHC 2+ and ISH+	129 (15.8)	133 (16.3)
• IHC 2+ and ISH-	2 (0.2)	0
• IHC 1+ and ISH+	11 (1.3)	14 (1.7)

Characteristic, n (%)	T-DXd (n = 818)	T-DM1 (n = 817)
Hormone receptor status		
• Positive	581 (71.0)	583 (71.4)
• Negative	237 (29.0)	234 (28.6)
Operative status at disease presentation		
• Operable (cT1-3, N0-1, M0)	387 (47.3)	393 (48.1)
• Inoperable (cT4, N0-3, M0 or cT1-3, N2-3, M0)	431 (52.7)	424 (51.9)
Post-NAT pathological nodal status		
• Positive	660 (80.7)	658 (80.5)
• Negative	158 (19.3)	159 (19.5)
Neoadjuvant HER2-targeted therapy		
• Trastuzumab alone	176 (21.5)	171 (20.9)
• Trastuzumab + pertuzumab	637 (77.9)	641 (78.5)
• Trastuzumab + other HER2-targeted tx	3 (0.4)	3 (0.4)
• Trastuzumab + pertuzumab + other HER2-targeted tx	2 (0.2)	2 (0.2)
Neoadjuvant chemotherapy		
• Taxanes	818 (100)	817 (100)
• Platinum compounds	386 (47.2)	392 (48.0)
• Anthracycline	423 (51.7)	399 (48.8)
RT treatment		
• Adjuvant RT	764 (93.4)	759 (92.9)
– Concurrent	438 (53.5)	480 (58.8)
– Sequential	326 (39.9)	279 (34.1)
• No RT	54 (6.6)	58 (7.1)

KEY DATA

DESTINY-Breast05, post-neoadjuvant T-DXd vs T-DM1

Primary Endpoint: Invasive disease–free survival (IDFS)



	T-DXd (n = 818)	T-DM1 (n = 817)
3-yr IDFS	**92.4%** (89.7-94.4)	**83.7%** (80.2-86.7)
HR (95% CI)	**0.47** (0.34-0.66)	
P Value	**<0.0001**	

>72% of patients in each arm completed the planned 14 cycles of therapy

IDFS: time from randomization until the date of first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause

KEY DATA

DESTINY-Breast05, post-neoadjuvant T-DXd vs T-DM1

Secondary Endpoints: Disease-free survival, Distant-recurrence free interval, Brain metastasis–free interval, Overall Survival

	T-DXd (n = 818)	T-DM1 (n = 817)	HR (95% CI)	P Value
3-yr Disease-free survival (DFS)	**92.3%**	83.5%	**0.47** (0.34-0.66)	**<0.0001**
3-yr Distant recurrence free interval (DRFI)	**93.9%**	86.1%	**0.49** (0.34-0.71)	--
3-yr Brain metastasis–free interval (BMFI)	**97.6%**	95.8%	**0.64** (0.35-1.17)	--
3-yr Overall survival (OS)	**97.4%**	95.7%	**0.61** (0.34-1.10)	--

DESTINY-Breast05, post-neoadjuvant T-DXd vs T-DM1

Secondary Endpoints: Safety

TEAEs, n (%)	T-DXd (n = 806)	T-DM1 (n = 801)
Any grade	802 (99.5)	788 (98.4)
• Grade ≥3	408 (50.6)	416 (51.9)
Serious	140 (17.4)	109 (13.6)
Associated with drug discontinuation	144 (17.9)	103 (12.9)
• Drug-related ILD/pneumonitis	87 (10.8)	20 (2.5)
Associated with drug interruption	400 (49.6)	329 (41.1)
Associated with dose reduction	213 (26.4)	213 (26.6)
Associated with death*	3 (0.4)	5 (0.6)

AE, n (%)	T-DXd (n = 806)						T-DM1 (n = 801)					
	Grade						Grade					
	Any	1	2	3	4	5	Any	1	2	3	4	5
Adjudicated drug-related ILD	77 (9.6%)	16 (2.0%)	52 (6.5%)	7 (0.9%)	0	2 (0.2%)	13 (1.6%)	8 (1.0%)	5 (0.6%)	0	0	0
LV dysfunction	23 (2.9%)	1 (0.1%)	20 (2.5%)	2 (0.2%)	0	0	14 (1.7%)	0	11 (1.4%)	3 (0.4%)	0	0

*Causes of death:

- T-DXd (n = 3): ILD/pneumonitis (n = 2), and respiratory tract infection (n = 1)
- T-DM1 (n = 5): leiomyosarcoma of the uterus, aneurysm, nonneutropenic sepsis, ovarian cancer, and traumatic pneumothorax (n = 1 each).

SUMMARY

DESTINY-Breast05

- Post-neoadjuvant T-DXd was associated with significant and clinically meaningful improvements in IDFS and DFS compared to the previous standard T-DM1
  - 3-yr Invasive disease–free survival
    - 92.4% vs 83.7% (HR: 0.47; *P* <.0001)
  - T-DXd was associated with a trend toward improved distant recurrence–free interval and a reduction in CNS metastases and deaths vs T-DM1

- Grade ≥3 and dose reductions similar between the 2 arms
- ILD higher in T-DXd, mainly low grade

IMPACT

Trastuzumab deruxtecan is a novel effective treatment option for patients with high risk HER2+ early breast cancer with residual disease after neoadjuvant Rx

Data support T-DXd becoming a potential new standard of care- - - not yet FDA approved

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Polling question: neoadjuvant

*Based on the presented **DB-11 trial** data, and if approved by the FDA*: *would you change your recommendation for <u>neoadjuvant</u> HER2+ disease to T-DXd-THP in the majority of cases (instead of AC-THP or TCHP)?*

1. Yes
2. No
3. Unsure, need more data

Polling question: post-neoadjuvant

*Based on the presented **DB-05 trial** data, and if approved by the FDA: would you change your recommendation for post-neoadjuvant HER2+ disease to T-DXd (instead of T-DM1) in the majority of cases?*

1. Yes
2. No
3. Unsure, need more data

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*ESMO Presidential Session

CLINICAL QUESTION

DESTINY-Breast09

HER2+ 1st-line metastatic

Is the benefit of trastuzumab deruxtecan + pertuzumab (T-DXd + P) vs THP seen in DB-09 impacted by hormone receptor status and PI3K biomarker data?

KEY DATA

DESTINY-Breast09: 1st-line T-DXd + Pertuzumab vs Pertuzumab + Trastuzumab + Taxane in HER2+ mBC

Study Design: Open label, phase 3 study

- HER2+* (IHC3+ or ISH+) advanced or mBC
- No previous chemo or HER2-targeted therapy for advanced or metastatic disease
- Previous chemo/HER2-targeted therapy allowed in neoadjuvant setting if >6 mo from metastatic disease diagnosis
- One prior line of ET for mBC permitted
- Asymptomatic/inactive brain mets allowed
- ECOG PS 0/1

(N = 1157)

Stratified by de novo vs recurrent mBC
HR+ or HR-; PIK3CAm detected vs non-detected

T-DXd 5.4 mg/kg q3w
(Blinded until final PFS analysis)
(n=387)

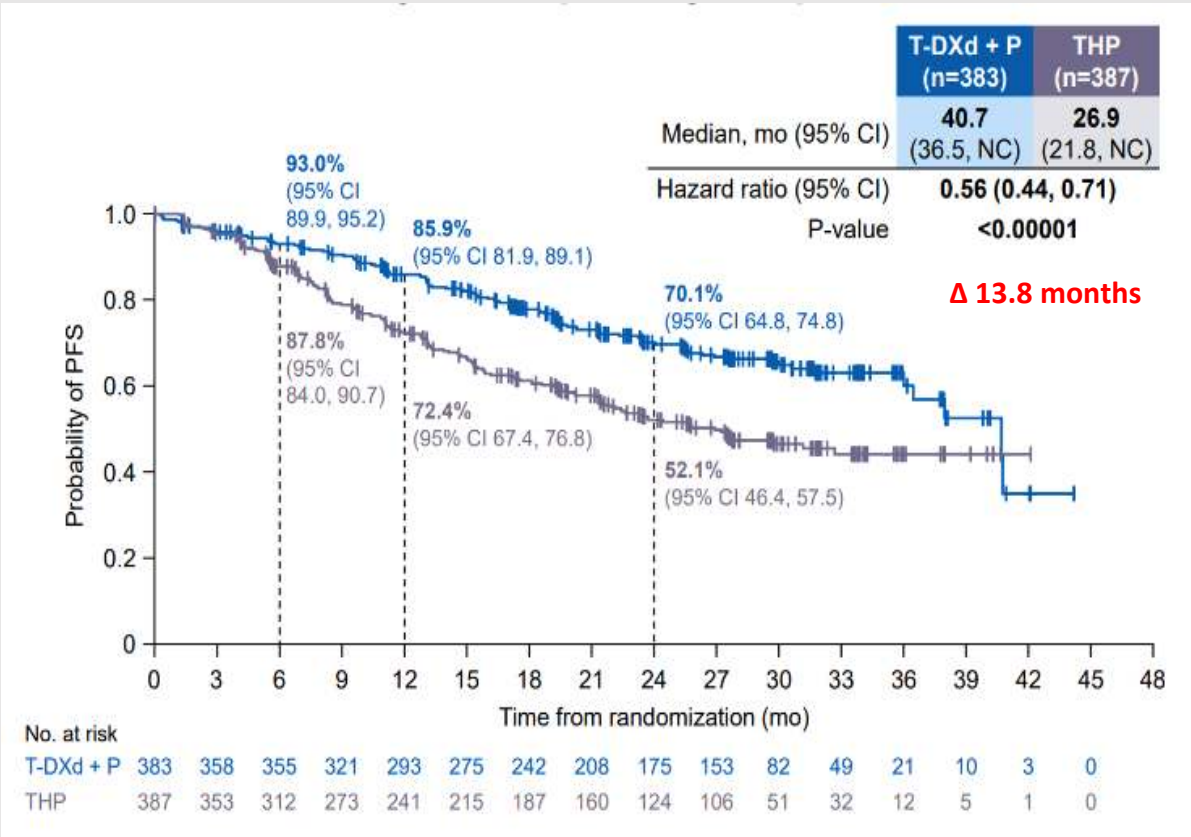
T-DXd 5.4 mg/kg q3w **+ Pertuzumab (n=383)**

Taxane + Pertuzumab + Trastuzumab (THP)†ǂ (n=387)

*Locally assessed and prospectively centrally confirmed.
†Investigator's choice: docetaxel or paclitaxel IV.
Concurrent use of ET (AI or tamoxifen) was allowed for those with HR+ disease after six cycles of T-DXd or discontinuation of taxane in the THP arm

Primary endpoint: PFS by BICR (per RECIST 1.1) up to 5 yr
Secondary endpoints: PFS by investigator, OS, ORR (BICR and investigator), DoR (BICR and investigator), PFS2, safety

Primary Endpoint: PFS by BICR
Interim analysis presented at ASCO 2025



ASCO 2025 Abstr. 1008

DESTINY-Breast09: 1st-line T-DXd + Pertuzumab vs Pertuzumab + Trastuzumab + Taxane in HER2+ mBC, subgroup analysis at ESMO 2025

Subgroup analysis: PFS by treatment status, HR status and *PIK3CA*m status

Subgroup	T-DXd + Pertuzumab (median PFS)	THP (median PFS)	Hazard Ratio (HR)
Treatment Status			
De novo disease	**Not calculable** (95% CI 36.5–NC)	31.2 mo (95% CI 23.5–NC)	**0.49** (95% CI 0.35–0.70)
Recurrent disease	**38.0 mo** (95% CI 26.9–NC)	22.5 mo (95% CI 18.1–NC)	**0.63** (95% CI 0.46–0.87)
Hormone Receptor (HR) Status			
HR-positive	**38.0 mo** (95% CI 36.0–NC)	27.7 mo (95% CI 22.4–NC)	**0.61** (95% CI 0.44–0.84)
HR-negative	**40.7 mo** (95% CI 40.7–NC)	22.6 mo (95% CI 17.3–32.7)	0.**52** (95% CI 0.37–0.73)
PIK3CA Mutation Status			
Mutation detected	**36.0 mo** (95% CI 29.7–NC)	18.1 mo (95% CI 15.1–25.6)	**0.52** (95% CI 0.35–0.77)
Mutation not detected	**40.7 mo** (95% CI 38.0–NC)	32.7 mo (95% CI 24.4–NC)	**0.57** (95% CI 0.43–0.77)

PFS by blinded independent central review

SUMMARY

DESTINY-Breast09

IMPACT

Subgroup analysis of DESTINY-Breast09:

- 1L treatment with T-DXd + P demonstrated a clinically meaningful PFS benefit vs THP regardless of prior treatment, HR, or PIK3CAm status, reflecting results in the overall population

Trastuzumab deruxtecan is an effective treatment option for patients with HER2+ metastatic breast cancer in the 1L setting

Potential new treatment optio not yet FDA approved

(PDUFA date Jan 23, 2026)

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1st-line HER2+ MBC trials

CLEOPATRA THP		PATINA TH±P → Palbo + anti-HER2 + ET		DESTINY-Breast09 T-DXd + Pertuzumab	
Current approved 1st-line SoC		***Not yet FDA approved***			
• **No prior chemotherapy or biological treatment for metastatic disease** • **HR pos or neg**		• **Completion of induction chemotherapy and no evidence of disease progression (CR, PR, or SD)** • **HR pos**		• **No previous chemo or HER2-targeted therapy for metastatic disease** • **HR pos or neg**	
Pertuzumab + trastuzumab + docetaxel (n=402)	Placebo + trastuzumab + docetaxel (n=406)	**Palbociclib** + trastuzumab ± pertuzumab + endocrine therapy (n=261)	Placebo + trastuzumab ± pertuzumab + endocrine therapy (n=261)	**T-DXd** + pertuzumab (n=383)	Taxane + pertuzumab + trastuzumab (TCP)† (n=387)
Medium follow-up: **99.9 months**	Medium follow-up: 98.7 mo	Medium follow-up: **52 mo**		Medium follow-up: **29.2 mo**	
mPFS: **18.7**	12.4 months	**mPFS: 44.3**	29.1 months	**mPFS: 40.7**	26.9 months
8-year landmark PFS rates: **16%** vs 10%		**HR: 0.74** (0.58 – 0.94); P = 0.0074		**HR: 0.56** (0.44 – 0.71); P = 0.00001	
mOS: **57.1**	40.8 months	*Not evaluable* (*OS immature*)	77 months	*Not calculable*	*Not calculable*
8-year landmark OS rate: **37%** vs 23%		**3-year OS rate: 87.0%** vs 84.7 %		HR 0.84 (*OS immature*)	
N Engl J Med. 2012;366(2):109-19.		SABCS 2024 Abstract GS2-12		ASCO 2025 Abstr. 1008; ESMO 2025 LBA18	

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Cleopatra and DB-09 start randomization on D1; PATINA starts after 4-6 months of initial Rx

2025 ESMO Key Studies

Breast Cancer

- *DESTINY-Breast11
- *DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*

- evERA BC
- VIKTORIA-1
  - *Polling Question*

GU GI

- *KEYNOTE-905/EV-303
- *IMvigor-011
  - *Polling Question*
- *PSMAddition
  - *Rapid Review*: CAPItello-281
- *Polling Question*
- *FORTITUDE-101
- *AGITG-DYNAMIC-III
  - *Polling Question*
- *RC48-C016
  - *Rapid Review*: POTOMAC

Lung Cancer and Other Notable Studies

- *HARMONI-6
- FLAURA2
  - *Polling Question*
- *OptiTROP-Lung04
  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

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*ESMO Presidential Session

CLINICAL QUESTION

ASCENT-03

TNBC 1st-line MBC; PD-L1 negative or treated in PD-1 agent in early setting

Does sacituzumab govitecan (SG) benefit patients with untreated mTNBC unable to receive PD-L1 inhibitors when compared to single agent or combination chemotherapy?

(Sacituzumab govitecan vs chemo)

KEY DATA

ASCENT-03: 1st-line Sacituzumab govitecan (SG) vs chemo in untreated mTNBC with tumors lacking PD-L1 expression *or* previously treated with anti-PD-L1 in early-stage setting

Study Design: Open-label, phase III

- Previously untreated locally advanced, unresectable, or metastatic TNBC
- **Not candidates for PD-L1 inhibitors**
  - PD-L1-ve CPS <10
  - PD-L1+ve CPS ≥10 and previously treated with a PD-L1 agent in the curative setting
  - Ineligible due to comorbidities
- **≥6 months since treatment in the curative setting**
- Previously treated, stable CNS mets allowed
- ECOG PS 0 or 1

N=558

Stratified by curative treatment-free interval (de novo vs recurrence within 6-12 mo vs recurrence after >12 mo), geographic region (US/Canada/W Europe vs RoW)

Sacituzumab govitecan 10 mg/kg IV
Day 1 and 8 of a 21-day cycle (n=279)

→ *Standard of care*

Gemcitabine 1000 mg/m² + Carboplatin AUC 2
IV Day 1 and day 8 of 21-day cycle
OR
Paclitaxel 90 mg/m² IV or nab-Paclitaxel 100 mg/m² IV Day 1, 8, and 15 of 28-day cycle
(n=279)

→ *Crossover to 2L SG permitted from chemotherapy arm upon progression*

Primary Endpoint: PFS by BICR

Secondary Endpoints: OS, ORR, DOR, TTR (time to response) by BICR, Safety, PROs

ESMO 2025. Abstr LBA20. NEJM. 2025 [Epub].

KEY DATA

ASCENT-03: 1st-line Sacituzumab govitecan (SG) vs chemo in untreated mTNBC with tumors lacking PD-L1 expression *or* previously treated with anti-PD-L1 in early-stage setting

Baseline Characteristics

Characteristic	SG (n = 279)	CT (n = 279)
Female sex, n (%)	278 (>99)	277 (99)
Median age, yr (range)	56 (28-84)	54 (23-86)
• ≥65	65 (23)	78 (28)
Race/ethnicity, n (%)		
• White	178 (64)	178 (64)
• Asian	66 (24)	65 (23)
• Black	10 (4)	7 (3)
• Other/not specified	25 (9)	29 (10)
Geographic region, n (%)		
• US/Canada/W Europe	89 (32)	89 (32)
• Rest of the World	190 (68)	190 (68)
Curative treatment-free interval, n (%)		
• De novo	87 (31)	88 (32)
• Recurrent within 6-12 mo	58 (21)	57 (20)
• Recurrent >12 mo	134 (48)	134 (48)

Characteristic, n (%)	SG (n = 279)	CT (n = 279)
PD-L1 status		
• Negative	277 (99)	278 (>99)
• Positive	1 (<1)	1 (<1)
Metastatic sites		
• Lung	166 (59)	170 (61)
• Liver	81 (29)	72 (26)
• Brain	15 (5)	14 (5)
CT selected prior to randomization		
• Taxane	154 (55)	155 (56)
• Gem/carbo	125 (45)	124 (44)
Prior (neo)adjuvant therapy	185 (66)	191 (68)
• Taxanes	162 (58)	162 (58)
• Capecitabine	50 (18)	57 (20)
• Platinum agents	51 (18)	49 (18)
• PD-1/PD-L1 inhibitors	13 (5)	11 (4)

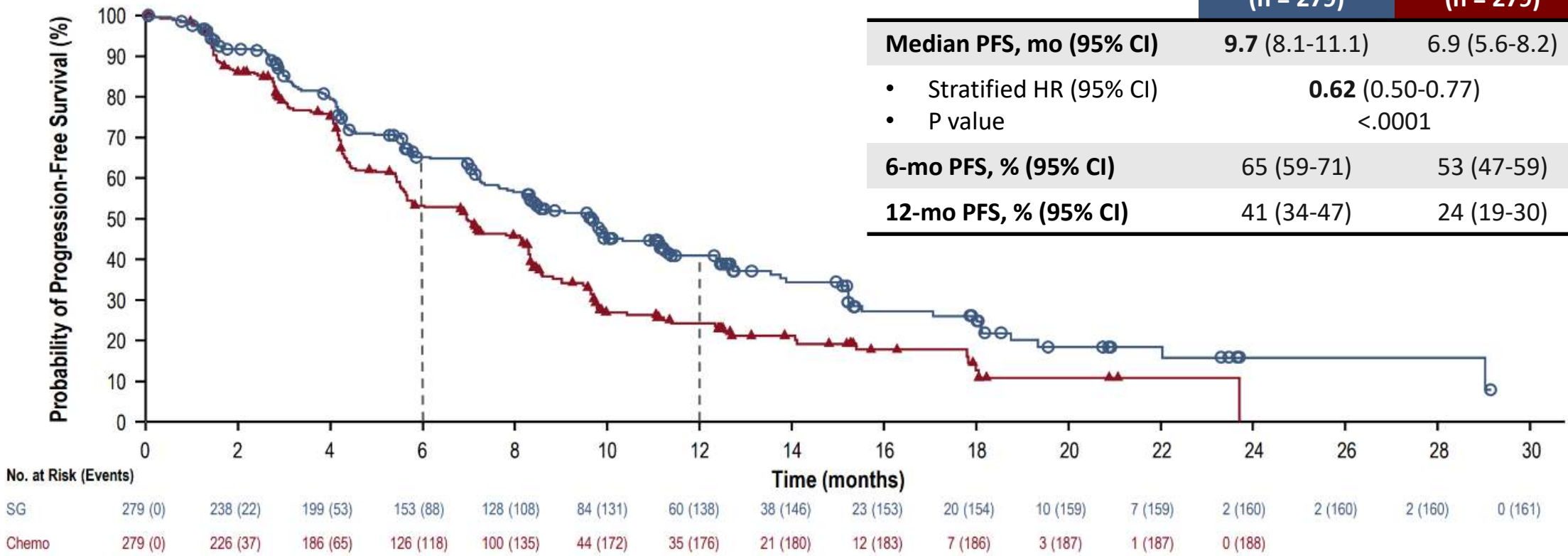
Data cutoff date: April 2, 2025

KEY DATA

ASCENT-03: 1st-line Sacituzumab govitecan (SG) vs chemo in untreated mTNBC with tumors lacking PD-L1 expression *or* previously treated with anti-PD-L1 in early-stage setting

Essentially all TNBC, PD-L1 negative

Primary Endpoint: PFS by BICR



Outcome	SG (n = 279)	CT (n = 279)
Median PFS, mo (95% CI)	**9.7** (8.1-11.1)	6.9 (5.6-8.2)
• Stratified HR (95% CI)	**0.62** (0.50-0.77)	
• P value	<.0001	
6-mo PFS, % (95% CI)	65 (59-71)	53 (47-59)
12-mo PFS, % (95% CI)	41 (34-47)	24 (19-30)

Data cutoff date: April 2, 2025

ESMO 2025. Abstr LBA20. Cortes. NEJM. 2025 [Epub].

KEY DATA

ASCENT-03: 1st-line Sacituzumab govitecan (SG) vs chemo in untreated mTNBC with tumors lacking PD-L1 expression *or* previously treated with anti-PD-L1 in early-stage setting

Essentially all TNBC, PD-L1 negative

Subgroup analysis of PFS by BICR

	SG		Chemo		Unstratified HR (95% CI)	Unstratified HR (95% CI)
	n	Median PFS, mo (95% CI)	n	Median PFS, mo (95% CI)		
ITT population	279	9.7 (8.1-11.1)	279	6.9 (5.6-8.2)		0.66 (0.53-0.82)
Age group						
< 65 years	214	9.6 (7.6-10.3)	201	5.7 (4.4-7.0)		0.58 (0.45-0.74)
≥ 65 years	65	11.1 (7.3-13.9)	78	9.0 (8.3-10.0)		0.91 (0.58-1.44)
ECOG PS						
0	183	11.2 (9.7-13.5)	187	7.3 (6.0-8.3)		0.61 (0.47-0.80)
1	96	7.1 (5.4-8.5)	92	5.5 (4.2-7.2)		0.74 (0.52-1.05)
Geographic region						
United States/Canada/Western Europe	89	9.9 (7.8-13.9)	89	7.1 (5.4-8.3)		0.54 (0.36-0.79)
Rest of the world	190	9.6 (7.2-11.1)	190	6.9 (5.5-8.3)		0.72 (0.55-0.92)
Disease Status						
De novo	87	8.3 (5.6-12.4)	88	5.5 (4.2-7.3)		0.65 (0.45-0.94)
Recurrent 6-12 mo	58	8.3 (5.6-9.9)	57	5.6 (4.2-6.7)		0.46 (0.29-0.72)
Recurrent > 12 mo	134	11.1 (8.4-13.5)	134	8.4 (7.2-9.8)		0.72 (0.52-1.00)
PD-L1 status						
CPS < 1	102	8.5 (7.2-12.5)	98	8.3 (5.4-9.6)		0.74 (0.51-1.06)
1 ≤ CPS < 10	175	9.8 (7.6-11.3)	180	6.9 (5.5-8.1)		0.64 (0.49-0.83)
Chemo selected prior to randomization						
Taxane	154	11.1 (8.1-12.7)	155	5.7 (4.3-8.1)		0.51 (0.38-0.68)
Gemcitabine/carboplatin	125	8.5 (6.9-9.9)	124	8.1 (5.7-8.3)		0.89 (0.64-1.22)

Data cutoff date: April 2, 2025

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KEY DATA

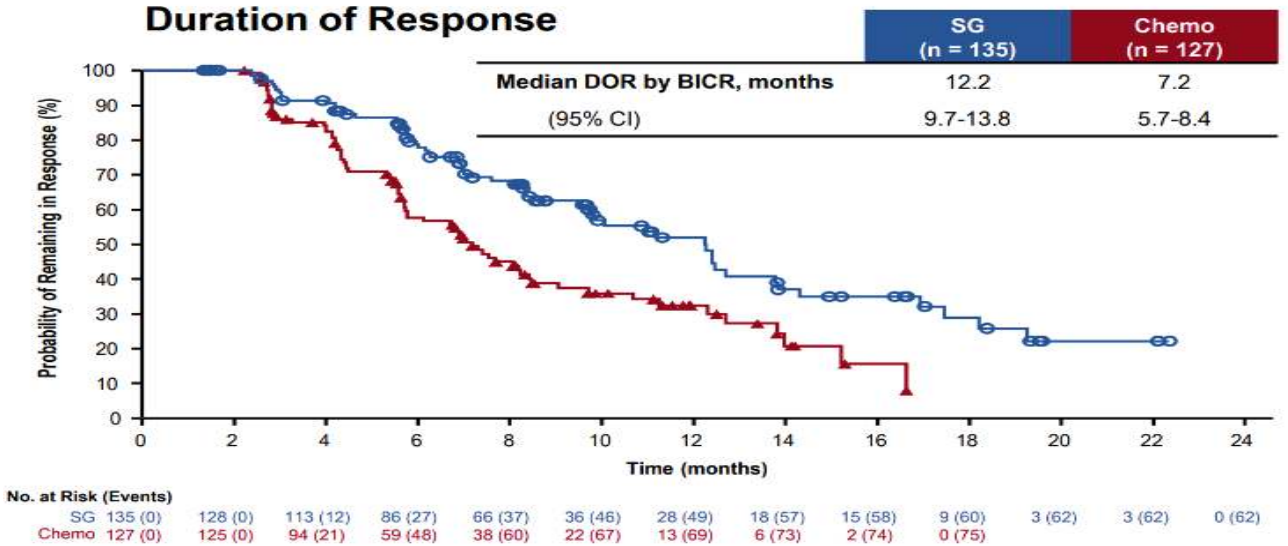
ASCENT-03: 1st-line Sacituzumab govitecan (SG) vs chemo in untreated mTNBC with tumors lacking PD-L1 expression *or* previously treated with anti-PD-L1 in early-stage setting

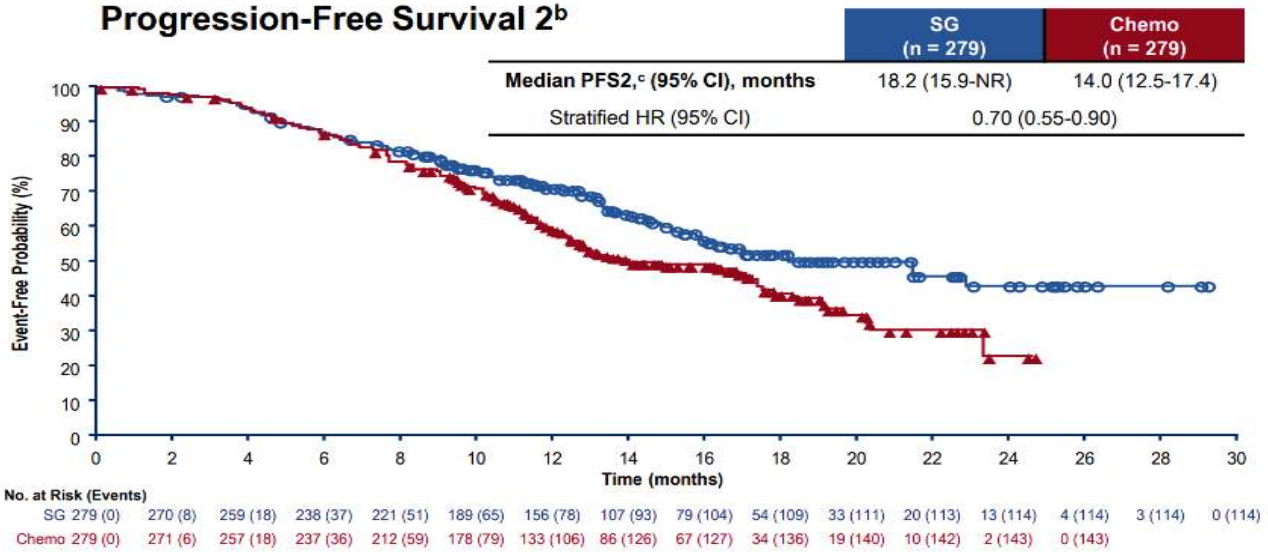
Essentially all TNBC, PD-L1 negative

Secondary Endpoints

Outcome	SG (n = 279)	CT (n = 279)
ORR by BICR, % (95% CI)	48 (42-54)	46 (40-52)
• Stratified OR (95% CI)	1.1 (0.8-1.6)	
BOR by BICR, n (%)		
• CR	20 (7)	15 (5)
• PR	115 (41)	112 (40)
• SD	113 (41)	101 (36)
– SD ≥6 mo	37 (13)	32 (11)
• PD	14 (5)	36 (13)
• NE	17 (6)	15 (5)
Median Time To Response by BICR, mo (range)	1.6 (0.7-16.7)	1.6 (0.9-6.8)

Overall survival not yet mature





ESMO 2025. Abstr LBA20. Cortes. NEJM. 2025 [Epub].

SUMMARY

ASCENT-03

- SG demonstrated significantly improved PFS vs chemo in patients with previously untreated advanced TNBC ineligible for PD-1/PD-L1 inhibitors
  - Median PFS: 9.7 vs 6.9 mo (HR: 0.62; 95% CI: 0.50-0.77; P <.0001)
    - Benefit observed across all subgroups
  - Similar ORR but more durable responses with SG vs chemo (12.2 vs 7.2 mo)
  - PFS2 was improved (median PFS2 4.2 mo longer with SG vs chemo)
  - OS data immature at analysis
- Study design factors: essentially all PD-L1 neg; few had received neoadjuvant CPI; pts ≥6 months since treatment in the curative setting; crossover agent SG provided if pt developed tumor prog after chemo

IMPACT

Sacituzumab govitecan is an effective 1st-line treatment option for patients with PD-L1 negative TNBC

Data support SG becoming a potential new SOC option to replace chemo; not yet FDA approved

2025 ESMO Key Studies

Breast Cancer

- *DESTINY-Breast11
- *DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09

- ASCENT-03
- TROPION-Breast02
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  - *Polling Question*
- *OptiTROP-Lung04
  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

*ESMO Presidential Session

CLINICAL QUESTION

TROPION-Breast02

TNBC 1st-line MBC; PD-L1 negative or treated in PD-1 agent in early setting

Does datopotamab deruxtecan (Dato-DXd) benefit patients with untreated mTNBC unable to receive PD-L1 inhibitors vs single agent chemotherapy?

Dato-DXd vs chemo

KEY DATA

TROPION-Breast02: 1st-line Dato-DXd vs chemo in untreated mTNBC and unsuitable for anti-PD-L1

Study Design: Open-label, randomized phase III study

Stratified by Geographic region (US/Canada/Europe vs other geographic regions); PD-L1 status (high [CPS ≥10] vs low [CPS <10]); DFI history (de novo vs prior DFI 0–12 months vs prior DFI >12 months)

- Recurrent inoperable or metastatic TNBC*
- No prior chemotherapy or targeted therapy in locally recurrent inoperable or metastatic setting
- Unsuitable for immunotherapy†
- ECOG PS ≤1
- **No minimum DFI‡**

N=558

Dato-DXd
6 mg/kg IV Day 1 q3w
(n=323)

Investigator's choice of chemotherapy (ICC)
Paclitaxel, nab-paclitaxel, capecitabine, eribulin mesylate/eribulin, carboplatin
(n=321)

- *Following progression or discontinuation of study treatment, patients could receive subsequent therapies, including approved ADCs or chemotherapy, at the investigator's discretion*

*According to ASCO/CAP criteria.
†Including patients with PD-L1-low tumors, or patients with PD-L1-high tumors with (a) disease relapse after prior PD-(L)1 inhibitor therapy for early-stage breast cancer (b) comorbidities precluding PD-(L)1 inhibitor therapy, or (c) no regulatory access to PD-(L)1 inhibitor therapy
‡**DFI defined as time between date of completion of treatment with curative intent and date of first documented local or distant disease recurrence.**

Primary Endpoint: Dual primary: OS and PFS by BICR per RECIST v1.1
Secondary Endpoints: PFS (investigator-assessed), ORR, DoR, Safety

ICC: If no prior taxane, or prior taxane in the (neo)adjuvant setting and DFI >12 months: paclitaxel 80 mg/m^2 IV, D1, 8, 15, Q3W, or nab-paclitaxel 100mg/m^2 IV, D1, 8, 15, Q4W; if prior taxane and DFI 0–12 months: capecitabine 1000 or 1250 mg/m^2 po bid, D1–14, q3w (dose determined by standard institutional practice), or eribulin mesylate 1.4 mg/m^2/ eribulin 1.23 mg/m^2 IV, Day 1, 8, q3w, or carboplatin AUC6 IV, D1, q3w.

In the Dato-DXd vs ICC arm, 65% vs 72% of patients received any subsequent therapy in any treatment line; 14% vs 30% received a subsequent ADC (sacituzumab govitecan, sacituzumab tirumotecan, trastuzumab deruxtecan).

ESMO 2025. Abstr LBA21.

KEY DATA

TROPION-Breast02: 1st-line Dato-DXd vs chemo in untreated mTNBC and unsuitable for anti-PD-L1

90% TNBC, PD-L1 negative

Baseline Characteristics

Characteristic		Dato-DXd (n = 323)	Investigator's Choice of CT (n = 321)
Median age, yr (range)		56 (27 - 85)	57 (23 - 83)
Female, n (%)		323 (100)	319 (99)
Race, n (%)			
• Black		13 (4)	14 (4)
• Asian		151 (47)	131 (41)
• White		131 (41)	153 (48)
• Other		28 (9)	23 (7)
Geographic region, n (%)			
• US/Canada/W Europe		120 (37)	120 (37)
• Other regions		203 (63)	201 (63)
Disease Free Interval, n (%)	• De novo	109 (34)	110 (34)
	• Prior: 0-6 mo	47 (15)	51 (16)
	• Prior: 0-12 mo	67 (21)	66 (21)
	• Prior: >12 mo	147 (46)	145 (45)

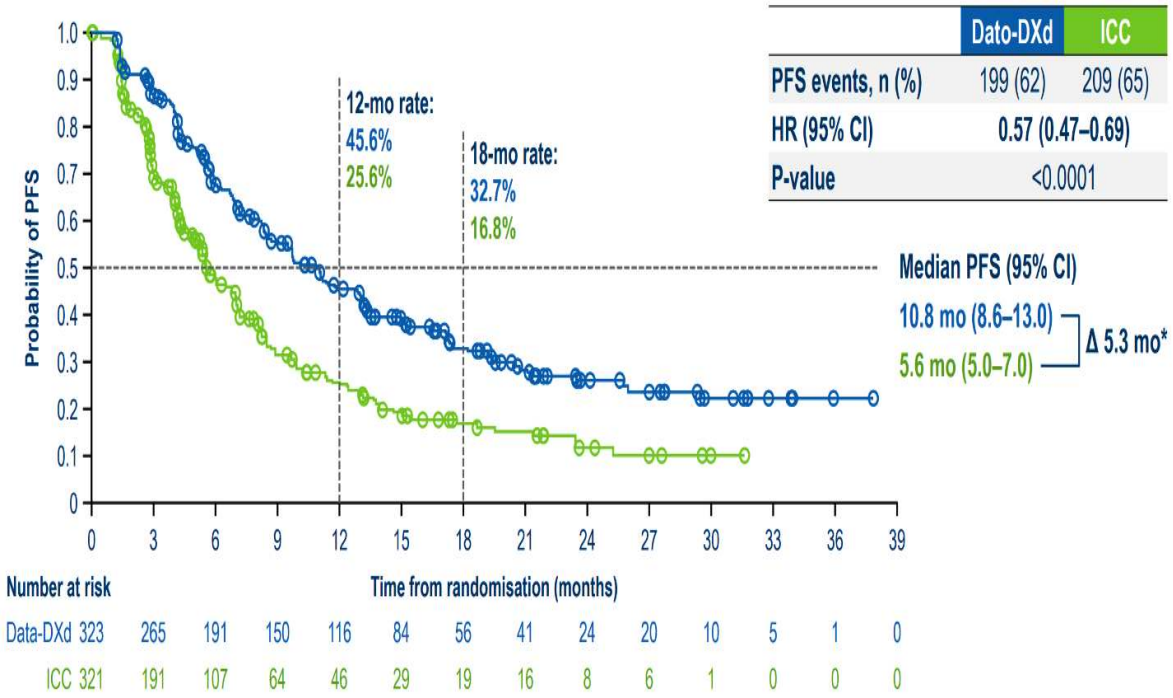
Characteristic, n (%)	Dato-DXd (n = 323)	Investigator's Choice of CT (n = 321)
PD-L1 status		
• Low (CPS <10)	287 (89)	291 (91)
• High (CPS ≥10)	34 (11)	29 (9)
Metastatic sites		
• Visceral	253 (78)	233 (73)
• Liver	93 (29)	98 (31)
• Brain	36 (11)	28 (9)
No of metastatic sites		
• <3	207 (64)	215 (67)
• ≥3	116 (36)	106 (33)
Preselected CT		
• Nab-paclitaxel	180 (56)	172 (54)
• Paclitaxel	82 (25)	92 (29)
• Eribulin	43 (13)	35 (11)
• Carboplatin	11 (3)	14 (4)
• Capecitabine	7 (2)	8 (2)

KEY DATA

TROPION-Breast02: 1st-line Dato-DXd vs chemo in untreated mTNBC and unsuitable for anti-PD-L1

90% TNBC, PD-L1 negative

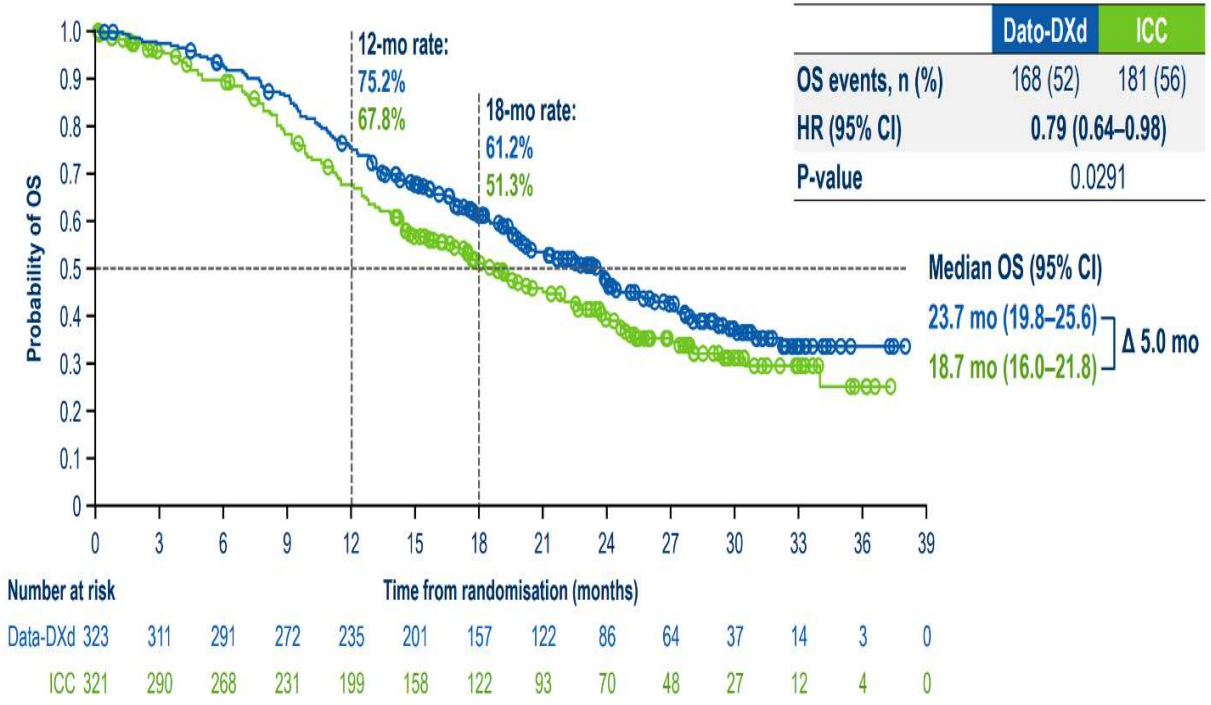
Dual Primary Endpoint: PFS by BICR



	Dato-DXd	ICC
PFS events, n (%)	199 (62)	209 (65)
HR (95% CI)	0.57 (0.47–0.69)	
P-value	<0.0001	

PFS benefit with Dato-DXd observed across all subgroups

Dual Primary Endpoint: OS by BICR



	Dato-DXd	ICC
OS events, n (%)	168 (52)	181 (56)
HR (95% CI)	0.79 (0.64–0.98)	
P-value	0.0291	

OS benefit with Dato-DXd observed across most subgroups; exception geographical region cohort US, Canada, Europe
Ad hoc analysis of the US Cohort showed comparable OS HR to the ITT population

KEY DATA

TROPION-Breast02: 1st-line Dato-DXd vs chemo in untreated mTNBC and unsuitable for anti-PD-L1

90% TNBC, PD-L1 negative

Secondary Endpoint: ORR

Outcome	Dato-DXd (n = 323)	Investigator's Choice of CT (n = 321)
Confirmed objective response, n (%)	**202 (62.5)**	94 (29.3)
• Odds ratio (95% CI)	4.24 (3.03-5.95)	
Best confirmed objective response, n (%)		
• CR	**29 (9.0)**	8 (2.5)
• PR	173 (53.6)	86 (26.8)
• SD	87 (26.9)	151 (47.0)
• PD	27 (8.4)	52 (16.2)
• Not evaluable	7 (2.2)	24 (7.5)
Median DoR, mo (95% CI)	**12.3** (9.1-15.9)	7.1 (5.6-8.9)
• Number of responders, n	202	94
• Progression events, n (%)	112 (55)	59 (63)

ORR benefit with Dato-DXd observed across all subgroups

ESMO 2025. Abstr LBA21.

KEY DATA

TROPION-Breast02: 1st-line Dato-DXd vs chemo in untreated mTNBC and unsuitable for anti-PD-L1

90% TNBC, PD-L1 negative

Safety

TRAE, n (%)	Dato-DXd (n = 319)	Investigator's Choice of CT (n = 309)
All grades • Grade ≥3	296 (93) **105 (33)**	257 (83) **89 (29)**
Serious TRAEs	29 (9)	26 (8)
Associated with dose interruption	76 (24)	60 (19)
Associated with dose reduction	85 (27)	56 (18)
Associated with discontinuation	14 (4)	23 (7)
Associated with death	0	0
Total treatment duration, mo (range)	8.5 (0.7 - 38.0)	4.1 (0.1-32.0)
Total exposure >12 mo, %	35.1	9.4

AE of special interest, n (%)	Dato-DXd (n = 319)			Investigator's Choice of CT (n = 309)		
	Grade 1	Grade 2	Grade ≥3	Grade 1	Grade 2	Grade ≥ 3
Oral mucositis/ stomatitis • Stomatitis	78 (24) 72 (23)	87 (27) 83 (26)	27 (8) 27 (8)	22 (7) 19 (6)	8 (3) 8 (3)	0 0
Ocular surface events • Dry eye • Keratitis • Conjunctivitis	76 (24) 51 (16) 21 (7) 7 (2)	50 (16) 21 (7) 14 (4) 13 (4)	23 (7) 4 (1) 7 (2) 1 (<1)	9 (3) 6 (2) 1 (<1) 0	5 (2) 3 (1) 0 0	1 (<1) 0 0 0
Adjudicated drug-related ILD/pneumonitis	1 (<1)	7 (2)	1 (<1)	1 (<1)	1 (<1)	0

Treatment-related oral mucositis/stomatitis:

- In the Dato-DXd arm, events led to dose interruption, reduction, and discontinuation in 11 (3%), 36 (11%), and 0 patients, respectively
- Grade ≥2 events resolved to grade ≤1 in 103/114 patients (90%) at data cutoff

Treatment-related ocular surface events:

- In the Dato-DXd arm, events led to dose interruption, reduction, and discontinuation in 18 (6%), 14 (4%), and 3 (<1%) patients, respectively
- Grade ≥2 events resolved to grade ≤1 in 49/73 patients (67%) at data cutoff

ESMO 2025. Abstr LBA21.

SUMMARY

TROPION-Breast02

- Dato-DXd vs investigator's choice of chemotherapy in the IL setting for mTNBC demonstrated improvement for coprimary endpoints of OS and PFS (by BICR per RECIST v1.1)
  - Dato-DXd vs investigator's choice of chemotherapy yielded ~5 mo gains for median OS and PFS
    - OS 23.7 vs 18.7 mo, HR: **0.79** (95% CI: 0.64-0.98; P = 0.0291)
    - PFS 10.8 vs 5.6 mo, HR: **0.57** (95% CI: 0.47-0.69; P <.0001)
- Study design factors: recurrence at any time; few pts had received neoadjuvant checkpoint inhibitor, no crossover to experimental agent Dato-DXd

IMPACT

Datopotomab deruxtecan is a potential new 1st-line treatment option for patients with PD-L1 negative metastatic TNBC

Data support Dato-DXd becoming a SOC option to replace chemo; not yet FDA approved

cornerstone specialty network™

Cross-study comparison of 1st-line single agent Trop-2 targeted ADCs for TNBC: PD-L1 negative

Not yet FDA approved	TROPION-Breast02 (N=644)	ASCENT-03 (N=558)
Study Design	**No crossover to Dato-DXd** **Comparator: single agent chemo**	**Crossover to SG** **Comparator: single or combination chemo**
Efficacy	**Dato-DXd** (n=323) vs *ICC (n=321)	**SG** (n=279) vs ‡Chemotherapy (n=279)
• **mPFS (mo)**	10.8 vs 5.6 (**HR=0.57**)	9.7 vs 6.9 **(HR=0.62)**
• **mOS (mo)**	23.7 vs 18.7 (HR=0.79)	21.5 vs 20.2 (data not mature)
• **ORR**	62.5% vs 29.3%	48% vs 46%
• **mDOR (mo)**	12.3 vs 7.1	12.2 vs 7.2
Safety	**Dato-DXd** (n=319)	**SG** (n=275)
• **Grade ≥3 TRAEs**	33% vs 29%	61% vs 53%
	European Society for Medical Oncology (ESMO) Congress; 2025; LBA21.	European Society for Medical Oncology (ESMO) Congress; 2025; LBA20

*Investigators choice chemotherapy: Paclitaxel, nab-paclitaxel, capecitabine, carboplatin, eribulin mesylate/eribulin

‡ Chemotherapy: Paclitaxel, nab-paclitaxel, gemcitabine + carboplatin

*For **ASCENT03** and **TROPION-Breast02** only 5% of patients had prior neoadjuvant IO therapy; waiting on data for subgroup analysis for patients with prior neoadjuvant IO therapy*

Polling question: PD-L1 negative TNBC

*If **datopotamab deruxtecan (TROPION-Breast02)** and **sacituzumab govitecan (ASCENT-03)** receive regulatory approval, which agent would you be most likely to incorporate first into frontline treatment for PD-L1 negative metastatic TNBC?*

1. Dato-DXd first, sacituzumab govitecan second
2. Sacituzumab govitecan first, Dato-DXd second
3. Unsure, need more data

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*ESMO Presidential Session

CLINICAL QUESTION

evERA BC

HR+ metastatic

Does giredestrant (GIRE+ everolimus (E) benefit patients with ER-positive, HER2-negative metaststic breast cancer (ER+, HER2– aBC) previously treated with a CDK4/6 inhibitor?

Giredestrant: investigational oral SERD (selective estrogen antagonist and degrader)

evERA BC: Giredestrant + everolimus vs ET + everolimus in previously treated ER+ HER2- mBC

Study Design: Open-label, randomized phase III

Stratified by prior treatment (yes/no), ESR1m (yes/no), site of disease (visceral vs non-visceral)

- ER+/HER2- aBC
- 1-3 prior lines of therapy with ≤2 prior lines of ET for aBC
- PD or relapse during/after CDK4/6i + ET
- No prior CT for aBC
- Measurable disease or evaluable bone mets

N=373

Giredestrant (30 mg) + everolimus (10 mg)† (n=183)

SOC ET (Exemestane/fulvestrant/tamoxifen) + everolimus (10 mg)† (n=190)

Until PD or unacceptable toxicity

† Dexamethasone mouthwash prophylaxis and treatment was strongly recommended per SWISH trial protocol

SOC ET: 141 exemestane; 39 fulvestrant; 6 tamoxifen; 4 not treated

Co-Primary Endpoint: Investigator-assessed (INV)-PFS in ESR1m and in the ITT population

Secondary Endpoints: OS, INV-assessed ORR, DoR

SOC = standard of care

ET = endocrine therapy

evERA BC: Giredestrant + everolimus vs ET + everolimus in previously treated ER+ HER2- mBC

Baseline Characteristics

Characteristic	Giredestrant + Everolimus (n = 183)	SoC ET + Everolimus (n = 190)
Median age, yr (range)	62.0 (27-83)	60.0 (28-84)
Female sex, n (%)	182 (99.5)	187 (98.4)
Race, n (%)		
• White	103 (56.3)	119 (62.6)
• Asian	66 (36.1)	57 (30.0)
• Black	9 (4.9)	9 (4.7)
• Other	5 (2.7)	5 (2.6)
Region, n (%)		
• Asia-Pacific	58 (31.7)	49 (25.8)
• North America	69 (37.7)	75 (39.5)
• Western Europe	36 (19.7)	43 (22.6)
• Other	20 (10.9)	23 (12.1)
Visceral disease, n (%)	126 (68.9)	131 (68.9)
• Disease involving the liver	89 (48.6)	100 (52.6)
Bone-only involvement at screening, n (%)	24 (13.1)	22 (11.6)

Characteristic, n (%)	Giredestrant + Everolimus (n = 183)	SoC ET + Everolimus (n = 190)
Postmenopausal at screening (eCRF)	156 (85.2)	159 (83.7)
ESR1m detected at baseline	102 (55.7)	105 (55.3)
PIK3CAm detected at baseline	64 (35.0)	51 (26.8)
Prior lines of therapy for aBC		
• 0	3 (1.6)	5 (2.6)
• 1	140 (76.5)	132 (69.5)
• 2	40 (21.9)	52 (27.4)
Prior fulvestrant treatment (CRF)	86 (47.0)	89 (46.8)
Prior CDK4/6i	183 (100)	190 (100)
• Abemaciclib	53 (29.0)	49 (25.8)
• Palbociclib	104 (56.8)	119 (62.6)
• Ribociclib	52 (28.4)	54 (28.4)
Prior PI3Ki	6 (3.3)	7 (3.7)

evERA BC: Giredestrant + everolimus vs ET + everolimus in previously treated ER+ HER2- mBC

Co-Primary Endpoint: investigator assessed PFS in *ESR1*m population

	Giredestrant + everolimus n = 102	SOC ET + everolimus n = 105
Events, n (%)	63 (61.8)	89 (84.8)
Median, mo (95% CI)	**9.99** (8.08, 12.94)	5.45 (3.75, 5.62)
Stratified HR (95% CI)	**0.38** (0.27, 0.54); p < .0001	

PFS benefit with giredestrant + everolimus observed across all subgroups in ESR1m population

Co-Primary Endpoint: investigator assessed PFS in ITT population

	Giredestrant + everolimus n = 183	SOC ET + everolimus n = 190
Events, n (%)	126 (68.9)	163 (85.8)
Median, mo (95% CI)	**8.77** (6.60, 9.59)	5.49 (4.01, 5. 59)
Stratified HR (95% CI)	0.56 (0.44, 0.71); P <.0001	

PFS benefit with giredestrant + everolimus observed across all subgroups in ITT population

SUMMARY

evERA BC

IMPACT

- Giredestrant + everolimus improved investigator-assessed PFS vs SoC ET + everolimus in patients with ER+/HER2- aBC who had previously received CDK4/6i therapy
  - In ESR1m population, the combination led to 62% lower risk of disease progression or death (HR: **0.38**), with median INV-PFS of **9.99** mo vs 5.45 mo for the control arm
  - In ITT population, regimen achieved 44% lower risk of progression or death (HR: **0.56**), corresponding to median INV-PFS of **8.77** mo vs 5.49 mo for standard therapy
  - In ESR1 wild type (~45% of trial), the combination led to limited benefit, with median INV-PFS of 5.72 mo vs 5.52 mo (HR 0.84)
- Manageable safety profile; most common AEs - stomatitis, diarrhea, and anemia

Giredestrant + everolimus may be a new oral therapy option for ER+/HER2- metastatic breast cancer after CDK4/6i therapy

Not yet FDA approved

November 17, 2025: lidERA positive Phase III results for giredestrant in HR+, HER2- early-stage disease…to be presented at an upcoming meeting

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2025 ESMO Key Studies

Breast Cancer

- *DESTINY-Breast11
- *DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*

- evERA BC
- VIKTORIA-1
  - *Polling Question*

GU GI

- *KEYNOTE-905/EV-303
- *IMvigor-011
  - *Polling Question*
- *PSMAddition
  - *Rapid Review*: CAPItello-281
- *Polling Question*
- *FORTITUDE-101
- *AGITG-DYNAMIC-III
  - *Polling Question*
- *RC48-C016
  - *Rapid Review*: POTOMAC

Lung Cancer and Other Notable Studies

- *HARMONI-6
- FLAURA2
  - *Polling Question*
- *OptiTROP-Lung04
  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

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*ESMO Presidential Session

CLINICAL QUESTION

VIKTORIA-1

HR+ metastatic, after CDK4/6i

Does gedatolisib plus fulvestrant, +/- palbociclib, vs fulvestrant benefit patients with HR+/HER2-/PIK3CA wild-type metastatic breast cancer?

First Results

Gedatolisib: a PI3K/AKT/mTOR (PAM) inhibitor

KEY DATA

VIKTORIA-1: Gedatolisib + Fulvestrant ± Palbociclib vs Fulvestrant in HR+/HER2- Advanced Breast Cancer With PIK3CA Wild-Type Status

Study Design: Open-label, randomized phase III study

- Pre- and post-menopausal women and men
- HR+/HER2- metastatic BC with progression on/after CDK4/6i + NSAI
- ≤2 prior lines of ET for aBC
- Measurable disease (RECIST v1.1)
- No Type 2 diabetes with HbA1C >6.4% or Type 1 diabetes
- No prior mTORi, PI3Ki, or AKTi
- No prior chemotherapy
- Known *PIK3CA* status

N=392

Stratified by lung/liver metastases (yes vs no), TTP on last prior therapy (≤ vs >6 months), and region (US/Canada vs ROW)

***PI3KCA* WT**

***PI3KCA* Mut**

Gedatolisib* + Palbociclib† + Fulvestrant‡ (n = 131)

Gedatolisib* + Fulvestrant‡ (n = 130)

Fulvestrant‡ (n = 131)

*180 mg IV qw, 3 wk on, 1 wk off. †125 mg qd, 21 days on, 7 days off. ‡500 mg cycle 1, Days 1 and 15, then q4w.

Treatment arms: gedatolisib + palbo/fulv, gedatolisib + fulv, and alpelisib + fulvestrant

Optional cross-over at progression

Co-Primary Endpoint: **:** PFS (by BICR) of triplet regimen vs fulvestrant and PFS (by BICR) of doublet regimen vs fulvestrant
Secondary Endpoints: OS, response, safety, QoL

ESMO 2025. Abstr LBA17.

KEY DATA

VIKTORIA-1: Gedatolisib + Fulvestrant ± Palbociclib vs Fulvestrant in HR+/HER2- Advanced Breast Cancer With PIK3CA Wild-Type Status

Co-Primary Endpoint: PFS Gedatolisib Triplet vs. Fulvestrant, BICR Assessment

	Gedatolisib + Palbo + Fulvestrant (n = 131)	Fulvestrant (n = 131)
Median PFS, mo (95% CI)	**9.3** (7.2 – 16.6)	2.0 (1.8 – 2.3)
Adjusted HR (95% CI)	**0.24** (0.17 – 0.35); *P* < 0.0001	

Benefit observed across all subgroups with triplet regimen

Co-Primary Endpoint: PFS Gedatolisib Doublet vs. Fulvestrant, BICR Assessment

	Gedatolisib + Fulvestrant (n = 130)	Fulvestrant (n = 131)
Median PFS, mo (95% CI)	**7.4** (5.5 – 9.9)	2.0 (1.8 – 2.3)
Adjusted HR (95% CI)	**0.33** (0.24 – 0.48); *P* < 0.0001	

Benefit observed across subgroups with doublet regimen except for fast progressors (≤6 mo)

ESMO 2025. Abstr LBA17.

KEY DATA

VIKTORIA-1: Gedatolisib + Fulvestrant ± Palbociclib vs Fulvestrant in HR+/HER2- Advanced Breast Cancer With PIK3CA Wild-Type Status

Safety

AE, n (%)	Gedatolisib + Palbo + Fulvestrant (n = 130)			Gedatolisib + Fulvestrant (n = 130)			Fulvestrant (n = 123)		
Patients with ≥1 SAE	14 (10.8)			12 (9.2)			1 (0.8)		
Study tx discontinuation due to TRAE	3 (2.3)			4 (3.1)			0		
Deaths due to TRAE	2 (1.5)*			0			0		
	Gedatolisib + Palbo + Fulvestrant (n = 130)			**Gedatolisib + Fulvestrant (n = 130)**			**Fulvestrant (n = 123)**		
Specific AEs, n (%)	**Any Gr**	**Gr 3**	**Gr 4**	**Any Gr**	**Gr 3**	**Gr 4**	**Any Gr**	**Gr 3**	**Gr 4**
• **Stomatitis**	**90 (69.2)**	**25 (19.2)**	0	**74 (56.9)**	**16 (12.3)**	0	0	0	0
• **Neutropenia**	**85 (65.4)**	**68 (52.3)**	**13 (10.0)**	2 (1.5)	0	**1 (0.8)**	1 (0.8)	1 (0.8)	0
• Nausea	57 (43.8)	5 (3.8)	0	56 (43.1)	1 (0.8)	0	4 (3.3)	0	0
• Rash	36 (27.7)	6 (4.6)	0	42 (32.3)	7 (5.4)	0	0	0	0
• Vomiting	36 (27.7)	2 (1.5)	0	30 (23.1)	0	0	1 (0.8)	0	0
• Fatigue	29 (22.3)	2 (1.5)	0	27 (20.8)	1 (0.8)	0	5 (4.1)	0	0
• Diarrhea	22 (16.9)	2 (1.5)	0	16 (12.3)	1 (0.8)	0	0	0	0
• Hyperglycemia	12 (9.2)	3 (2.3)	0	15 (11.5)	3 (2.3)	0	0	0	0

*Triplet: 1 considered related to palbociclib (pneumonia) and 1 considered related to all 3 drugs (hepatic failure).

SUMMARY

VIKTORIA-1

- Gedatolisib plus fulvestrant ± palbociclib vs fulvestrant show improvement in PFS in patients with HR+/HER2- metastatic BC and PIK3CA wild-type status with tumor progression on prior CDK4/6i therapy
  - mPFS in triplet vs fulvestrant: **9.3** vs 2.0 mo (HR: **0.24**; 95% CI: 0.17-0.35; P <.0001)
  - mPFS doublet vs fulvestrant: **7.4** vs 2.0 mo (HR: **0.33**; 95% CI: 0.24-0.48; P <.0001)

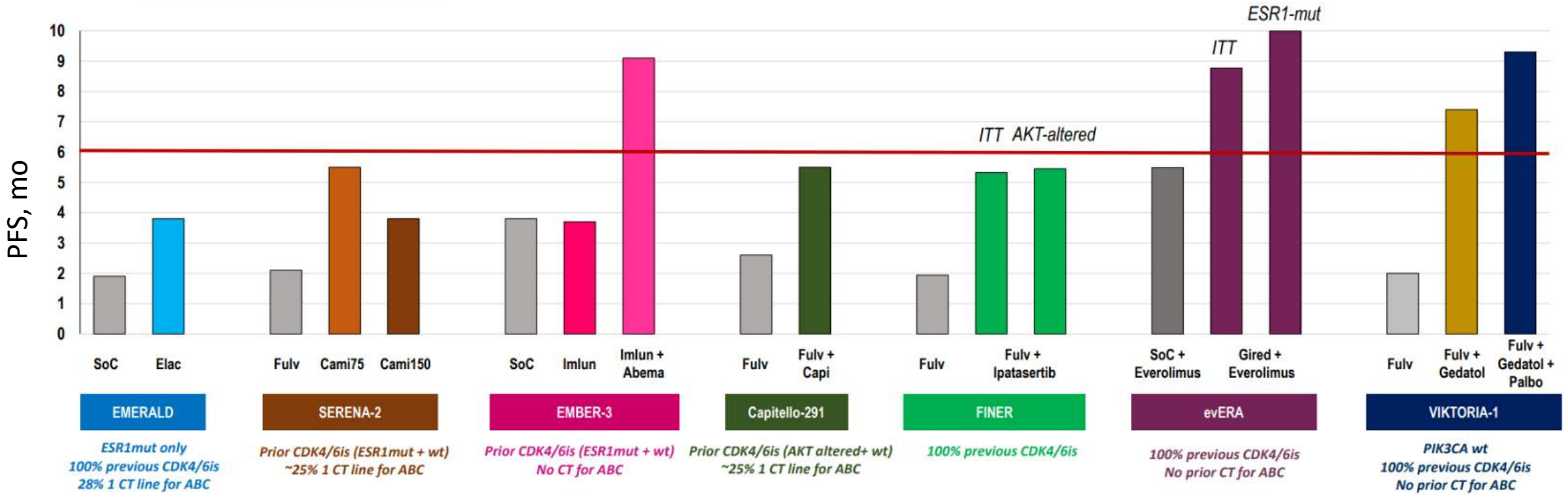
IMPACT

Gedatolisib as a triplet or doublet (with fulvestrant ± palbociclib) is a potential novel treatment option for patients with HR+, HER2- PIK3CA-wildtype metastatic breast cancer with tumor progressio on or after a CDK4/6i

NDA submitted, not yet FDA approved

Pushing beyond the 6-month PFS ceiling after CDK4/6 inhibitors

Combination of SERDs/SERMs with targeted therapies including PI3Ki and CDK4/6i represents the future of ET-based treatment in CDK4/6i-pretreated population



DESTINY-Breast06: HR+, HER2-low or -ultra low; ≥ 2 prior lines of ET ± targeted therapy for mBC; no prior chemo
HR+/HER2-low group: medium PFS 13.2 mo vs 8.1 mo (HR 0.62; 95% CI 0.51–0.74; p<0.0001).
HR+/HER2-low (IHC 1+ or IHC 2+/ISH–) and HER2-ultralow (IHC 0 with membrane staining) group: medium PFS 13.2 mo vs 8.1 mo (HR 0.64; 95% CI 0.54–0.76; p<0.0001).

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Bardia A et al SBACS 2021; Bidard FC et al JCO 2022; Oliveira M et al Lancet Oncol 2024; Jhaveri et al SABCS 2024 & NEJM 2024; Turner NC et al NEJM 2023; Chia S et al ASCO 2025; Mayer E et al ESMO 2025; Hurvitz S et al ESMO 2025 Courtesy of Alessandra Gennari; N Engl J Med. 2024 Dec 5;391(22):2110-2122.

Mini Oral Sesson– Breast Cancer, Metastatic
Invited Discussant 536MO, 555MO & 487MO
20th October 2025, Berlin
Janice Tsang (Dr.)

Polling question

If approved, where would you most likely position ***evERA BC*** (ER+, HER2- mBC) *and* ***VIKTORIA-1*** *in the current HR+/HER2- metastatic breast cancer treatment sequence?*

1. Immediately with tumor progression on CDK4/6 inhibitor
2. After tumor progression on CDK4/6 inhibitor and chemotherapy
3. Later-line therapy after multiple endocrine/targeted agents
4. Would consider T-DXd if HER2 IHC is IHC 0+ or 1+ or 2+
5. Would need more data

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ESMO 2025

Breast Cancer

Key Takeaways

Q&A

@EdithPerezMD

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DESTINY-Breast11*:* Neoadjuvant T-DXd→THP achieved a 67.3% pCR rate (vs 56.3% with ddAC→ THP), improving response and may become a standard of care in the curative intent setting for HER2+ early breast cancer – *not yet approved*

DESTINY-Breast05: Post-neoadjuvant T-DXd was associated with improvements in invasive disease-free survival vs T-DM1 at 3-yr 92.4% vs 83.7% (HR: 0.47; P <.0001) and may become a standard of care in the curative intent setting for HER2+ early breast cancer – *not yet approved*

DESTINY-Breast09: In first-line HER2+ metastatic breast cancer, T-DXd plus pertuzumab significantly improved PFS (median ~ 40.7 months vs 26.9 months; HR 0.56) versus THP irrespective of PI3Km or HR status– *not yet approved, PDUFA date of Jan 23, 2026*

ASCENT-03: In first-line metastatic TNBC patients ineligible for PD-1/PD-L1 inhibitors, sacituzumab govitecan reduced the risk of progression or death by 38% vs standard chemotherapy (median PFS 9.7 vs 6.9 months; HR 0.62) – *not yet approved*

TROPION-Breast02: In first-line metastatic TNBC patients ineligible for PD-1/PD-L1 inhibitors, datopotamab deruxtecan improved OS (23.7 vs 18.7 mo, HR: 0.79) and PFS (10.8 vs 5.6 mo, HR: 0.57) by ~5 months versus chemotherapy – *not yet approved*

evERA BC: In ER+/HER2– advanced breast cancer post-CDK4/6 inhibitors, giredestrant + everolimus reduced the risk of progression by ~44% in the overall population and ~62% in ESR1-mutant patients versus standard endocrine therapy + everolimus – *not yet approved*

VIKTORIA-1: Gedatolisib plus fulvestrant ± palbociclib improved PFS in PIK3CA wild-type, HR+/HER2– advanced breast cancer post-CDK4/6 inhibitors (triplet HR 0.24, doublet HR 0.33 vs fulvestrant) – *not yet approved*

2025 ESMO Key Studies

Breast Cancer

- *DESTINY-Breast11
- *DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*

- evERA BC
- VIKTORIA
  - *Polling Question*

GU GI

- *KEYNOTE-905/EV-303
- *IMvigor-011
  - *Polling Question*
- *PSMAddition
  - *Rapid Review*: CAPItello-281
- *Polling Question*
- *FORTITUDE-101
- *AGITG-DYNAMIC-III
  - *Polling Question*
- *RC48-C016
  - *Rapid Review*: POTOMAC

Lung Cancer and Other Notable Studies

- *HARMONI-6
- FLAURA2
  - *Polling Question*
- *OptiTROP-Lung04
  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

*ESMO Presidential Session

CLINICAL QUESTION

KEYNOTE-905/EV-303

* Presidential Symposium

Does Preoperative Enfortumab Vedotin Plus Pembrolizumab Benefit Patients with Muscle-invasive Bladder Cancer Who Are Cisplatin-ineligible?

*On **November 21, 2025**, the FDA approved **pembrolizumab** (Keytruda, Merck) or pembrolizumab and berahyaluronidase alfa-pmph (Keytruda Qlex, Merck) with **enfortumab vedotin-ejfv** (Padcev, Astellas Pharma) as neoadjuvant treatment followed by adjuvant treatment after cystectomy for adults with **muscle invasive bladder cancer (MIBC) who are ineligible for cisplatin** based on KEYNOTE-905/EV-303*

cornerstone specialty network

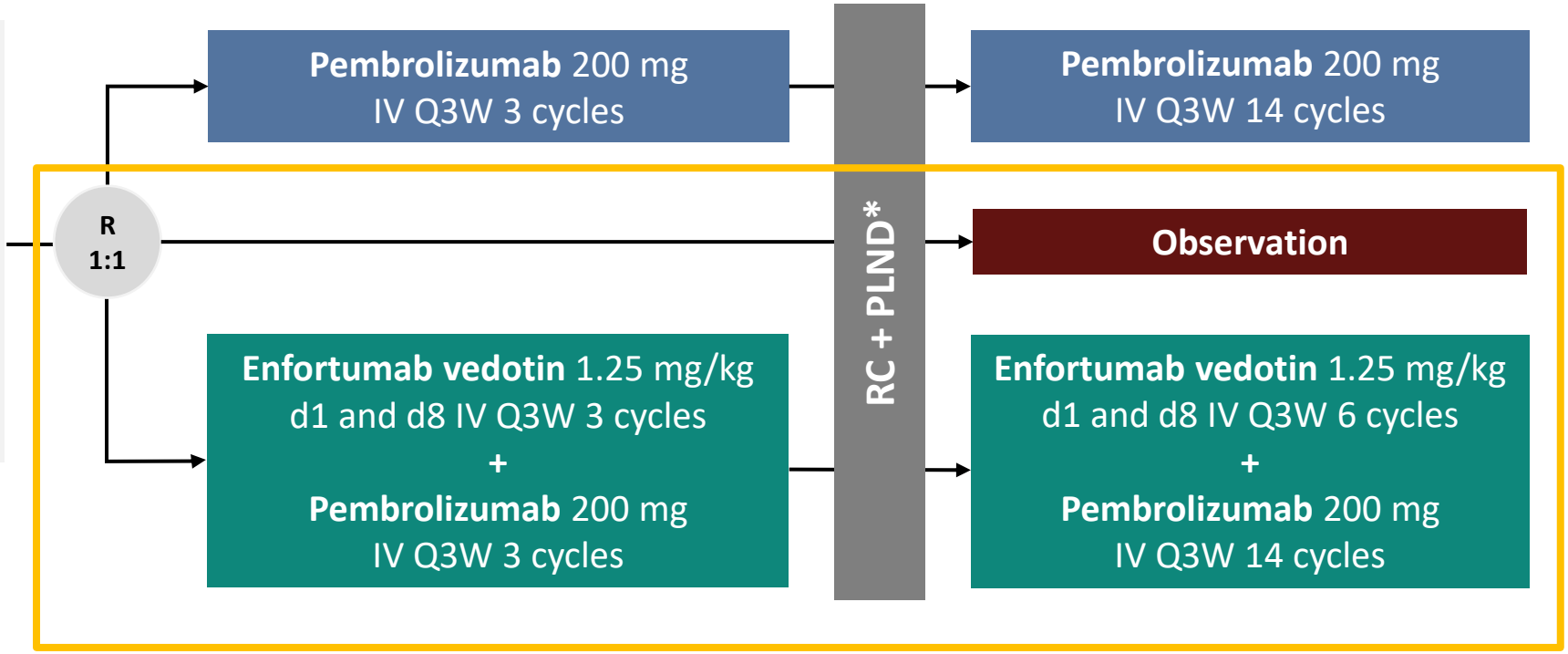
KEY DATA

KEYNOTE-905/EV-303: Perioperative EV + pembro in cisplatin-ineligible muscle-invasive bladder cancer

Study Design: Randomized, open-label, phase 3

- Adults with MIBC
- Clinical stage T2-T4aN0M0 or T1-T4aN1M0 by central assessment
- ≥50% Urothelial histology
- Cisplatin-ineligible per Galsky criteria or cisplatin-declining
- ECOG PS 0-1

Stratified by cisplatin ineligible (ineligible vs eligible but declining), clinical stage (T2N0 vs. T3/T4aN0 vs T1-4aN1), and region (US vs EU vs Most of World)



*Note: radical cystectomy (RC) with pelvic lymph node dissection (PLND)

Primary endpoint: Event free survival (EFS) by BICR

Key Secondary endpoint: OS and pathological complete response (pCR; pT0N0, i.e. absence of viable tumor in examined tissue from surgery) by central pathologist review

KEY DATA

KEYNOTE-905/EV-303 : Perioperative EV + pembro in cisplatin-ineligible muscle-invasive bladder cancer

Baseline characteristics

Characteristic, n (%)	EV+ pembro (n = 170)	Control (n = 174)
Median age (range), yrs	74.0 (47-87)	72.5 (46-87)
• ≥65 yr to <75	63 (37.1)	77 (44.3)
• ≥75 yr	78 (49.2)	68 (39.1)
Male	137 (80.6)	131 (75.3)
ECOG PS		
• 0	102 (60.0)	96 (54.6)
• 1	47 (27.6)	53 (30.5)
• 2	21 (12.4)	26 (14.9)
Region		
• United States	21 (12.4)	23 (13.2)
• European Union	78 (45.9)	77 (44.3)
• Most of World	71 (41.8)	74 (42.5)
Cisplatin eligibility status		
• Ineligible	142 (83.5)	139 (79.9)
• Eligible but declining	28 (16.5)	35 (20.1)

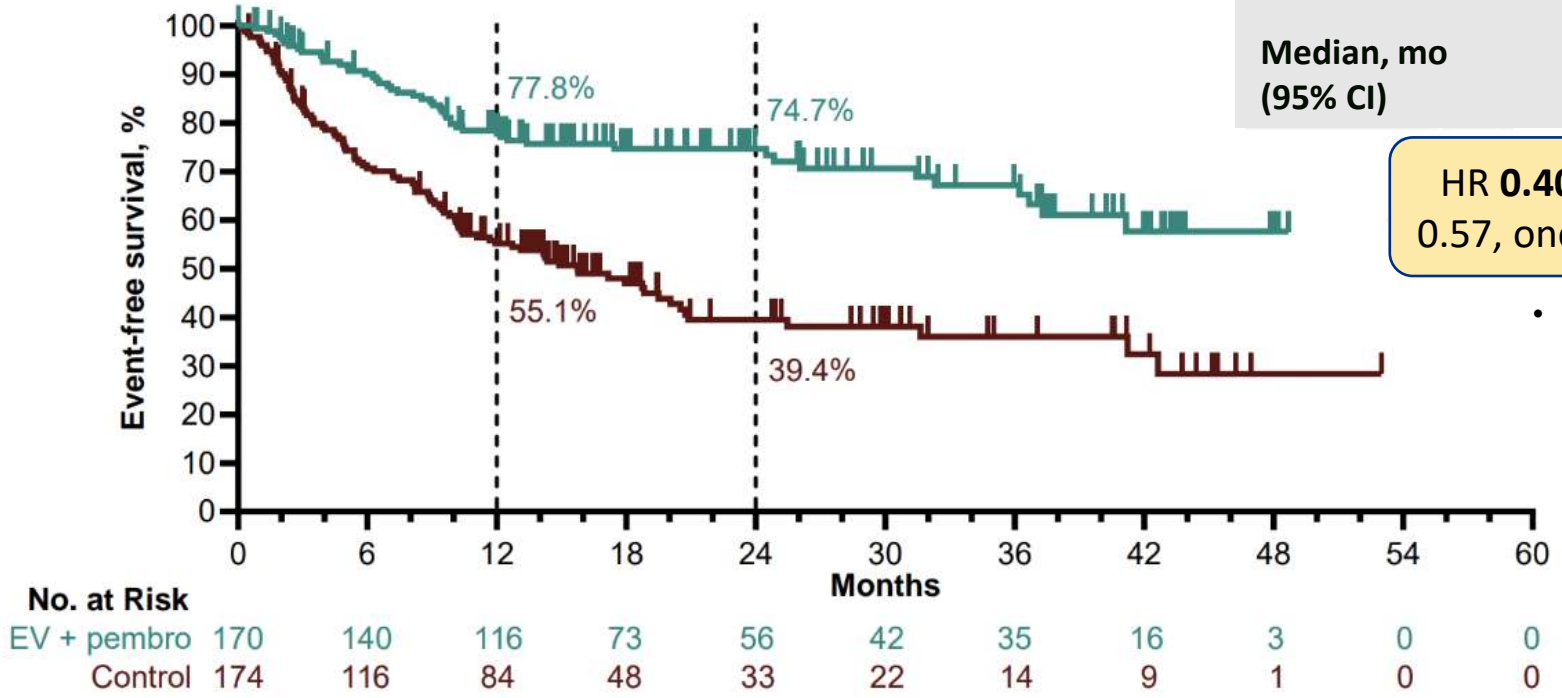
Characteristic, n (%)	EV+ pembro (n = 170)	Control (n = 174)
PD-L1 combined positive score (CPS) ≥10	80 (47.1)	83 (47.7)
Tumor stage at baseline		
• T2N0	30 (17.6)	32 (18.4)
• T3/T4aN0	133 (78.2)	35 (20.1)
• T1-4aN1	7 (4.1)	83 (47.7)
Creatinine clearance		
• ≥60 mL/min	68 (40.0)	72 (41.4)
• ≥30 and <60 mL/min	102 (60.0)	101 (58.0)
• <30 mL/min	0	1 (0.6)
Pure urothelial carcinoma histology	152 (89.4)	161 (92.5)

KEYNOTE-905/EV-303 : Perioperative EV + pembro in cisplatin-ineligible muscle-invasive bladder cancer

Primary Endpoint: EFS by BICR (ITT Population)

	EV+ pembro (n = 170)	Control (n = 174)
Events, n (%)	48 (28.2)	95 (54.6)
Median, mo (95% CI)	**NR** (37.3-NR)	15.7 (10.3-20.5)

HR **0.40**, 95% CI 0.28-0.57, one-sided P<.0001



- 29/174 patients (16.7%) in the control arm received adjuvant nivolumab as of data cutoff per local guidelines/ prescribing information

EFS by BICR (ITT Population) favored EV + pembro across all subgroups

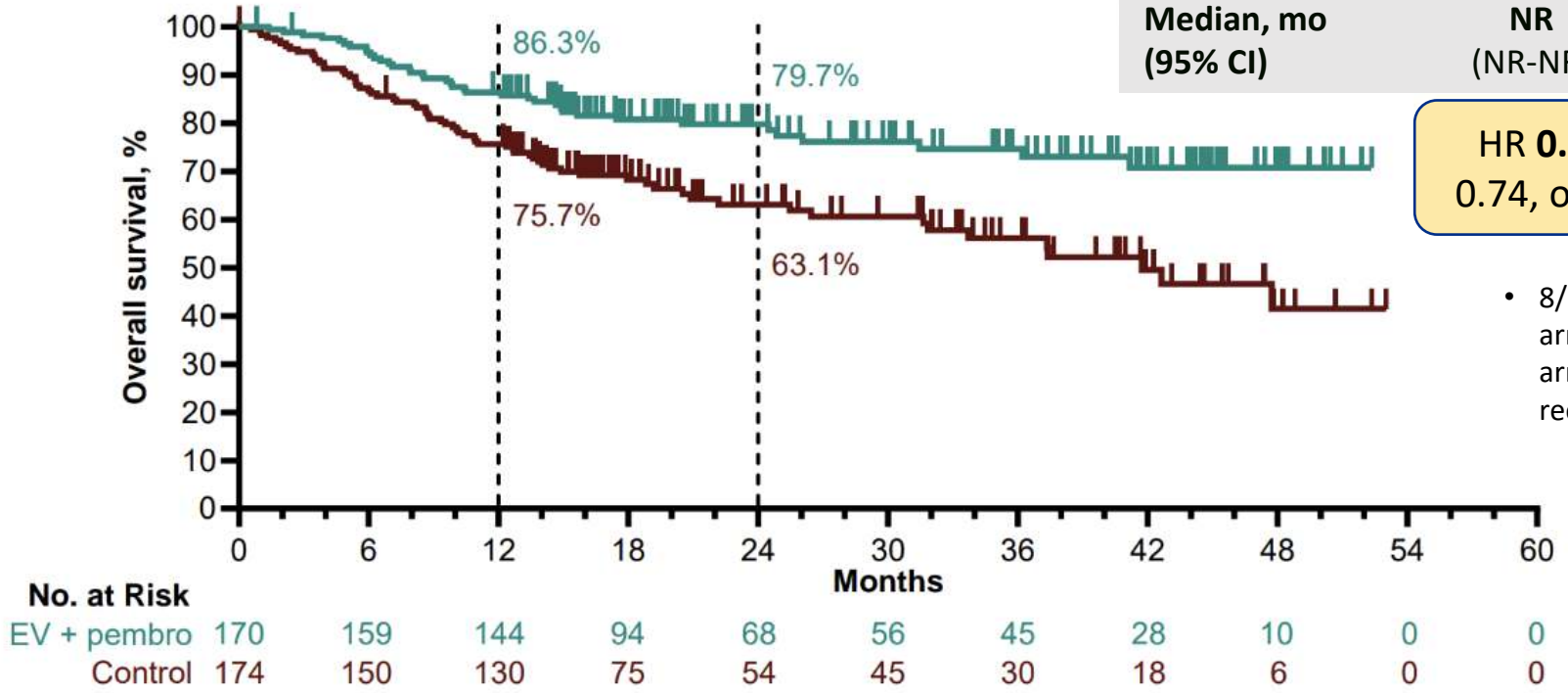
Data cutoff date: June 6, 2025

KEYNOTE-905/EV-303 : Perioperative EV + pembro in cisplatin-ineligible muscle-invasive bladder cancer

Key Secondary Endpoints: Overall Survival (OS)

	EV+ pembro (n = 170)	Control (n = 174)
Events, n (%)	38 (22.5)	68 (39.1)
Median, mo (95% CI)	**NR** (NR-NR)	41.7 (31.8-NR)

HR **0.50**, 95% CI 0.33-0.74, one-sided P=.0002



- 8/170 pts (4.7%) in the EV + pembro arm and 46/174 (26.4% in the control arm received subsequent therapy for recurrent/ metastatic disease

KEYNOTE-905/EV-303 : Perioperative EV + pembro in cisplatin-ineligible muscle-invasive bladder cancer

Key Secondary Endpoints: Pathological Complete Response (pCR)

	EV+ pembro (n = 170)	Control (n = 174)
pCR, n	97	15
Median, mo (95% CI)	57.1 (49.3-64.6)	8.6 (4.9-13.8)

Δ 48.5%

Status: pCR		
	EV+ pembro (n = 97)	**Control (n = 15)**
Events, n (%)	16 (16.5)	5 (33.3)
Median, mo (95% CI)	NR (NR-NR)	41.2 (12.7-NR)
HR (95% CI)	0.43 (0.16-1.16)	

Status: No pCR		
	EV+ pembro (n = 73)	**Control (n = 159)**
Events, n (%)	32 (43.8)	90 (56.6)
Median, mo (95% CI)	26.1 (10.1-41.2)	14.2 (10.1-19.5)
HR (95% CI)	0.76 (0.51-1.14)	

- **pCR**: absence of viable tumor (pT0N0) in examined tissue from TC + PLND
- Patients who did not undergo surgery, including those with clinical complete response after neoadjuvant therapy, were considered non-responders

KEYNOTE-905/EV-303 : Perioperative EV + pembro in cisplatin-ineligible muscle-invasive bladder cancer cancer

Safety Summary

Characteristic, n (%)	EV+ pembro (n = 167)	Control (n = 159)
Any grade TEAE • Surgery phase only	167 (100) 99/146 (67.8)	103 (64.8) 103 (64.8)
Grade ≥3 TEAE • Surgery phase only	119 (71.3) 52.146 (35.6)	73 (45.9) 73 (45.9)
Serious TEAE • Surgery phase only	97 (58.1) 42/146 (28.8)	65 (40.9) 65 (40.9)
AE leading to surgery delay	6/149 (4.0)	1/156 (0.6)
TEAE leading to dose reduction of EV	28 (16.8)	NA
TEAE leading to dose reduction of EV	69 (41.3)	NA
TEAE leading to dose reduction of EV	57 (34.1)	NA
TEAE leading to dose reduction of EV • Surgery phase only	13 (7.8) 4/146 (2.7)	9 (5.7) 9 (5.7)

KEYNOTE-905/EV-303

SUMMARY

- Neoadjuvant EV + pembro, before and after RC and PLND compared with surgery alone significantly improved EFS, OS, and pCR rate in patients with MIBC who are ineligible for or decline cisplatin-based chemotherapy
  - EFS and PS benefit was generally consistent across key subgroups
- The safety profile of perioperative EV plus pembro was manageable and consistent with prior reports of this regimen in the locally advanced/metastatic urothelial carcinoma setting
  - No new safety signals were observed
- The first phase 3 study to show improved efficacy outcomes with perioperative therapy relative to surgery for patients with MIBC who are ineligible for cisplatin-based chemotherapy

IMPACT

Preoperative enfortumab vedotin plus pembrolizumab added to RC + PLND should be considered a new standard of care for patients with muscle-invasive bladder cancer ineligible for or decline cisplatin-based chemotherapy

Now approved - November 21, 2025!

2025 ESMO Key Studies

Breast Cancer

- *DESTINY-Breast11
- *DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09

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- TROPION-Breast02
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  - *Polling Question*

GU GI

- *KEYNOTE-905/EV-303
- *IMvigor-011
  - *Polling Question*
- *PSMAddition
  - *Rapid Review*: CAPItello-281
- *Polling Question*
- *FORTITUDE-101
- *AGITG-DYNAMIC-III
  - *Polling Question*
- *RC48-C016
  - *Rapid Review*: POTOMAC

Lung Cancer and Other Notable Studies

- *HARMONI-6
- FLAURA2
  - *Polling Question*
- *OptiTROP-Lung04
  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

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*ESMO Presidential Session

IMvigor011

* Presidential Symposium

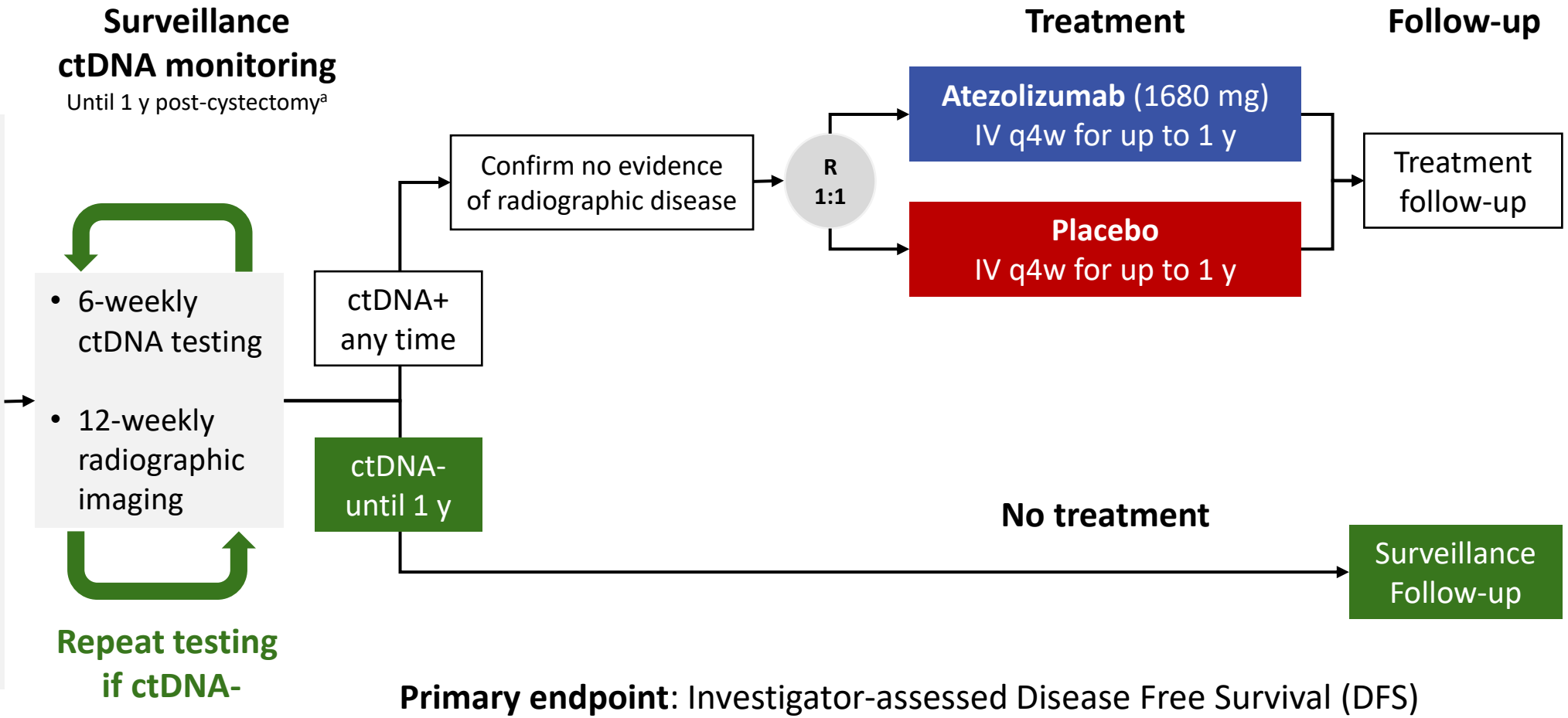
Does the circulating tumor (ct) DNA-guided adjuvant atezolizumab vs placebo benefit patient with muscle-invasive bladder cancer?

KEY DATA

IMvigor011: ctDNA monitoring for adjuvant atezolizumab in muscle-invasive bladder cancer

Study Design: Global, randomized, double-blind, phase 3

- MIBC within 6-24 weeks of radical cystectomy
- Histologically confirmed (y)pT2-T4aN0M0 or (y)pT0-T4aN+M0 urothelial cancer
- No evidence of radiographic disease
- Prior neoadjuvant chemotherapy permitted
- ECOG PS 0 – 2



Primary endpoint: Investigator-assessed Disease Free Survival (DFS)
Key Secondary endpoint: Overall Survival (OS)

[a]Early versions of the protocol included a 21-mo surveillance ctDNA monitoring period

KEY DATA

IMvigor011: ctDNA monitoring for adjuvant atezolizumab in muscle-invasive bladder cancer

Baseline characteristics

Characteristic, n (%)	Atezolizumab (n = 167)	Placebo (n = 83)	No treatment (n=357)
Age, median (range), y	69 (42-87)	67 (44-84)	69 (36-90)
Male	141 (84.4)	67 (80.7)	278 (77.9)
Region			
• Asia-Pacific	51 (30.5)	27 (32.5)	137 (38.4)
• Central and South American	14 (8.4)	6 (7.2)	25 (7.0)
• Europe	101 (60.5)	49 (59.0)	191 (53.3)
• North America	1 (0.6)	1 (1.2)	4 (1.1)
ECOG PS			
• 0	113 (67.7)	53 (63.9)	232 (65.7)
• 1	52 (31.1)	29 (34.9)	110 (31.2)
• 2	2 (1.2)	1 (32)	11 (3.1)
PD-L1 status			
• IC0/1 (<5%)	108 (64.7)	53 (63.9)	189 (53.1)
• IC2/3 (≥5%)	59 (35.3)	30 (36.1)	167 (46.9)
Histological variants present	18 (10.8)	8 (9.6)	56 (15.7)
Prior neoadjuvant chemotherapy			
• Yes	80 (47.9)	33 (39.8)	168 (47.1)
• No	87 (52.1)	50 (60.2)	189 (52.9)

Characteristic, n (%)	Atezolizumab (n = 167)	Placebo (n = 83)	No treatment (n=357)
Tumor stage post-cystectomy			
• <T2	46 (27.5)	24 (28.9)	116 (46.8)
• T3/4	121 (72.5)	59 (71.1)	189 (53.2)
Nodal status			
• Negative	71 (42.5)	35 (42.2)	285 (79.8)
• Positive	96 (57.5)	48 (57.8)	72 (20.2)
Pathological staging at cystectomy			
• pT2N0	8 (4.8)	3 (3.7)	62 (17.5)
• ypT2N0	15 (9.0)	5 (6.1)	61 (17.2)
• (y)pT2N+	30 (18.0)	18 (22.0)	43 (12.1)
• (y)pT3-4N0	49 (29.3)	26 (31.7)	160 (45.1)
• (y)pT3-4N+	65 (38.9)	30 (36.6)	29 (8.2)
Time from cystectomy to first ctDNA+ sample			
• <20 weeks	117 (70.1)	59 (71.1)	NA
• >20 weeks	50 (29.9)	24 (28.9)	NA
Achieved ctDNA+ status			
• At initial test	99 (59.3)	49 (59.0)	NA
• At subsequent tests	68 (40.7)	34 (41.0)	NA

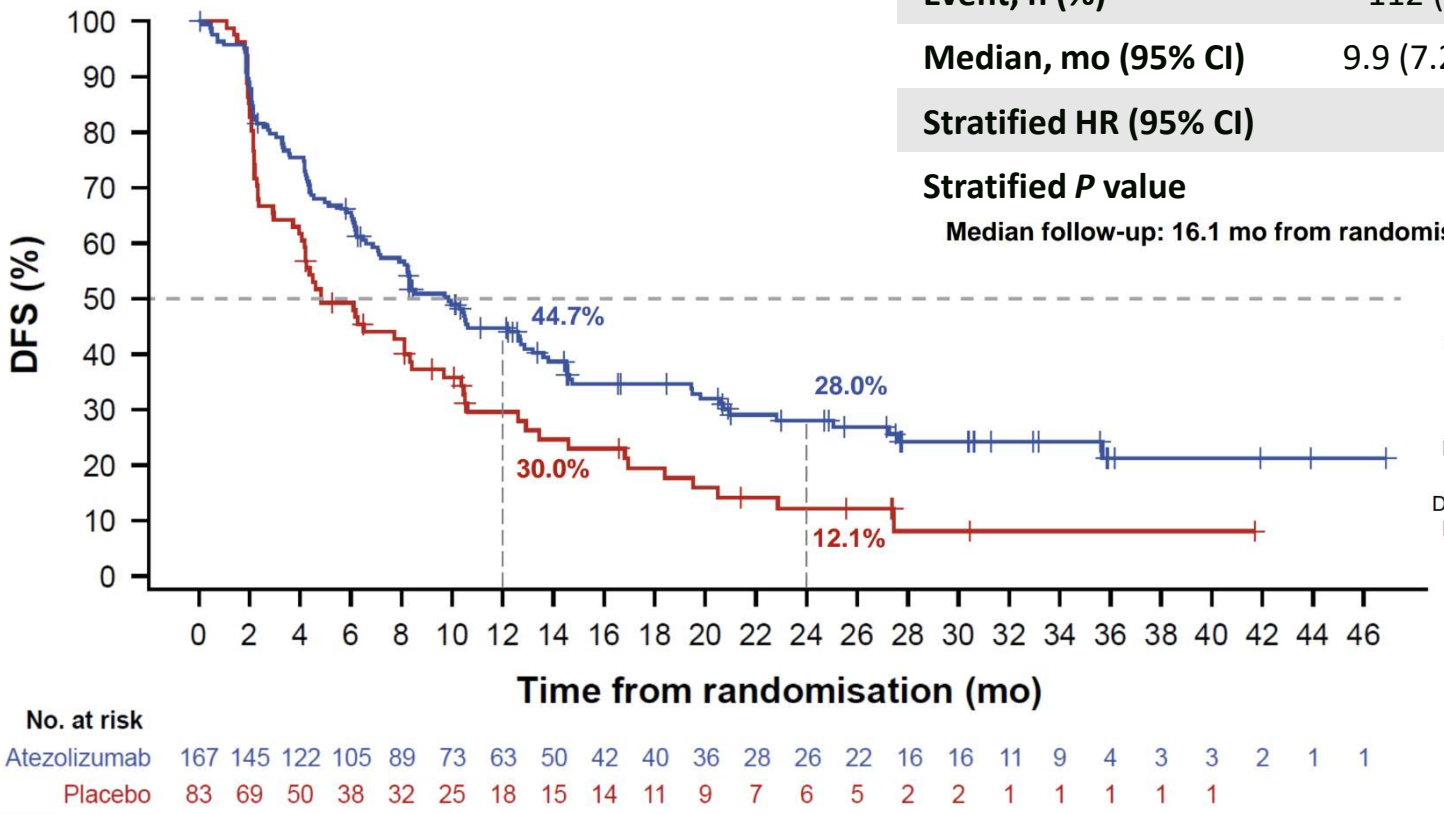
KEY DATA

IMvigor011: ctDNA monitoring for adjuvant atezolizumab in muscle-invasive bladder cancer

Primary Endpoint: Investigator-assessed Disease Free Survival (DFS)

	Atezolizumab (n = 167)	Placebo (n = 83)
Event, n (%)	112 (67.1)	66 (79.5)
Median, mo (95% CI)	9.9 (7.2-12.7)	4.8 (4.1-8.3)
Stratified HR (95% CI)	**0.64 (0.47-0.87)**	
Stratified *P* value	**0.0047**	

Median follow-up: 16.1 mo from randomisation



Consistent benefit in relevant secondary endpoints:

DFS per IRF:
HR, 0.66 (95% CI: 0.48, 0.91)

Distant-metastasis free survival:
HR, 0.66 (95% CI: 0.47, 0.94)

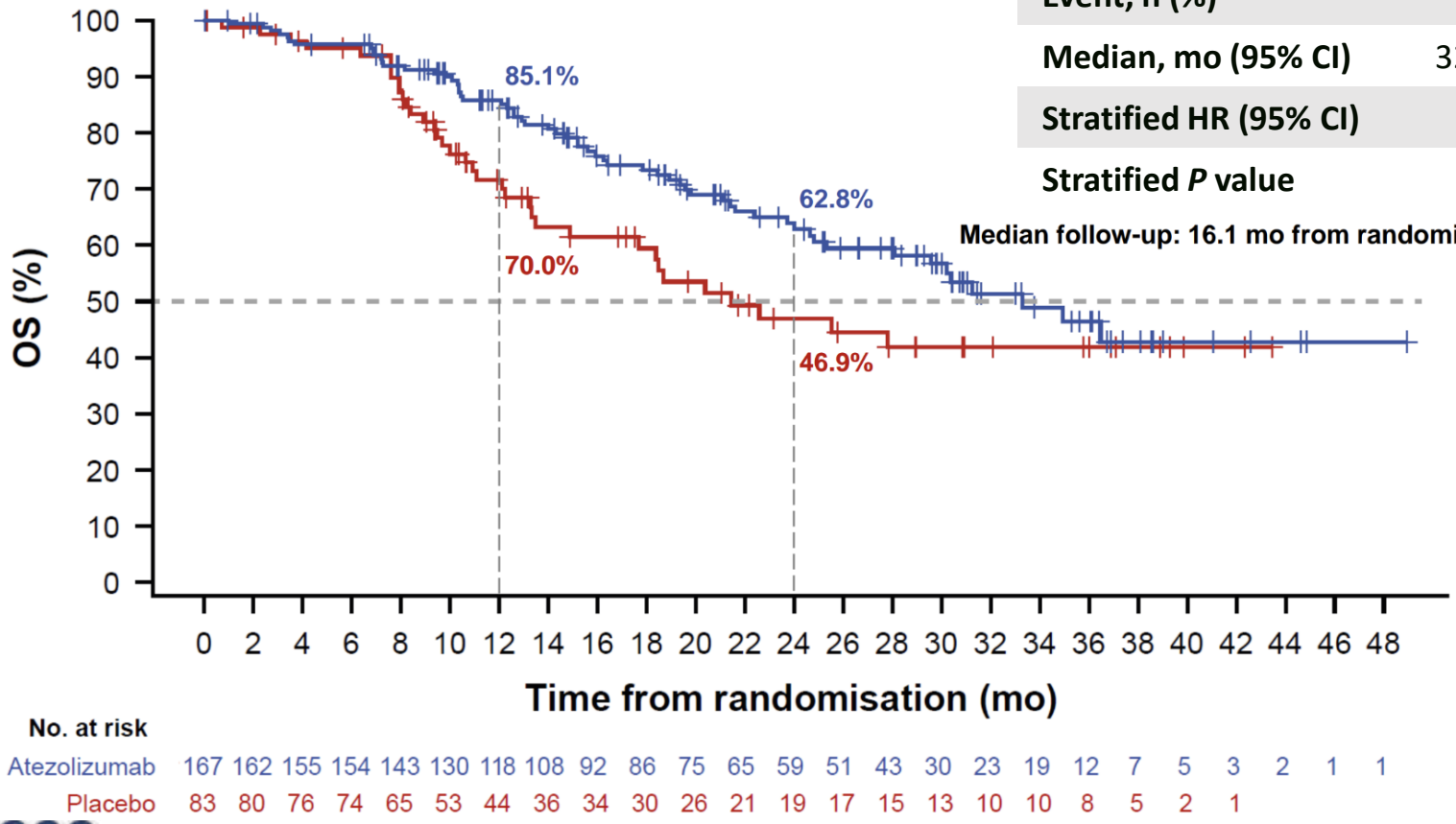
Clinical cutoff: June 15, 2025

KEY DATA

IMvigor011: ctDNA monitoring for adjuvant atezolizumab in muscle-invasive bladder cancer

Key Secondary Endpoint: Overall Survival (OS)

	Atezolizumab (n = 167)	Placebo (n = 83)
Event, n (%)	60 (35.9)	36 (43.4)
Median, mo (95% CI)	32.8 (27.7, NE)	21.2 (14.7, NE)
Stratified HR (95% CI)	**0.59 (0.39, 0.90)**	
Stratified *P* value	**0.0131**	



Consistent benefit in relevant secondary endpoints:

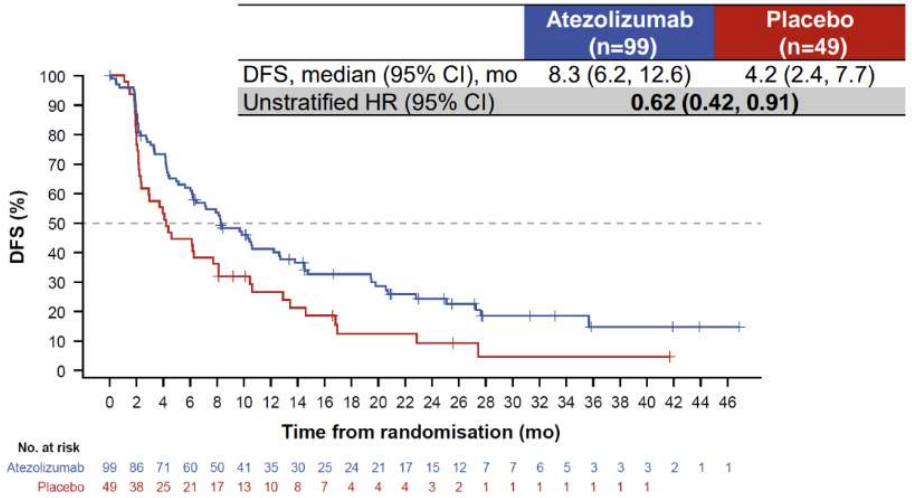
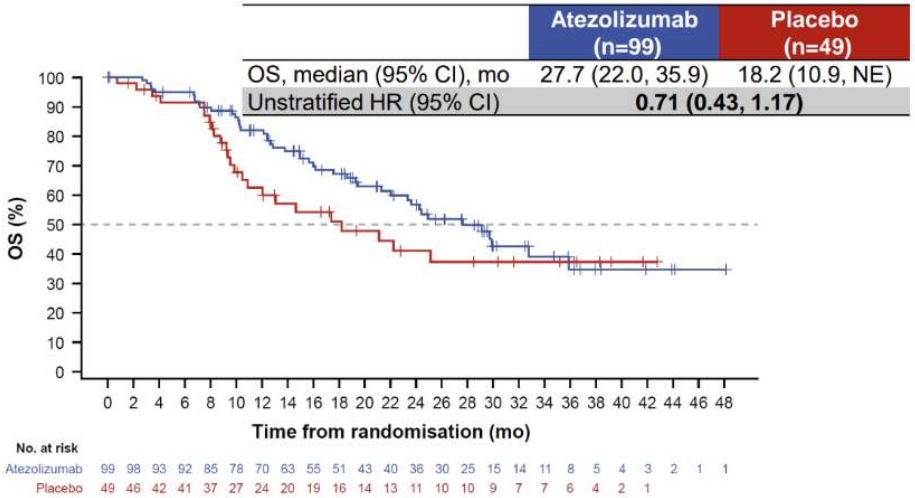
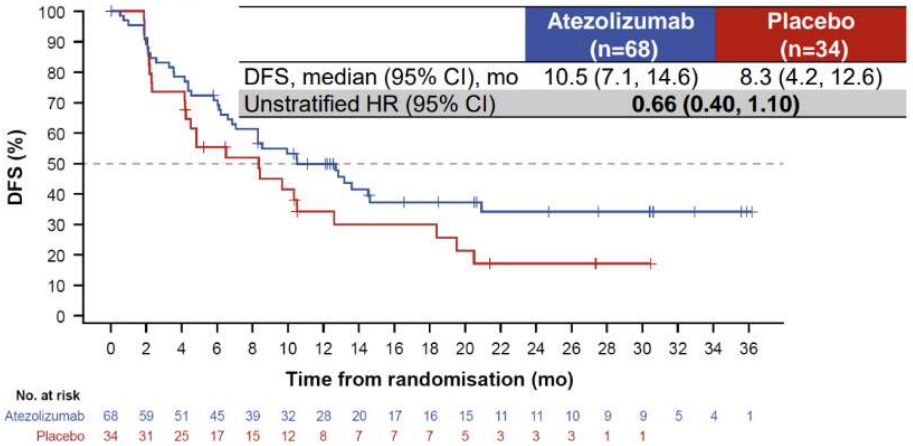
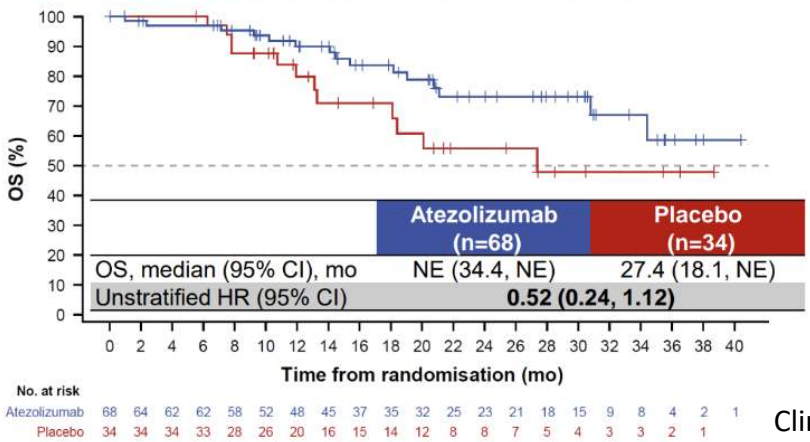
Disease-specific survival:
HR, 0.64 (95% CI: 0.40, 1.05)

Clinical cutoff: June 15, 2025

KEY DATA

IMvigor011: ctDNA monitoring for adjuvant atezolizumab in muscle-invasive bladder cancer

DFS and OS in Key Subgroups

	INV-assessed DFS	OS
ctDNA+ at initial test (148/250; 59.2%)		
ctDNA+ at subsequent test (102/250; 40.8%)		

INV: investigator

Clinical cutoff: June 15, 2025
Median follow-up: 16.1 mo

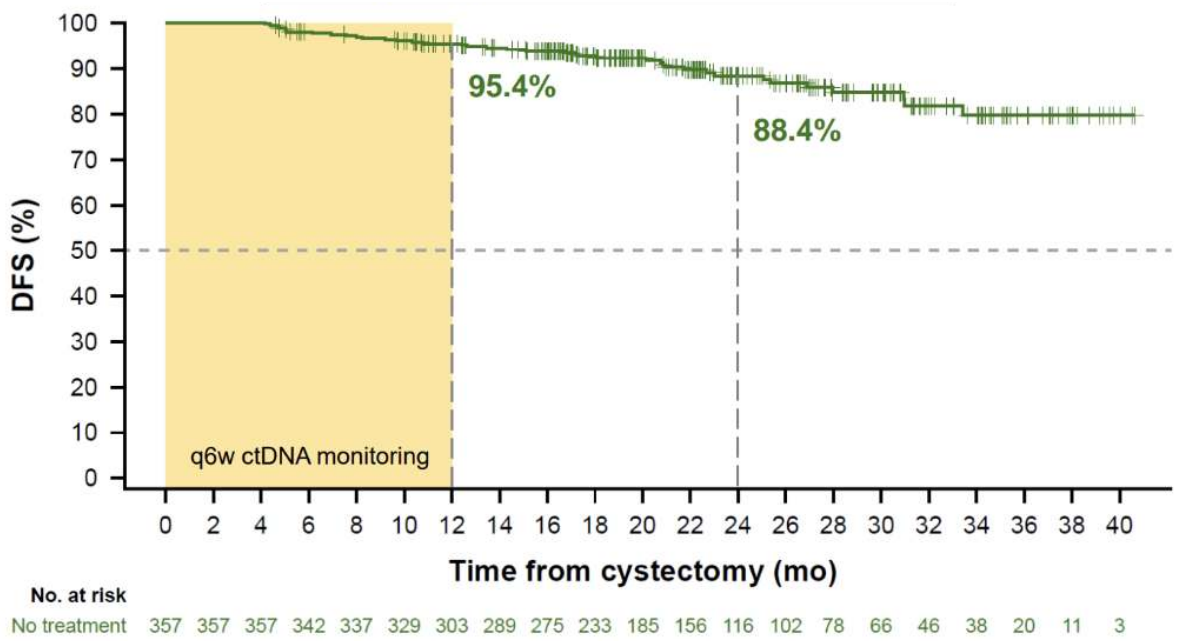
KEY DATA

IMvigor011: ctDNA monitoring for adjuvant atezolizumab in muscle-invasive bladder cancer

DFS and OS in patients who persistently tested ctDNA-negative

INV-assessed DFS

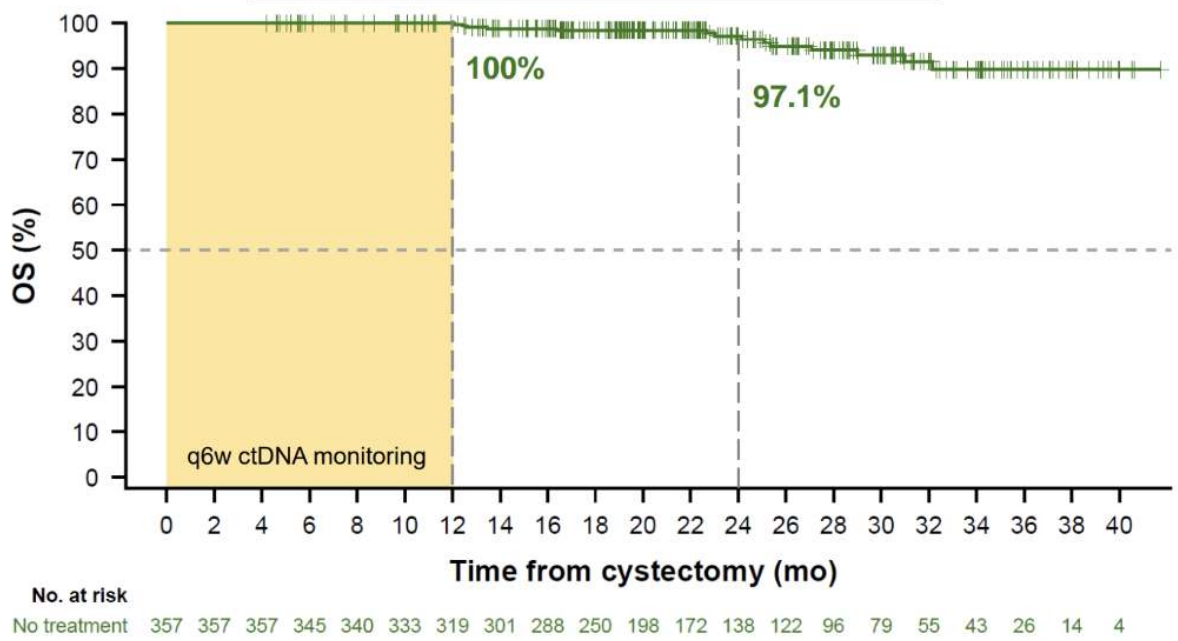
	No treatment (n = 357)
Event, n (%)	39 (10.9)
DFS, median (95% CI), mo	NE (NE)



Median follow-up: 21.8 mo from cystectomy

OS

	No treatment (n = 357)
Event, n (%)	14 (3.9)
DFS, median (95% CI), mo	NE (NE)



8 DFS events were deaths not clearly attributed to disease recurrence

15 patients (4.2%) who experienced disease recurrence during the ctDNA monitoring period were discontinued from the study and censored for OS

Clinical cutoff: June 15, 2025

KEY DATA

IMvigor011: ctDNA monitoring for adjuvant atezolizumab in muscle-invasive bladder cancer

Safety

Patients with ≥1 AE, n (%)	Atezolizumab (n = 165)	Placebo (n = 83)
Any-grade AE	138 (83.6)	71 (85.5)
• Any-grade treatment-related AE	81 (49.1)	42 (50.6)
Grade 3/4 AE	47 (28.5)	18 (21.7)
• Grade 3/4 treatment-related AE	12 (7.3)	3 (3.6)
Death due to AE	5 (3.0)	2 (2.4)
• Death due to treatment-related AE	3 (1.8)	0
Serious AE	44 (26.7)	17 (20.5)
• Treatment-related serious AE	9 (5.5)	0
AE leading to discontinuation of atezolizumab or placebo	15 (9.1)	3 (3.6)
AE leading to treatment interruption of atezolizumab or placebo	39 (23.6)	16 (19.3)
Immune-mediated AE	64 (38.8)	10 (12.0)
• Grade 3/4 immune-mediated AE	8 (4.8)	1 (1.2)
• Death due to immune-mediated AE	1 (0.6)	0

Clinical cutoff: June 15, 2025; median follow-up: 16.1 mo

SUMMARY

IMvigor011

- Adjuvant atezolizumab improved both DFS and OS in ctDNA-positive MIBC patients identified through serial MRD testing, with consistent benefit across key subgroups
- ctDNA status refined risk beyond traditional pathology, with similar efficacy in patients who were ctDNA+ at baseline or became ctDNA+ on repeat testing, while persistently ctDNA– patients had very low recurrence risk
- Atezolizumab showed a tolerable safety profile with no new safety signals

IMPACT

ctDNA monitoring can identify patients with muscle-invasive bladder cancer who benefit form adjuvant atezolizumab

Potential new personalized treatment guidance, not yet FDA approved

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Polling Question

*Based on the data from **KEYNOTE-905** and **IMVigor011** presented at ESMO 2025, which study do you believe will have the greater impact on your management approach for muscle-invasive bladder cancer (MIBC) or high-risk NMIBC?"*

KEYNOTE-905/EV-303 now approved

- KEYNOTE-905 (perioperative pembrolizumab +/– trimodality therapy)
- IMVigor011 (adjuvant atezolizumab guided by ctDNA positivity)
- Both equally
- Unsure

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2025 ESMO Key Studies

Breast Cancer

- *DESTINY-Breast11
- *DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*

- evERA BC
- VIKTORIA
  - *Polling Question*

GU GI

- *KEYNOTE-905/EV-303
- *IMvigor-011
  - *Polling Question*
- *PSMAddition
  - *Rapid Review*: CAPItello-281
- *Polling Question*
- *FORTITUDE-101
- *AGITG-DYNAMIC-III
  - *Polling Question*
- *RC48-C016
  - *Rapid Review*: POTOMAC

Lung Cancer and Other Notable Studies

- *HARMONI-6
- FLAURA2
  - *Polling Question*
- *OptiTROP-Lung04
  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

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*ESMO Presidential Session

PSMAddition

* Presidential Symposium

Does [177Lu]Lu-PSMA-617 combined with ADT + ARPI benefit patients with PSMA-positive metastatic hormone-sensitive prostate cancer?

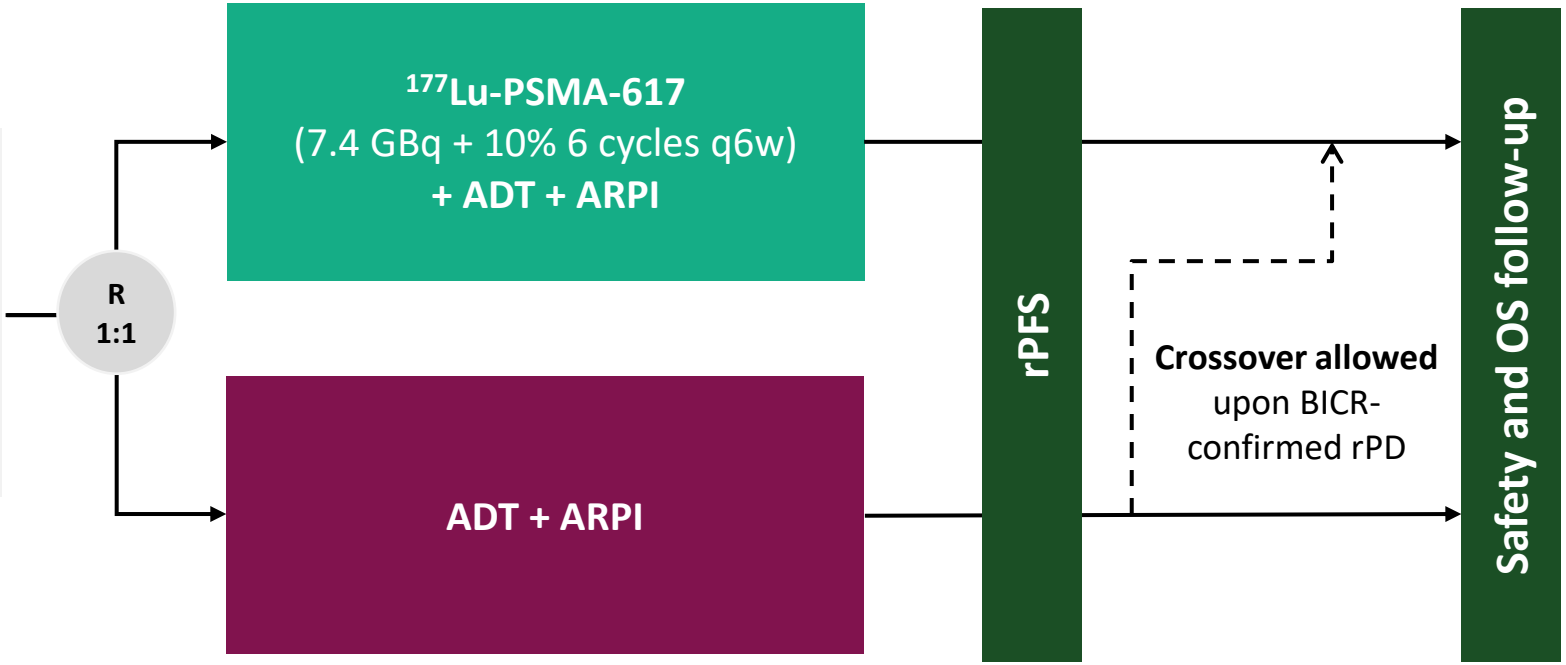
KEY DATA

PSMAddition: ^{177}Lu-PSMA-617 with ADT + ARPI in PSMA-positive metastatic hormone-sensitive prostate cancer

Study Design: Global, multicenter, randomized, phase 3 trial

- Untreated or minimally treated mHSPC
- ECOG PS 0-2
- >1 PSMA+ metastatic lesion on Ga-PSMA-11 PET/CT
- Appropriate for ADT + ARPI

Stratified by disease volume (high/low) – per CHAARTED criteria, age ≥70 years (yes/no), previous or planned treatment of primary tumor by radiation or prostatectomy (yes/no)



Primary Endpoint: radiographic PFS (rPFS) by BICR per PCWG3/RECIST v1.1

Key Secondary Endpoint: Overall Survival (OS)

Other secondary Endpoints: PSA90 Response, Time to mCRPC, PFS and PFS2, PSA <0.2 ng/mL at 12, 24, and 48 weeks, ORR, DCR, TTR, DOR, and TTSTP by BIRC per RECIST v1.1, safety and tolerability, time to worsening in patient-reported HRQoL and pain, time to first SSE

mHSPC: non-metastatic hormone-sensitive biochemical recurrence prostate cancer

KEY DATA

PSMAddition: ^{177}Lu-PSMA-617 with ADT + ARPI in PSMA-positive metastatic hormone-sensitive prostate cancer

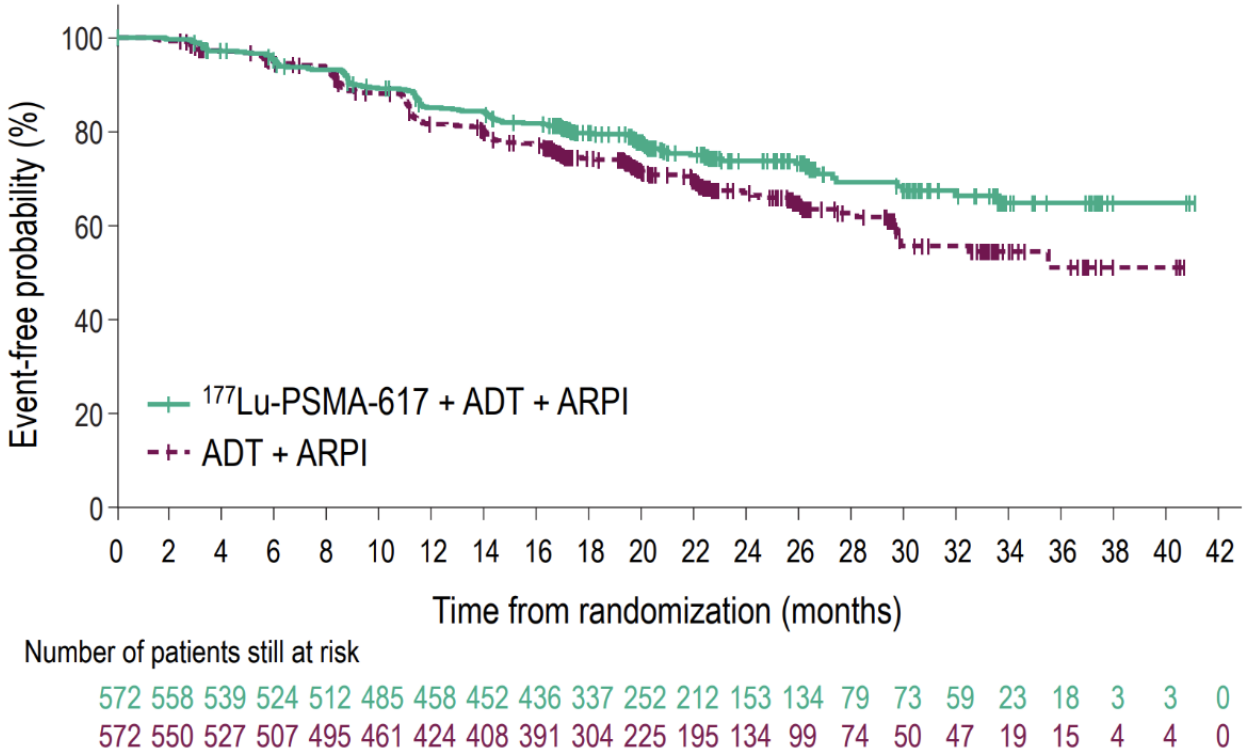
Baseline characteristics

Characteristic, n (%)	^{177}Lu-PSMA-617 + ADT + ARPI (n = 572)	ADT + ARPI (n = 572)
Age, years - median (range)	68.0 (38-91)	68.0 (36-90)
• ≥70 years	246 (43.0)	246 (43.0)
ECOG PS		
• 0	397 (69.4)	407 (71.2)
• 1	174 (30.4)	155 (27.1)
• 2	1 (0.2)	7 (1.2)
Site of disease		
• Soft tissue	342 (59.8)	338 (59.1)
• Bone	522 (91.3)	521 (91.1)
• Visceral	225 (39.3)	238 (41.6)
PSA level, ng/mL – median (interquartile range)	12.06 (3.16-53.34)	11.64 (2.83-44.15)
Gleason score 8-10 (grade group 4-5)	389 (68.0)	406 (71.0)
High tumor volume	389 (68.0)	390 (68.2)
De novo mHSPC	298 (52.1)	274 (47.9)

KEY DATA

PSMAddition: ^{177}Lu-PSMA-617 with ADT + ARPI in PSMA-positive metastatic hormone-sensitive prostate cancer

Primary Endpoint: rPFS by BIRC



	^{177}Lu-PSMA-617 + ADT + ARPI (n = 572)	ADT + ARPI (n = 572)
Event, n (%)	139 (24.3)	173 (30.1)
• rPD	112 (19.6)	152 (26.6)
• Death without rPD	27 (4.7)	30 (3.5)
HR (95% CI)	**0.72** (0.58, 0.90)	
***p* value**	0.002[a]	
Median rPFS (95% CI), mo	NR (NE, NE)	NR (29.7, NE)

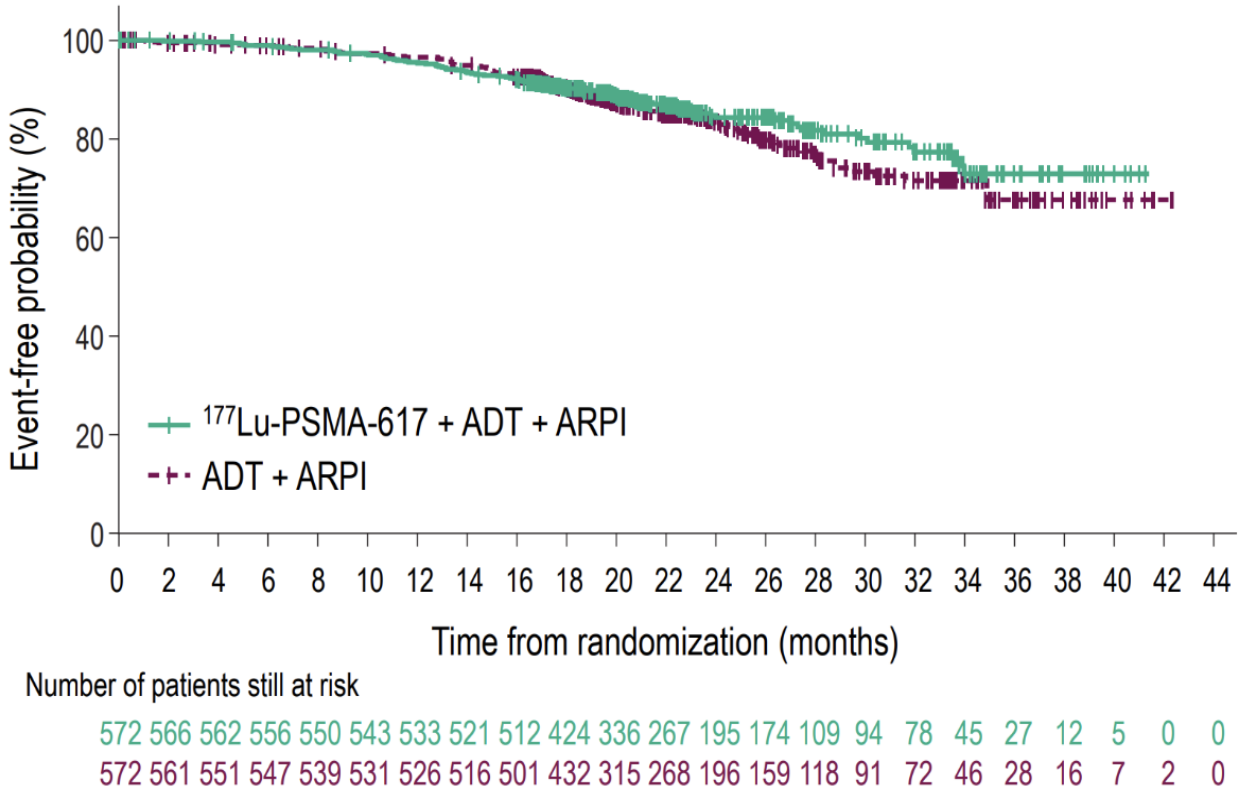
[a]Significance threshold at rPFS IA2: 0.009 (one-sided; stratified log-rank test); information fraction, 74.4%
NR: not reached

rPFS by subgroup analysis: favored ^{177}Lu-PSMA-617 with ADT + ARPI across all subgroups

KEY DATA

PSMAddition: ^{177}Lu-PSMA-617 with ADT + ARPI in PSMA-positive metastatic hormone-sensitive prostate cancer

Key Secondary Endpoint: Interim Overall Survival (prespecified intent-to-treat analysis, follow-up continues)



	^{177}Lu-PSMA-617 + ADT + ARPI (n = 572)	ADT + ARPI (n = 572)
Event, n (%)	85 (14.9)	99 (17.3)
Censored, n(%)	487 (85.1)	473 (82.7)
HR (95% CI)	**0.84** (0.63, 1.13)	
***p* value**	0.125	
Median rPFS (95% CI), mo	**NR** (NE, NE)	**NR** (NE, NE)

NR: not reached

KEY DATA

PSMAddition: ^{177}Lu-PSMA-617 with ADT + ARPI in PSMA-positive metastatic hormone-sensitive prostate cancer

Safety Summary

Patients with on-treatment AE, n (%)[a]	^{177}Lu-PSMA-617 + ADT + ARPI (n = 564)		ADT + ARPI (n = 565)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	555 (98.4)	286 (50.7)	546 (96.6)	243 (43.0)
• Related to any study treatment	504 (89.4)	128 (22.7)	394 (69.7)	69 (12.2)
• ^{177}Lu-PSMA-617-related	441 (78.2)	78 (13.8)	-	-
• ADT and/or APRI-related	418 (74.1)	81 (14.4)	394 (69.7)	69 (12.2)
Serious	180 (31.9)	150 (26.6)	162 (28.7)	129 (22.8)
• Related to any study treatment	39 (6.9)	31 (5.5)	14 (2.5)	12 (2.1)
• ^{177}Lu-PSMA-617-related	17 (3.0)	13 (5.5)	-	-
• ADT and/or APRI-related	27 (4.8)	22 (3.9)	14 (2.5)	12 (2.1)
Leading to death	15 (2.7)	15 (2.7)	14 (2.5)	14 (2.5)
• Treatment-related	0	0	0	0
Leading to discontinuation of any study treatment	91 (16.1)	46 (8.2)	51 (9.0)	23 (4.1)
Leading to ^{177}Lu-PSMA-617				
• Discontinuation	45 (8.0)	28 (5.0)	-	-
• Dose reduction	22 (3.9)	12 (2.3)	-	-
• Dose delay	68 (12.1)	27 (4.8)	-	-

[a]Investigator-assessed grade, seriousness and relationship

SUMMARY

PSMAddition

- Combining ^{177}Lu-PSMA-617 with ADT + ARPI improved rPFS in patients with PSMA-positive mHSPC
- OS data are immature
- Safety findings were consistent with the known profile of ^{177}Lu-PSMA-617 with ADT + ARPI with no unexpected concerns about combination with ADT+ARPI
- There were no clinically significant differences in time to worsening in HRQoL and pain

IMPACT

^{177}Lu-PSMA-617 with ADT + ARPI is a potential new treatment option for patients with PSMA-positive metastatic hormone-sensitive prostate cancer

Not yet FDA approved

cornerstone specialty network™

Polling Question

*Based on the **PSMAddition** results how likely are you to incorporate ^{177}Lu-PSMA-617 if approved in the mHSPC setting as an upfront treatment for eligible patients?*

Currently approved in PSMA-positive metastatic castration-resistant prostate cancer

- Very likely — the PSMAddition data are practice-changing
- Somewhat likely — will use for select high-risk patients
- Unsure — need to see longer-term survival or toxicity outcomes
- Unlikely — benefits do not outweigh added toxicity/cost for most patients
- Not at all likely — will continue with ADT + radiation alone

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ESMO 2025: RAPID REVIEWS

CAPItello-281

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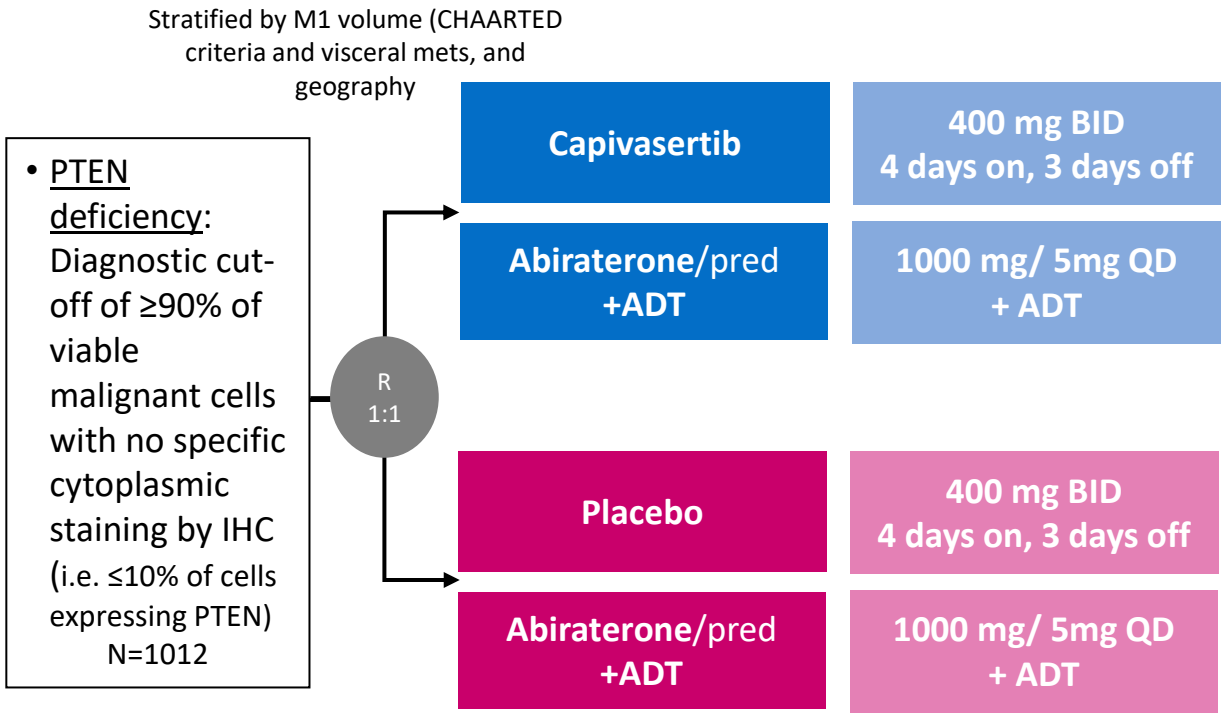
KEY DATA

CAPItello-281: Capivasertib + abiraterone in PTEN deficient de novo metastatic hormone-sensitive prostate cancer (Primary rPFS, data cutoff 7 Oct 2024; median rPFS follow-up 18 months)

Study Design: Global, multicenter, randomized, double-blind, phase 3 study



Primary endpoint: Investigator assessed radiographic PFS
Secondary endpoints: OS, time to first subsequent therapy, symptomatic skeletal-event free survival, time to pain progression, time to castration resistance, time to PSA progression

Select Baseline Characteristics

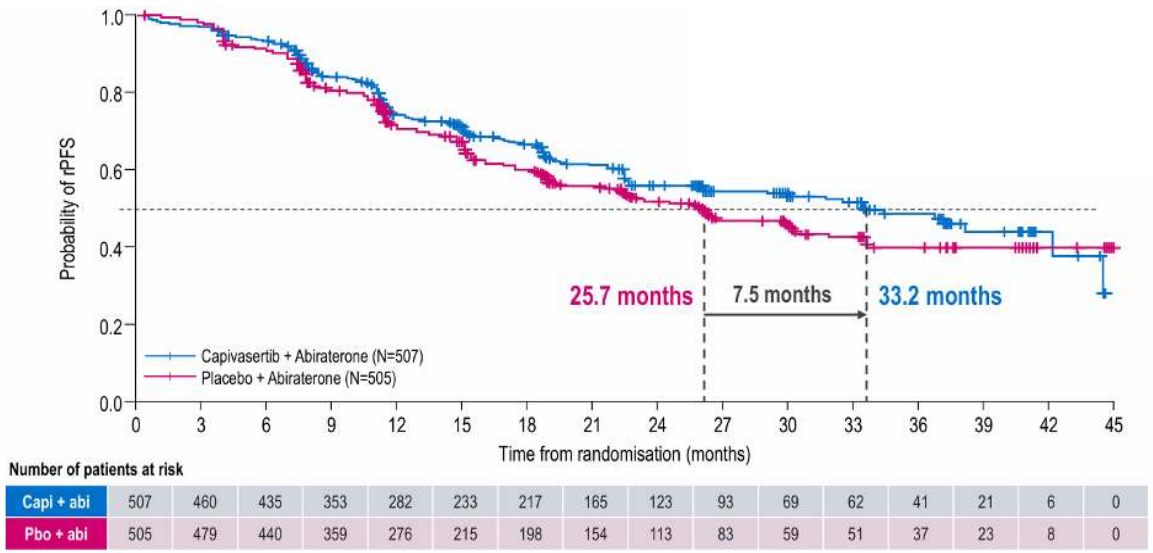
n (%)	Capi + abi (n=507)	Pbo + abi (n = 505)
Median age, years (range)	67.0 (42-87)	68.0 (43-88)
ECOG PS		
• 0	329 (64.9)	320 (63.4)
• 1	178 (35.1)	185 (36.6)
Metastases		
• Bone	462 (91.1)	467 (92.5)
• Liver	30 (5.9)	25 (5.0)
• Lung	69 (13.6)	72 (14.3)
• Non-regional lymph node	217 (42.8)	214 (42.4)
Median time form diagnosis to randomization, months (range)	2.46 (0.3-12.8)	2.45 (0.6-27.4)
Total Gleason score at diagnosis		
• Elevated (38-1,000 U/mL)	94 (61.3)	95 (18.8)
• High (>1,000 U/mL)	398 (78.5)	399 (79.0)
Disease risk		
• High	311 (61.3)	333 (65.9)
• Low	184 (36.3)	164 (32.5)
M1 volume/ visceral metastases		
• High vol. disease w/ visceral mets	98 (19.3)	95 (18.8)
• High vol. disease w/o visceral mets	276 (54.4)	283 (56.0)
• Low vol. disease	131 (25.8)	126 (25.0)

Ann Oncol. 2025 Oct 19:S0923-7534(25)04936-1

KEY DATA

CAPItello-281: Capivasertib + abiraterone in PTEN deficient de novo metastatic hormone-sensitive prostate cancer

Primary Endpoint: Investigator assessed rPFS

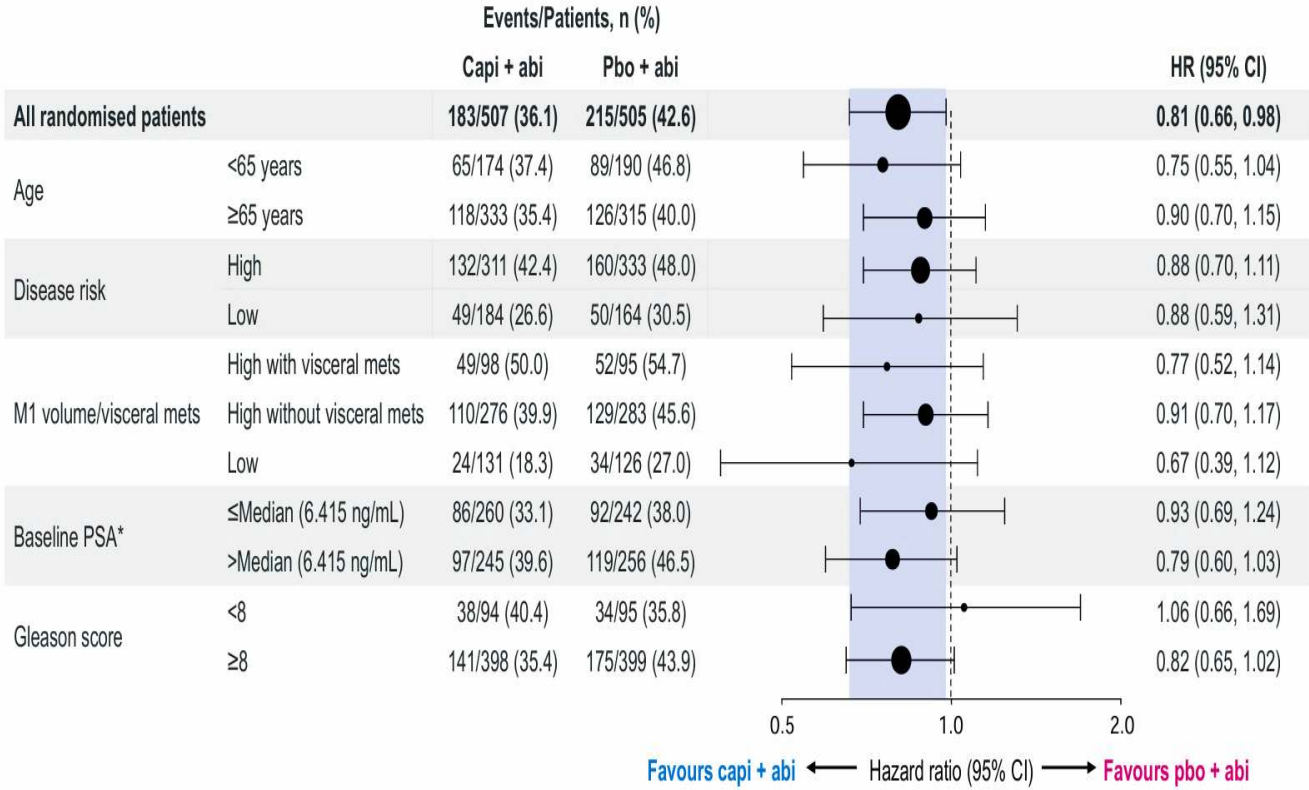


Number of patients at risk

Capi + abi	507	460	435	353	282	233	217	165	123	93	69	62	41	21	6	0
Pbo + abi	505	479	440	359	276	215	198	154	113	83	59	51	37	23	8	0

	Capi + abi (n=507)	Pbo + abi (n = 505)
Events, n (%)	183 (36.1)	215 (42.6)
Median rPFS, months (95% CI)	**33.2** (25.8, 44.2)	**25.7** (22.0, 29.9)
HR (95% CI)	**0.81 (0.66, 0.98)**	
***P*-value**	0.034	

Investigator-assessed rPFS by prespecified subgroups



Ann Oncol. 2025 Oct 19:S0923-7534(25)04936-1

KEY DATA

CAPItello-281: Capivasertib + abiraterone in PTEN deficient de *novo* metastatic hormone-sensitive prostate cancer

Secondary Endpoints

	Events, n (%)	Capi + abi	Pbo + abi	HR (95% CI)
Overall survival **Interim** (26% data maturity)	267 (26.4)	NC	NC	0.90 (0.71, 1.15)
Time to next treatment	398 (39.3)	37.0	28.5	0.91 (0.75, 1.11)
Time to SSE-FS	326 (32.2)	42.5	37.3	0.82 (0.66, 1.02)
Time to pain progression	87 (8.6)	NC	NC	1.14 (0.75, 1.75)
CRPC	416 (41.1)	29.5	22.0	0.77 (0.63, 0.95)
PSA progression	142 (14.0)	NC	NC	0.73 (0.52, 1.01)

Safety Summary	Capi + abi (n=507)	Pbo + abi (n = 505)
AEs of any cause	497 (98.8)	463 (92.0)
Any AE Grade ≥3	337 (67.0)	203 (40.4)
Any SAE	214 (42.5)	131 (26.0)
Any AE leading to death	36 (7.2)	26 (5.2)
Any AE leading to discontinuation of capi/pbo	92 (18.3)	24 (4.8)
Any AE leading to discontinuation of abiraterone	48 (9.5)	27 (5.4)
Any AE leading to interruption of capi/pbo	316 (62.8)	135 (26.8)
Any AE leading to interruption of abiraterone	238 (47.3)	127 (25.2)
Any AE leading to reduction of capi/pbo	146 (29.0)	18 (3.6)
Any AE leading to reduction of abiraterone	49 (9.7)	27 (5.4)

Capivasertib + abiraterone is a potential new targeted treatment option for patients with PTEN deficient de novo metastatic hormone-sensitive prostate cancer – not yet approved *(only approved in breast cancer)*

Ann Oncol. 2025 Oct 19:S0923-7534(25)04936-1

2025 ESMO Key Studies

Breast Cancer

- *DESTINY-Breast11
- *DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*

- evERA BC
- VIKTORIA
  - *Polling Question*

GU GI

- *KEYNOTE-905/EV-303
- *IMvigor-011
  - *Polling Question*
- *PSMAddition
  - *Rapid Review*: CAPItello-281
- *Polling Question*
- *FORTITUDE-101
- *AGITG-DYNAMIC-III
  - *Polling Question*
- *RC48-C016
  - *Rapid Review*: POTOMAC

Lung Cancer and Other Notable Studies

- *HARMONI-6
- FLAURA2
  - *Polling Question*
- *OptiTROP-Lung04
  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

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*ESMO Presidential Session

CLINICAL QUESTION

FORTITUDE-101

* Presidential Symposium

Does bemarituzumab (BEMA) plus chemotherapy benefit patients with advanced or metastatic FGFR2b overexpressing gastric or gastroesophageal junction cancer (G/GEJC)?

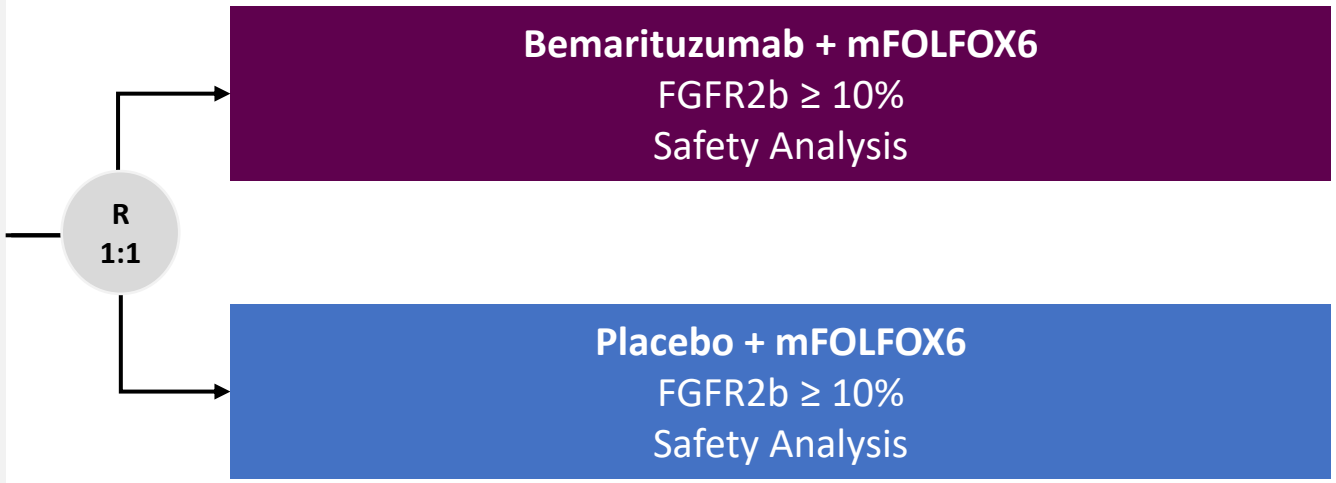
KEY DATA

FORTITUDE-101: 1L bemarituzumab + chemotherapy in advanced or metastatic FGFR2b overexpressing Gastric/GEJ

Study Design: A global phase 3, randomized, double blind trial

- No prior therapy for locally irresectable or metastatic gastric or GEJ adenocarcinoma
  - One cycle of mFOLFOX permitted
- FGFR2b overexpression (2+/3+) at any % of tumor cells by central UHC, later amended to ≥ 10% 2+/3+ tumor cells staining*
- Not know to be HER2-positive

Stratified by geography (US/EU vs Japan/South Korea vs ROW), ECOG (0 vs 1), PD-L1 status (CPS ≥5 vs <5 or indeterminate)



Treatment on bemarituzumab (15 mg/kg Q2W +7.5 mg/kg on cycle 1 day 8)

Primary endpoint: Overall Survival (OS) in FGFR2b ≥ 10% 2+/3+ Tumor Cells

Key Secondary endpoint: Progression-free Survival (PFS) in FGFR2b ≥ 10% 2+/3+ Tumor Cells, ORR in FGFR2b ≥ 10% 2+/3+ Tumor Cells, safety in all randomized patients

KEY DATA

FORTITUDE-101: 1L bemarituzumab + chemotherapy in advanced or metastatic FGFR2b overexpressing Gastric/GEJ

Baseline characteristics

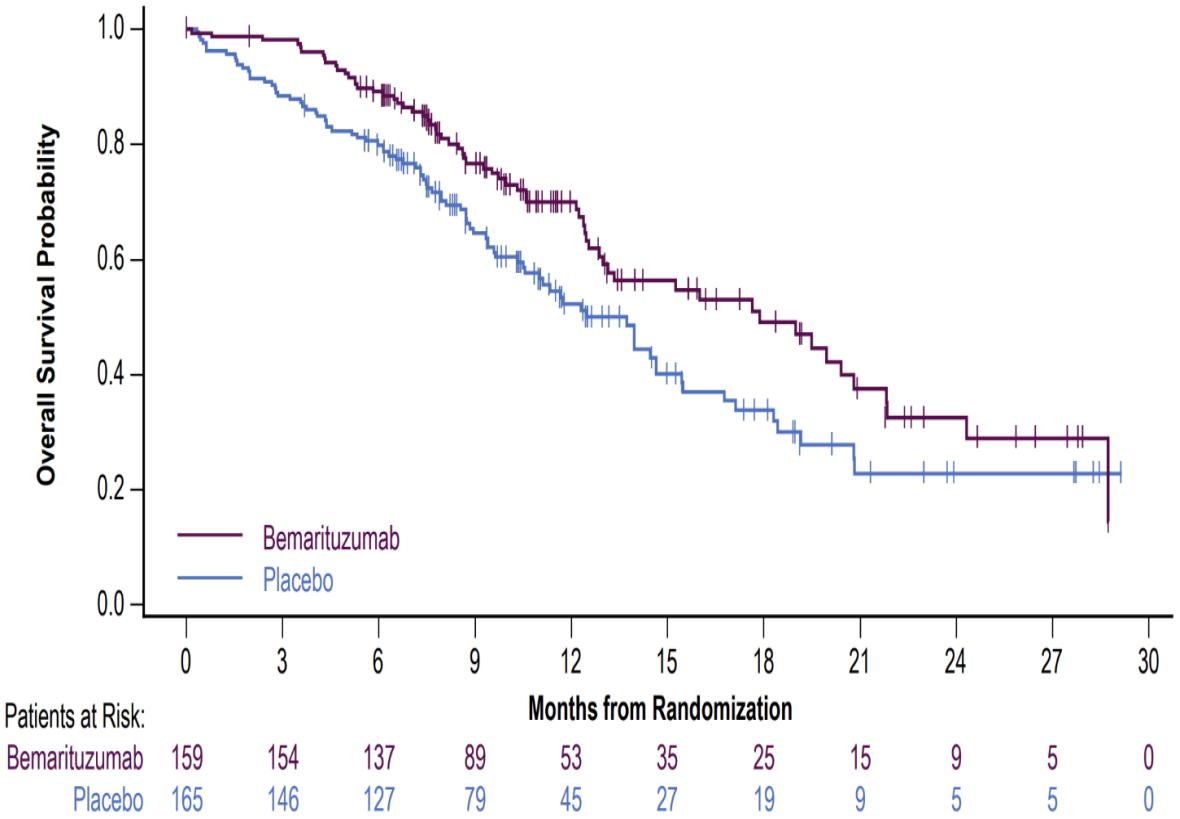
%	Efficacy Analysis Set FGFR2b Overexpression (≥ 10% of Tumor Cells)		Safety Analysis Set	
	Bemarituzumab (n=159)	Placebo (n= 165)	Bemarituzumab (n=275)	Placebo (n= 267)
Age, median (range), years	62 (25-82)	62 (27-83)	62 (21-86)	62 (26-88)
Male	68	67	71	66
Region				
• Asia	57	53	40	40
• Non-Asia	43	47	60	60
ECOG PS 1	61	58	54	56
Primary site				
• Gastric	80	81	78	84
• GEJ	20	19	22	16
Metastatic disease	96	95	98	96
Liver metastases	36	37	38	35
Lauren classification diffuse	22	22	27	29
PD-L1 CPS ≥ 5	37	38	34	32
Prior dose of mFOLFOX6	47	42	46	43

KEY DATA

FORTITUDE-101: 1L bemarituzumab + chemotherapy in advanced or metastatic FGFR2b overexpressing Gastric/GEJ

Primary Endpoint: Overall Survival (OS)

Patients with FGFR2b overexpression in ≥ 10 % of tumor cells



Median follow-up 11.8 mo	Bemarituzumab (n=159)	Placebo (n= 165)
mOS (95% CI)	**17.9** (13.0-20.8)	12.5 (10.5-14.7)
HR (95% CI)	**0.61** (0.43-0.86)	
p-value	0.005 (2-sided)	

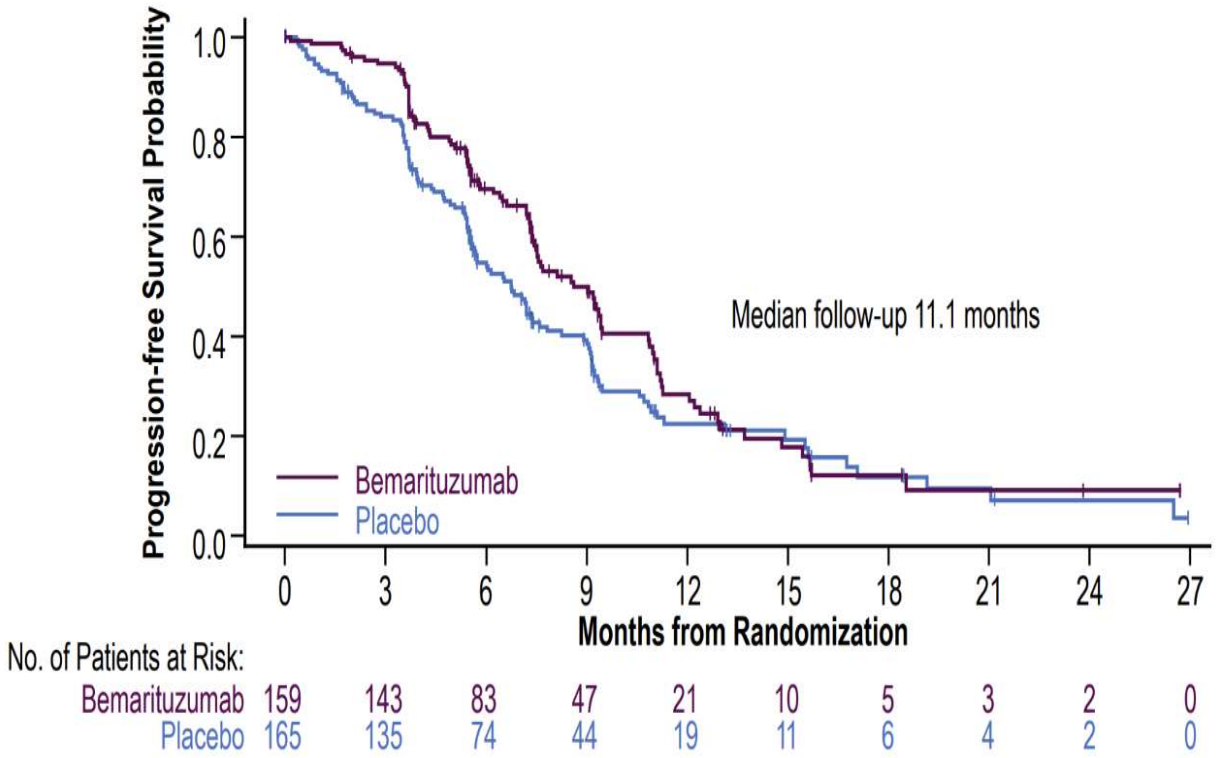
Longer follow-up

Median follow-up 19.4 mo	Bemarituzumab (n=159)	Placebo (n= 165)
mOS (95% CI)	**14.5** (13.0-17.9)	13.2 (10.9-14.7)
HR (95% CI)	**0.82 (0.62-1.08)**	

KEY DATA

FORTITUDE-101: 1L bemarituzumab + chemotherapy in advanced or metastatic FGFR2b overexpressing Gastric/GEJ

Key Secondary Endpoints: Progression Free Survival



	Bemarituzumab (n=159)	Placebo (n= 165)
Median PFS (95% CI), mo	8.6 (7.5-9.5)	6.7 (5.6-7.6)
HR (95% CI)	**0.71** (0.53, 0.95)	
p value	0.-19 (2-sided)	
Objective Response Rate (95% CI) %	45.9 (38.0-54.0)	44.8 (37.1-52.8)
P-value	0.90 (2-sided)	
Median Duration (95% CI), mo	7.0 (5.3-9.3)	5.8 (5.0-7.3)

KEY DATA

FORTITUDE-101: 1L bemarituzumab + chemotherapy in advanced or metastatic FGFR2b overexpressing Gastric/GEJ

Safety Summary

	Bemarituzumab (n=275)	Placebo (n= 267)
Duration of Bema/Placebo, median (range), weeks	22 (< 1-136)	25 (< 1-154)
Duration of mFOLFOX6, median (range), weeks	25 (< 1-148)	23 (< 1-154)
Treatment-emergent adverse events, %		
• Any grade	> 99	98
• Grade ≥3	90	79
• Leading to interruption of IP	68	40
• Leading to withdrawal of IP	28	6
Treatment-related adverse events, %		
• Any grade	89	66
• Grade ≥3	60	18
• Leading to interruption of IP	52	12
• Leading to withdrawal of IP	24	1
• Fatal adverse events	0	< 1

SUMMARY

FORTITUDE-101

IMPACT

- Bemarituzumab plus chemotherapy achieved overall survival and key secondary endpoint of PFS in patients with FGFR2b overexpression (≥10% of tumor cells)
- The overall survival benefit attenuated at a subsequent descriptive follow-up analysis
- Safety profile of bemarituzumab was manageable
  - Primarily corneal adverse events with associated decrease in visual acuity. Visual acuity reduction was transient and mostly reversable

Bemarituzumab plus chemotherapy is a potential new treatment option in the first-line setting for patients with advanced or metastatic FGFR2b overexpressing gastric or gastroesophageal junction cance

Not yet approved

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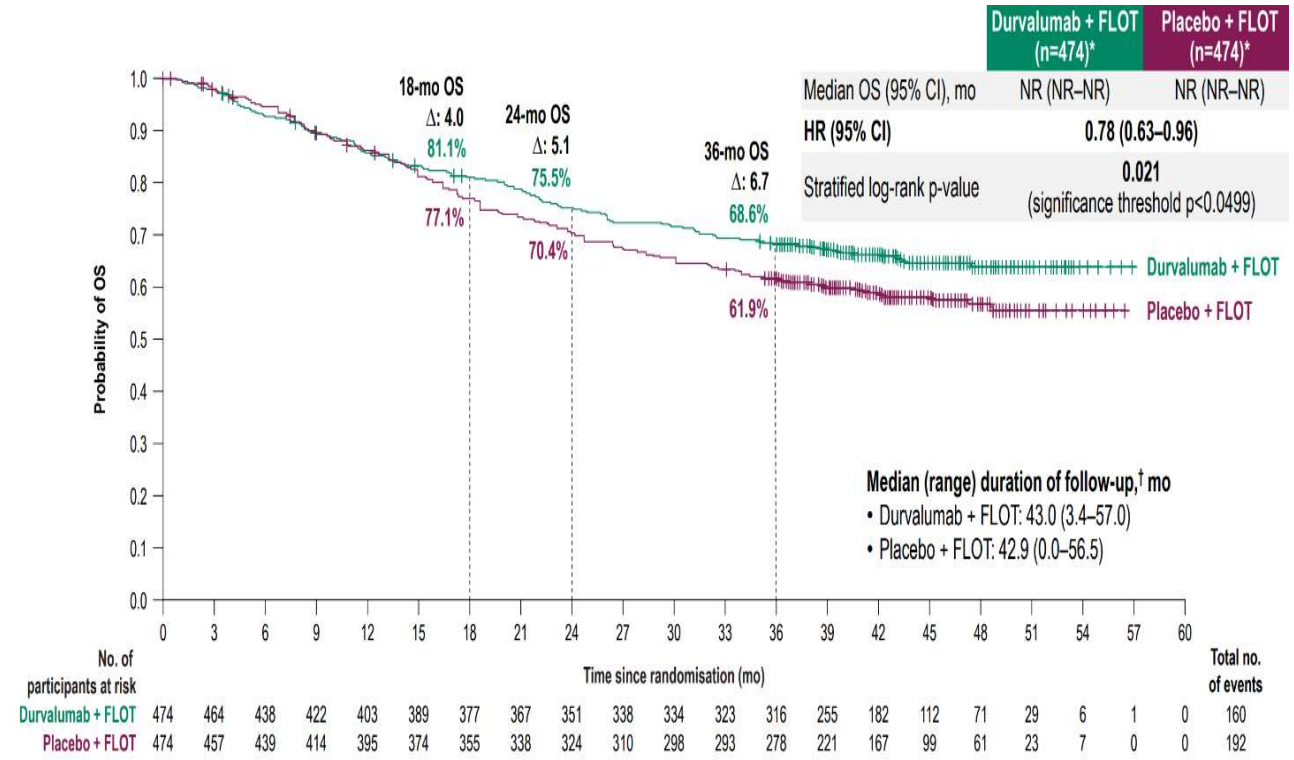
Recent FDA approval

- On **November 25, 2025**, the FDA approved **durvalumab (Imfinzi, AstraZeneca) with FLOT (**fluorouracil, leucovorin, oxaliplatin, and docetaxel) as **neoadjuvant and adjuvant** treatment, followed by single agent durvalumab, for adults with resectable gastric or gastroesophageal junction adenocarcinoma (GC/GEJC).
- **MATTERHORN:** a randomized, double-blind, placebo-controlled, multicenter trial conducted in 948 patients with previously untreated and resectable, Stage II to Stage IVA, GC/GEJC. Patients were randomized (1:1) to receive either durvalumab and FLOT or placebo and FLOT.

Final overall survival at ESMO 2025



ESMO 2025. Abstr. LBA81

2025 ESMO Key Studies

Breast Cancer

- *DESTINY-Breast11
- *DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09

- ASCENT-03
- TROPION-Breast02
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- evERA BC
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GU GI

- *KEYNOTE-905/EV-303
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- *FORTITUDE-101
- *AGITG-DYNAMIC-III
  - *Polling Question*
- *RC48-C016
  - *Rapid Review*: POTOMAC

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  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

*ESMO Presidential Session

CLINICAL QUESTION

AGITG DYNAMIC-III

* Presidential Symposium

Does ctDNA-Guided adjuvant chemotherapy treatment de-escalation benefit patients with stage III colon cancer?

KEY DATA

AGITG DYNAMIC-III: ctDNA-guided adjuvant chemotherapy treatment de-escalation in stage III colon cancer

Study Design: Randomized, Phase 2/3

- R0 resection
- ECOG 0-2
- Fit for at least a fluoropyrimidine (FP)
- Staging CT within 12 weeks
- Provision of adequate tumor tissue <6 weeks post-operation
- No synchronous colorectal cancer

Stratified by clinical risk (low vs high) and sites

R 1:1

ctDNA-Informed Management

- ctDNA-negative → De-escalate
- ctDNA-positive → Escalate

1 cycle of pre-planned chemotherapy allowed prior to ctDNA-informed regimen

Standard Management

- Treatment per clinician's choice (blinded to ctDNA results)

Pre-Planned SoC → De-escalation

6M → No chemo or 3M FP

3M Oxaliplatin + FP → 3-6M FP

6M Oxaliplatin + FP → 3M oxaliplatin + FP or 6M FP

FP = fluoropyrimidine

Primary endpoint: 3-year recurrence-free survival (RFS)

Key Secondary endpoint: Treatment adherence, safety

ESMO 2025. Abstr. LBA9
Nat Med (2025).

KEY DATA

AGITG DYNAMIC-III: ctDNA-guided adjuvant chemotherapy treatment de-escalation in stage III colon cancer

Secondary Endpoint: Treatment Delivery and Adherence: ctDNA-Negative

N (%)	ctDNA-Informed De-Escalation N = 353	Standard Management N = 349
Commenced per protocol treatment	319 (90.4)	347 (99.4)
Chemotherapy received		
▪ No chemotherapy	26 (7.4)	8 (2.3)
▪ 3M Single agent FP	119 (33.7)	1 (0.3)
▪ 6M Single agent FP	85 (24.1)	31 (8.9)
▪ 3M Oxaliplatin doublet	117 (33.1)	166 (47.6)
▪ 6M Oxaliplatin doublet	6 (1.7)	143 (41.0)
Time from surgery to commencing chemotherapy, median (IQR), days	56 (51, 63)	53 (48, 59)
Treatment duration, mean (SD), days	101 (43.4)	118 (48)
Completed planned treatment cycles	294 (89.9)	282 (82.7)

ESMO 2025. Abstr. LBA9
Nat Med (2025).

KEY DATA

AGITG DYNAMIC-III: ctDNA-guided adjuvant chemotherapy treatment de-escalation in stage III colon cancer

Secondary Endpoint: Safety (ctDNA-negative cohort)

N (%)	ctDNA-Informed De-Escalation N = 353	Standard Management N = 349	*P value*
Treatment-related hospitalization	30 (8.5)	46 (13.2)	0.047
Grade 3 or 4 TRAW of interest*, any	22 (6.2)	37 (10.6)	0.037
▪ Febrile neutropenia	3 (0.8)	5 (1.4)	
▪ Diarrhea	19 (5.4)	30 (8.6)	
▪ Oral mucositis	2 (0.6)	6 (1.6)	
▪ Nausea	11 (3.1)	15 (4.3)	
▪ Vomiting	8 (2.3)	8 (2.3)	

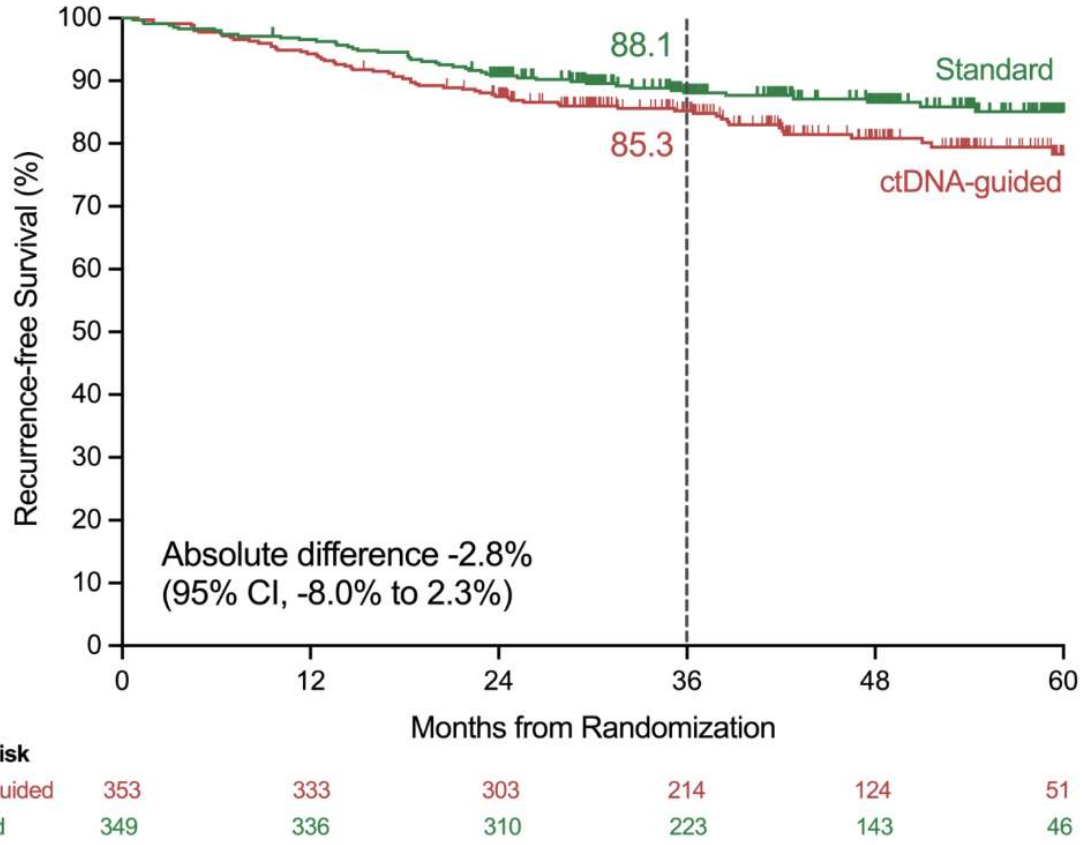
*Only high-grade adverse events of special interest were collected in the study given the well-known toxicity profile of all agent; TRAE=treatment related adverse events

ESMO 2025. Abstr. LBA9
Nat Med (2025).

KEY DATA

AGITG DYNAMIC-III: ctDNA-guided adjuvant chemotherapy treatment de-escalation in stage III colon cancer

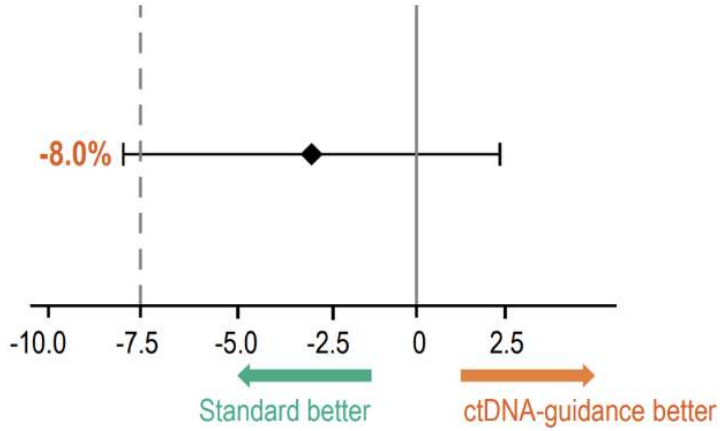
Primary Endpoint: Recurrence-Free Survival



Median follow-up 47 months (0.68 - 67.0)

	ctDNA (n=353)	Standard (n= 349)
Events	63	45
3-year RFS (95% CI)	85.3%	88.1%

Absolute Difference in 3-year RFS (95% CI)



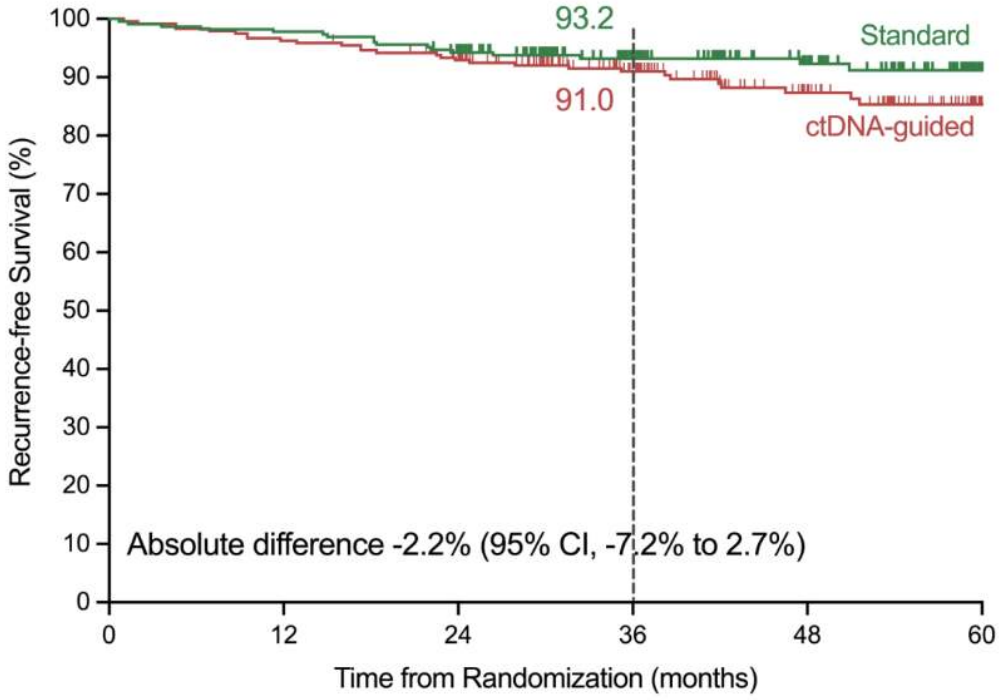
ESMO 2025. Abstr. LBA9
Nat Med (2025).

KEY DATA

AGITG DYNAMIC-III: ctDNA-guided adjuvant chemotherapy treatment de-escalation in stage III colon cancer

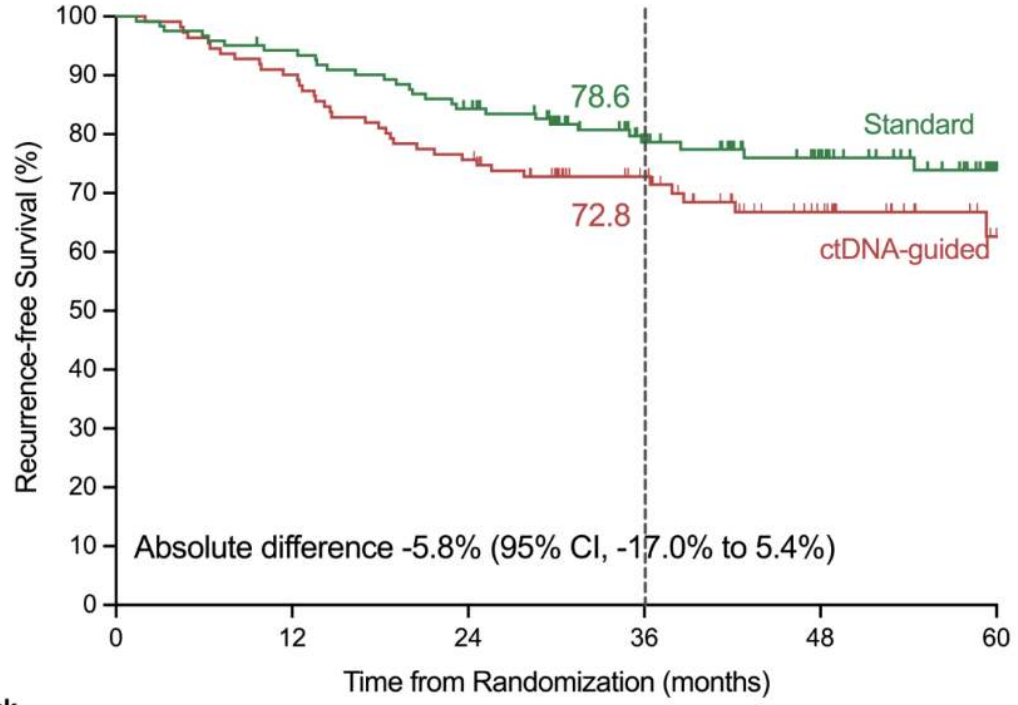
Recurrence-Free Survival by Clinical Risk

Clinical Low Risk (T1-3N1)



No. at Risk						
ctDNA-guided	242	233	219	160	93	39
Standard	227	222	209	152	95	32

Clinical High Risk (T1-3N1)



No. at Risk						
ctDNA-guided	111	100	84	54	31	12
Standard	122	114	101	71	48	14

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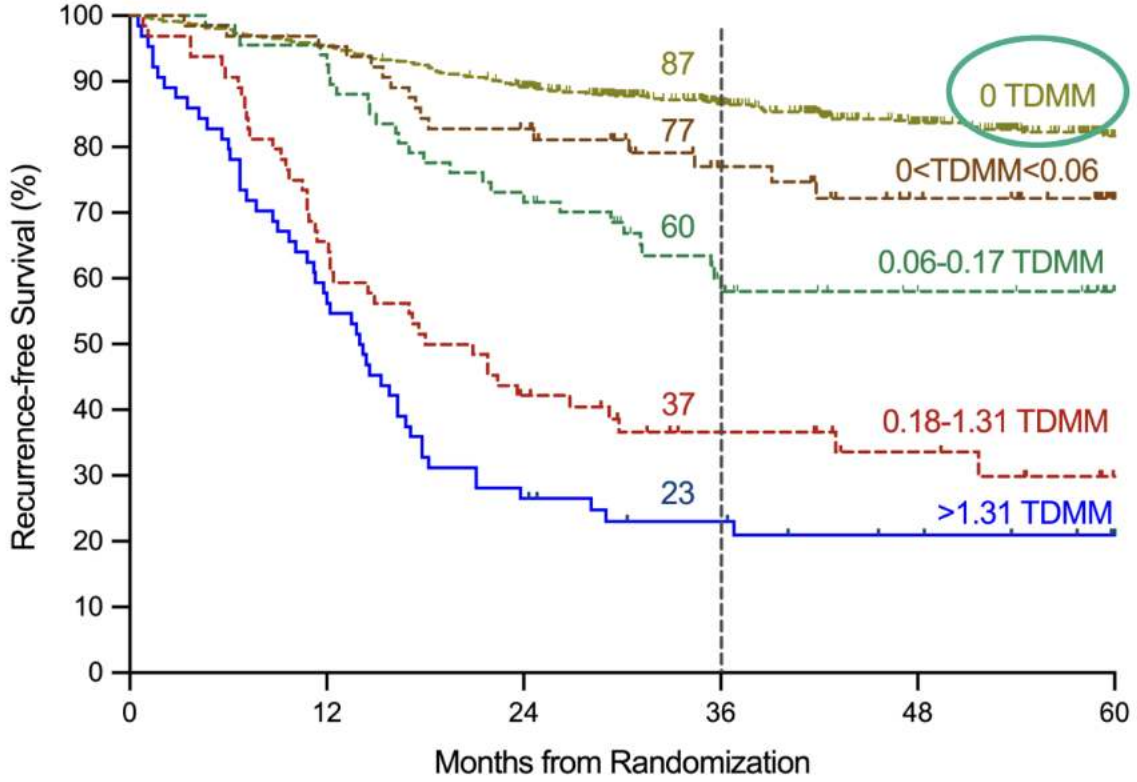
ESMO 2025. Abstr. LBA9
Nat Med (2025).

KEY DATA

AGITG DYNAMIC-III: ctDNA-guided adjuvant chemotherapy treatment de-escalation in stage III colon cancer

Recurrence-Free Survival: ctDNA-negative vs ctDNA positive



No. at Risk						
>1.31 TDMM	64	36	17	12	8	3
0.18-1.31 TDMM	64	42	25	16	10	3
0.06-0.17 TDMM	67	63	48	32	24	10
0<TDMM<0.06	64	61	52	34	22	6
0 TDMM	702	669	613	437	267	97

RFS by ctDNA Molecular Burden (Quartiles)

TDMM / mL	RFS HR (90% CI)	P-value
1.31	1	<.0001
0.18-1.31	0.67 (0.47, 0.94)	-
0.06-0.17	0.28 (0.19, 0.42)	-
>0 to <0.06	0.17 (0.10, 0.27)	-
0 (ctDNA-negative)	0.10 (0.07, 0.13)	-

TDMM – Tumor derived mutant molecule

ESMO 2025. Abstr. LBA9
Nat Med (2025).

SUMMARY

AGITG DYNAMIC-III

- ctDNA-guided de-escalation was feasible and safer, with high adherence, reducing oxaliplatin exposure, and fewer grade 3 AEs or hospitalizations
- Recurrence risk remained low in ctDNA-negative patients (3-yr RFS ~87%), though non-inferiority vs standard care wasn't confirmed overall; outcomes were similar in low-risk (T1–3N1) disease
- Findings support individualized risk–benefit discussions, and further investigation of ctDNA-informed de-escalation strategies is warranted

IMPACT

ctDNA-guided de-escalation of adjuvant chemotherapy treatment may be a new standard of care for patients with stage III colon cancer

Not yet FDA approved

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Polling Question

*The **AGITG DYNAMIC-III** trial evaluated the use of ctDNA-guided adjuvant chemotherapy decisions in stage II colorectal cancer. Based on these findings, how likely are you to integrate ctDNA-guided therapy to guide adjuvant chemotherapy in your stage II colon cancer patients?*

- Very likely — ctDNA guidance will help avoid unnecessary chemotherapy and tailor treatment
- Somewhat likely — will consider ctDNA results alongside other clinical factors
- Unsure — need more validation and longer follow-up data before widespread use
- Unlikely — prefer to rely on traditional clinicopathologic risk factors alone
- Very unlikely — will not change current practice based on this trial

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  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

*ESMO Presidential Session

CLINICAL QUESTION

RC48-C016

* Presidential Symposium

Disitamab vedotin (DV) plus toripalimab versus chemotherapy in first-line locally advanced or metastatic urothelial carcinoma (la/mUC) with HER2-expression?

RC48-C016: 1L HER2-positive or HER2-low la/mUC cancer

Study Design: Open-label, multicenter, randomized, phase 3 trial

- No prior systemic treatment for unresectable locally advanced or metastatic UC
- Central lab-confirmed HER2 IHC 1+, 2+, or 3+
- Measurable disease per RECIST v1.1
- Eligible for cisplatin or carboplatin
- ECOG PS 0 or 1

Stratified by cisplatin-eligibility (eligible vs ineligible), HER2 expression status (1+ vs 2+/3+), and visceral metastases (present vs absent)

R 1:1

Disitamab vedotin + Toripalimab (DV + T)
No set maximum cycles

1 cycle of pre-planned chemotherapy allowed prior to ctDNA-informed regimen

Gemcitabine + Cisplatin/Carboplatin
Maximum 6 cycles

Until disease progression/death, intolerable toxicity, or consent withdrawal

In the chemo group, assignment of cisplatin or carboplatin was protocol-defined. Chemo was administered for a maximun of 6 cycles
Statistical plan for analysis: the first analysis was planned to be performed after approximately 278 PFS (final) and 183 OS events (interim)

Dual Primary endpoints: Progression-free survival (PFS) by BICR and Overall Survival (OS)
Secondary endpoints: PFS assessed by investigators, ORR (per RECIST v1.1), DCR, and DoR assessed by BICR and investigators, safety, QoL, PK and immunogenics

RC48-C016: 1L HER2-positive or HER2-low la/mUC cancer

Baseline characteristics

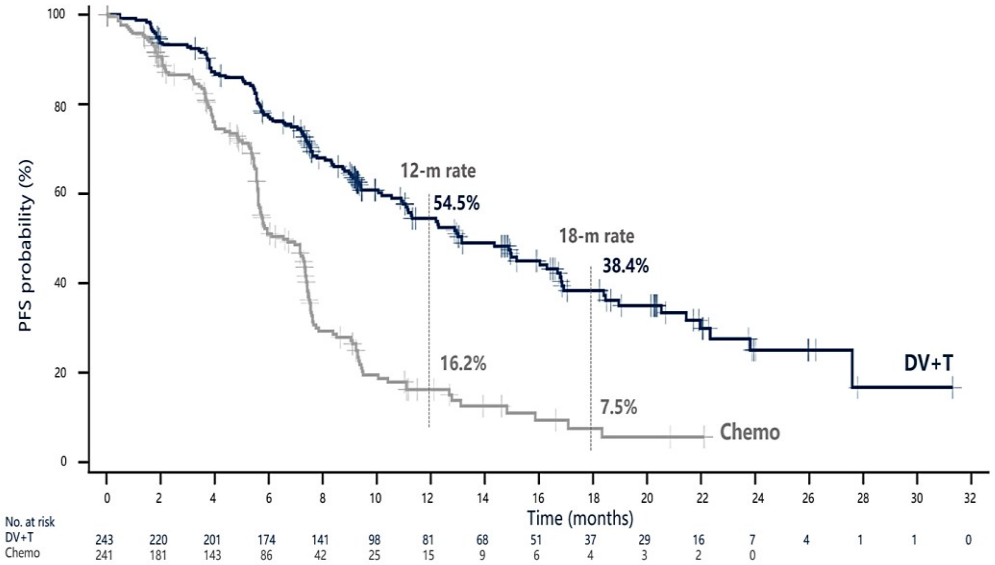
Characteristic, n (%)	DV + T (n = 243)	Chemo (n = 241)
Median (yrs), median (range)	66.0 (39-84)	67.0 (33-85)
Age ≥65 years	137 (56.4)	147 (61.0)
Sex		
• Male	176 (72.4)	168 (69.7)
• Female	67 (27.6)	73 (30.3)
ECOG PS		
• 0	61 (25.1)	65 (27.0)
• **1**	**182 (74.9)**	**176 (73.0)**
Clinical Stage		
• III	10 (4.1)	8 (3.3)
• **IV**	**233 (95.9)**	**233 (96.7)**
Primary site of origin of urothelial cancer		
• **Upper tract**	**111 (45.7)**	**122 (50.6)**
• Lower tract	130 (53.5)	119 (49.4)
• Other	2 (0.8)	0
Visceral metastases		
• Absent	119 (49.0)	115 (47.7)
• **Present**	**124 (51.0)**	**126 (52.3)**
HER2 expression		
• IHC 1+	55 (22.6)	53 (22.0)
• **IHC 2+ or 3+**	**188 (77.4)**	**188 (78.0)**
• IHC 2+	127 (52.3)	142 (58.9)
• IHC 3+	61 (25.1)	46 (19.1)
Cisplatin eligibility status		
• Eligible	127 (52.3)	128 (53.1)
• **Ineligible**	**116 (47.7)**	**113 (46.9)**
PD-L1 expression*		
• CPS <1	68/ 125 (54.4)	24/ 57 (42.1)
• CPS >1	57/ 125 (45.6)	33/ 57 (57.9)

*PD-L1 expression was assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Inc; CA 93013 United States)

RC48-C016: 1L HER2-positive or HER2-low la/mUC cancer

Dual Primary Endpoints: Progression-Free Survival (PFS) by BIRC

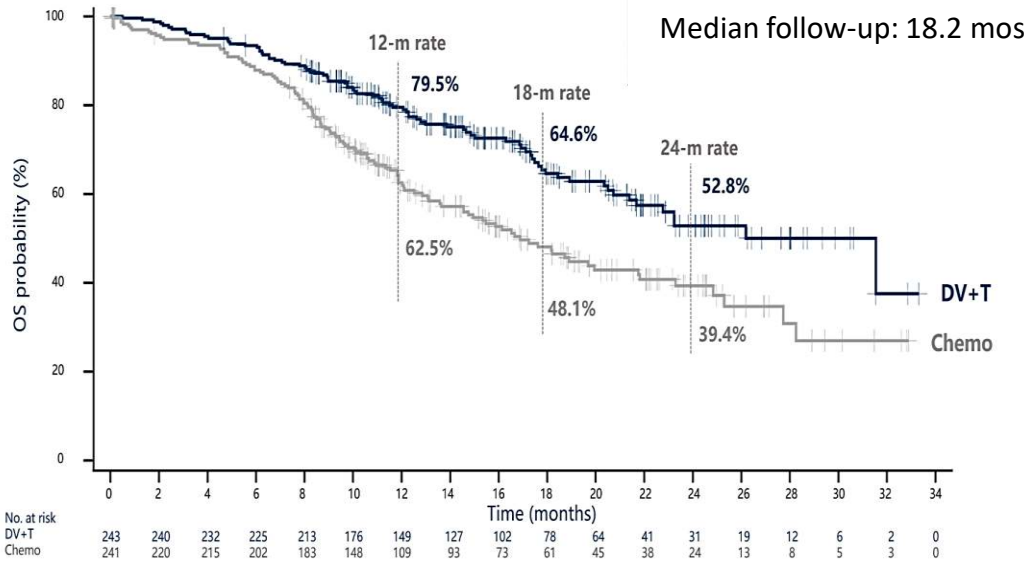
	DV + T (n = 243)	Chemo (n = 241)
Median PFS (95% CI), mo	**13.1** (11.1-16.7)	6.5 (5.7-7.4)
Stratified HR (95% CI)	**0.36** (0.28-0.46)	
2-sided P	<0.0001	



Overall Survival (OS)

	DV + T (n = 243)	Chemo (n = 241)
Median OS (95% CI), mo	**31.5** (21.7-NE)	16.9 (14.6-21.7)
Stratified HR (95% CI)	**0.54** (0.41-0.73)	
2-sided P	<0.0001	

Median follow-up: 18.2 mos

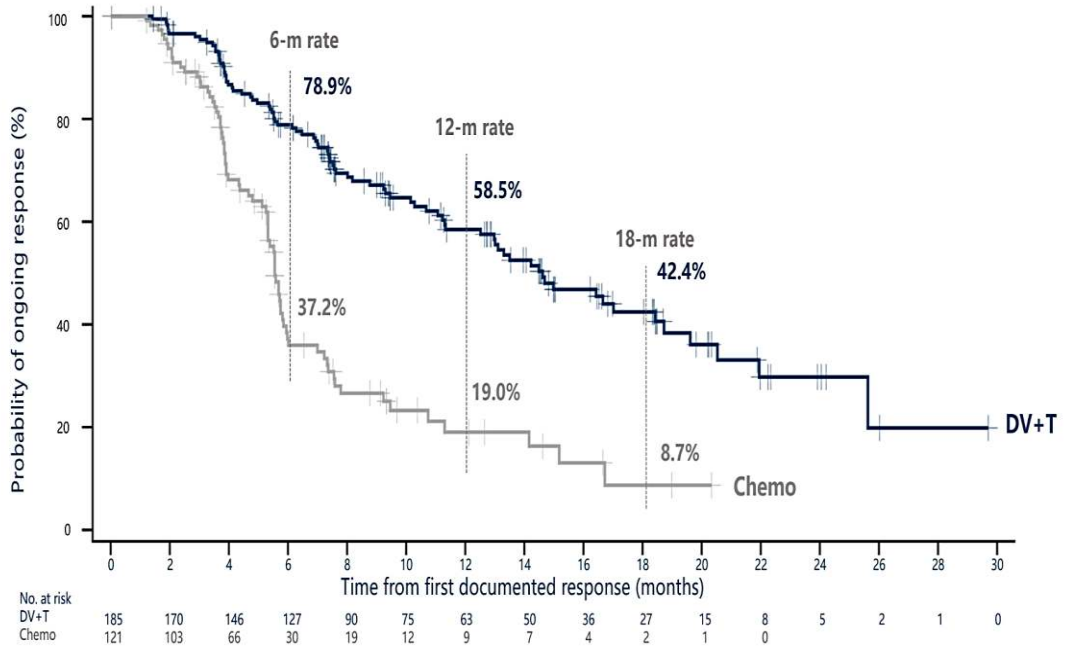


PFS and OS benefit in favor of DV+T across all subgroups, including HER2 expression status (1+ vs 2+/3+)

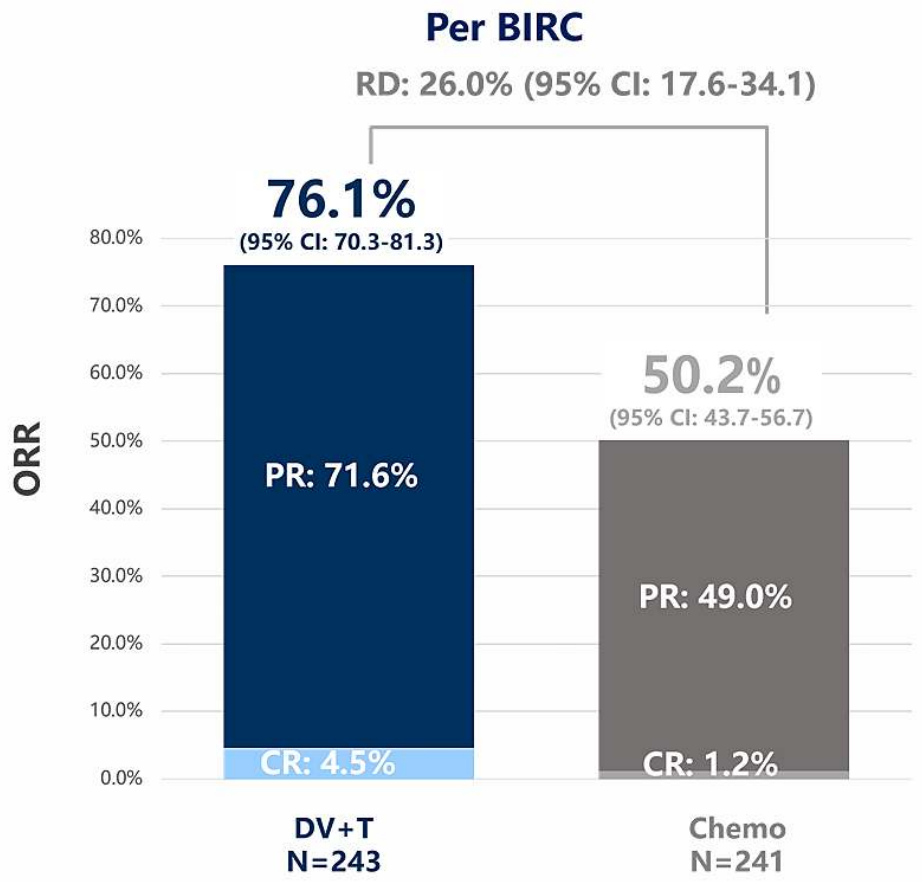
RC48-C016: 1L HER2-positive or HER2-low la/mUC cancer

Secondary Endpoints: Duration of Response (DoR)

	DV + T (n = 185)	Chemo (n = 121)
Median DoR (95% CI), mo	**14.6** (11.3-18.7)	5.6 (5.3-5.8)

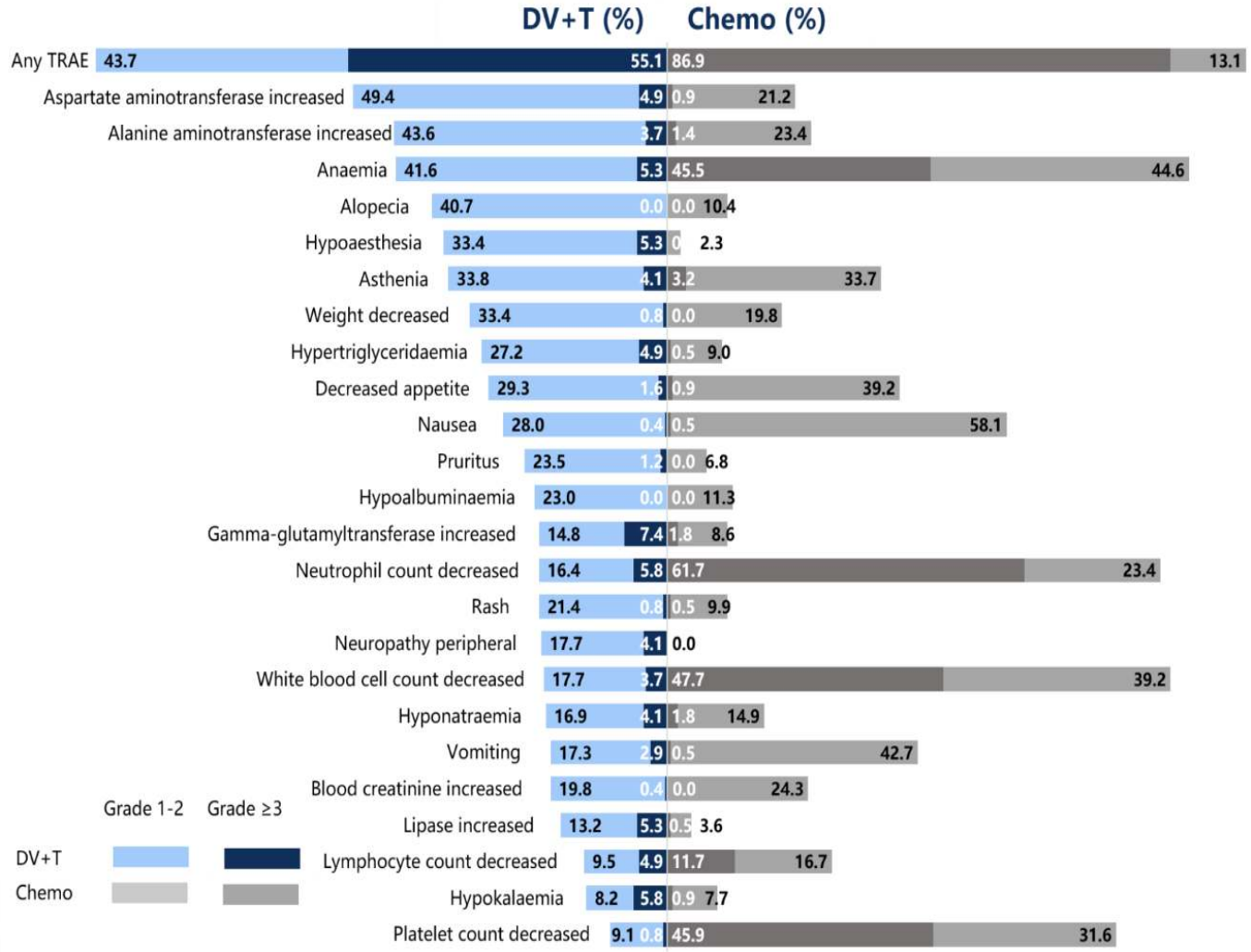


Secondary Endpoints: Objective Response Rate (ORR)



RC48-C016: 1L HER2-positive or HER2-low la/mUC cancer

Safety Summary



n (%)	DV + T (n = 243)	Chemo (n = 222)
TEAEs	243 (100)	222 (100)
TRAEs	240 (98.8)	222 (100)
Grade ≥3 TRAEs	134 (55.1)	193 (86.9)
• Grade 4	107 (44.0)	93 (41.9)
• Grade 4	24 (9.9)	97 (43.7)
• Grade 5	3 (1.2)	3 (1.4)
• Serious TRAEs	69 (28.4)	90 (40.5)
Immune-related adverse events		
• Any grade	114 (46.9)	-
• Grade ≥3	46 (18.9)	-
TRAE leading to discontinuation of any study treatment	30 (12.3)	23 (10.4)

SUMMARY

RC48-C016

- Disitamab vedotin + toripalimab improved survival vs chemotherapy in first-line HER2-expressing locally advanced or metastatic urothelial carcinoma
  - Median PFS was 13.1 vs 6.5 months (HR 0.36), and median OS was 31.5 vs 16.9 months (HR 0.54)
- Response rates were substantially higher and more durable with the combination
  - DoR 14.6 vs 5.6 months chemotherapy
- Safety was more favorable, with fewer grade ≥ 3 treatment-related adverse events (55.1% vs 86.9%) and good tolerability, suggesting a better risk/benefit balance than standard chemo.

IMPACT

Disitamab vedotin + toripalimab offers a new potential treatment option for first-line treatment of patients with HER2-expressing locally advanced or metastatic urotherlial carcinoma

Not yet approved

cornerstone specialty network™

ESMO 2025: RAPID REVIEWS

POTOMAC

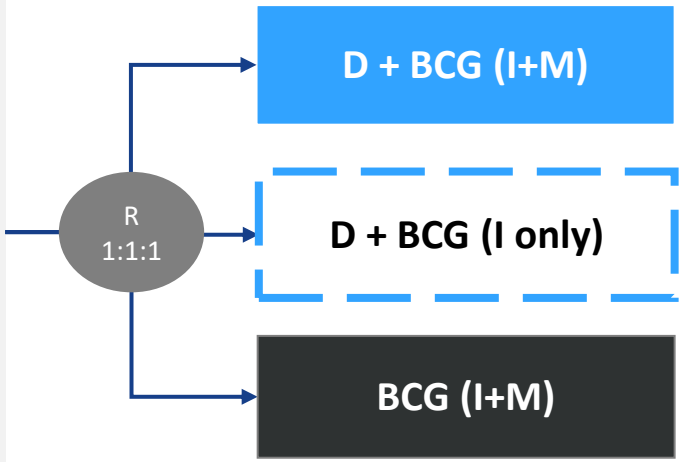
KEY DATA

POTOMAC: Durvalumab (D) + Bacillus Calmette-Guérin in BCG-naïve, high-risk non-muscle-invasive bladder cancer

Study Design: randomized, open-label, phase 3, global study

Stratified by higher risk papillary disease (yes vs no) and CIS (yes vs no)

- Age ≥18 years
- NMIBC
- BCG-naïve
- High-risk tumor defined as any of the following:
  - T1
  - High-grade/G3
  - CIS
  - Multiple and recurrent and large (≥3 cm)



Durvalumab was given IV (1,500 mg every 4 weeks) for 13 cycles, and BCG was given per standard induction + maintenance protocol (weekly × 6 weeks induction, then maintenance at defined intervals for up to 2 years).

Primary endpoint: Disease-Free Survival (DFS) D+BCG (I+M) vs BCG (I+M)
Key Secondary endpoints: DFS for D+BCG (I only) vs BCG (I+M) , DFS at 24 months, CRR at 6 months
Other secondary endpoints: Overall Survival at 5 years, safety, and EORTC QLQ-C30

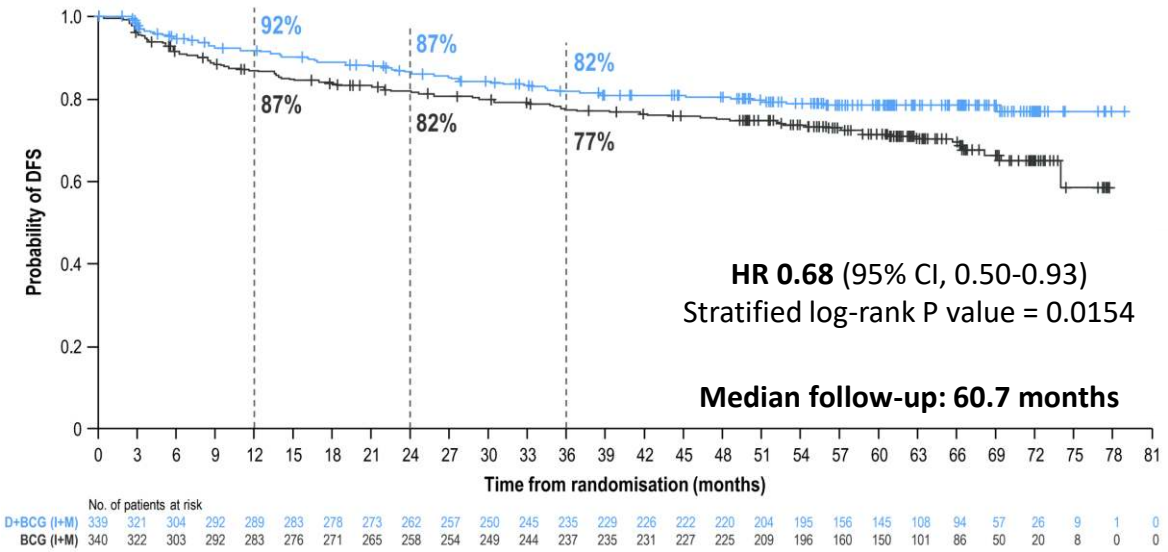
Select Baseline Characteristics

n, (%)	D+BCG (I+M) (n = 339)	D+BCG (I only) (n = 339)	BCG (I+M) (n = 340)
Age, median (range), yrs	68 (24-90)	68 (21-87)	67 (32-86)
ECOG PS			
• 0	294 (87)	305 (90)	304 (89)
• 1	45 (13)	34 (10)	36 (11)
Disease Stage			
• T1	195 (58)	191 (56)	211 (62)
• Ta	112 (33)	114 (34)	99 (29)
• CIS	125 (37)	125 (37)	125 (37)
Papillary disease only	217 (64)	222 (65)	220 (65)
Higher risk papillary disease	173 (51)	173 (51)	173 (51)
PD-L1 expression			
• High (≥TC/IC25%)	81 (24)	90 (27)	85 (25)
• Low/negative	235 (69)	228 (67)	232 (68)
• Missing/ not evaluable	23 (7)	21 (6)	23 (7)

KEY DATA

POTOMAC: Durvalumab + Bacillus Calmette-Guérin in BCG-naïve, high-risk non-muscle-invasive bladder cancer

Primary Endpoint: DFS for D+BCG (I+M) vs BCG (I+M)

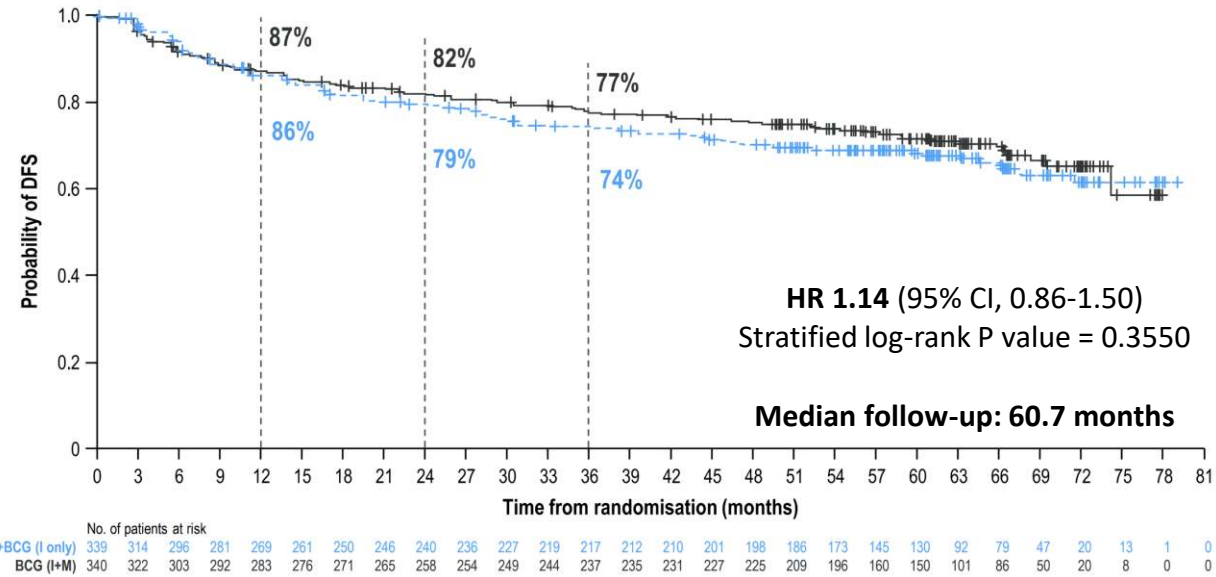


HR 0.68 (95% CI, 0.50-0.93)
Stratified log-rank P value = 0.0154

Median follow-up: 60.7 months

	D+BCG (I+M) (n = 339)	BCG (I+M) (n = 340)
Events, n (%)	67 (20)	98 (29)
Median DFS, months (95% CI)	NR (NR-NR)	NR (74.0-NR)

Key Secondary Endpoint: DFS for D+BCG (I only) vs BCG (I+M)



HR 1.14 (95% CI, 0.86-1.50)
Stratified log-rank P value = 0.3550

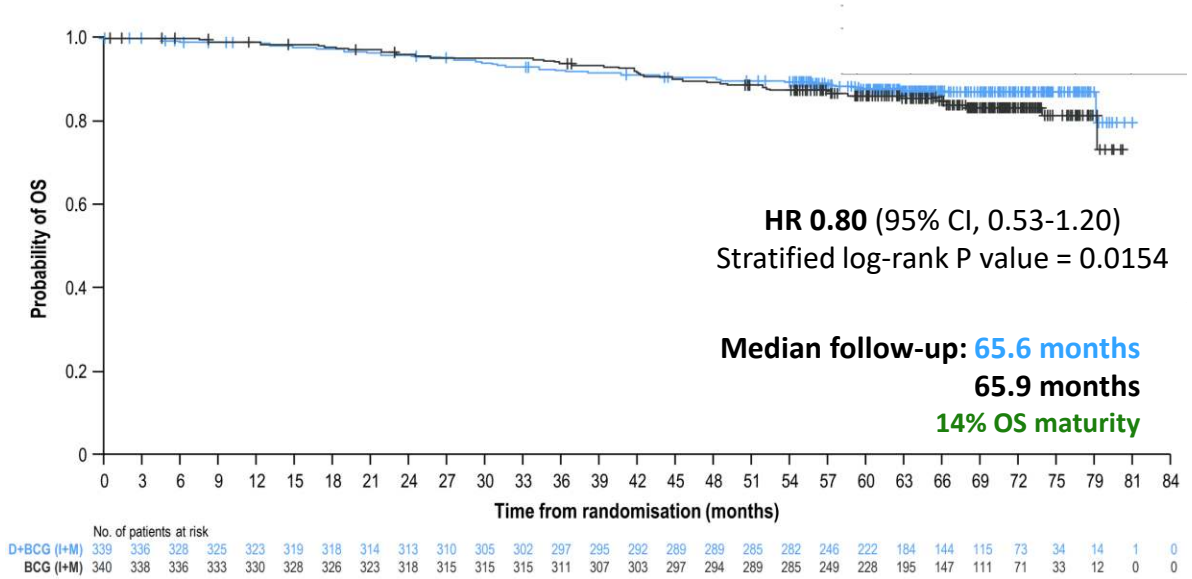
Median follow-up: 60.7 months

	D+BCG (I only) (n = 339)	BCG (I+M) (n = 340)
Events, n (%)	105 (31)	98 (29)
Median DFS, months (95% CI)	NR (NR-NR)	NR (74.0-NR)

KEY DATA

POTOMAC: Durvalumab + Bacillus Calmette-Guérin in BCG-naïve, high-risk non-muscle-invasive bladder cancer

Secondary Endpoints: Overall Survival



HR 0.80 (95% CI, 0.53-1.20)
Stratified log-rank P value = 0.0154

Median follow-up: 65.6 months
65.9 months
14% OS maturity

	D+BCG (I+M) (n = 339)	BCG (I+M) (n = 340)
Deaths, n (%)	41 (12)	51 (15)
Median DFS, months (95% CI)	NR (NR-NR)	NR (NR-NR)

Safety Summary

Events, n (%)	D+BCG (I+M) (n = 339)	D+BCG (I only) (n = 339)	BCG (I+M) (n = 340)
AEs of any cause	325 (97)	322 (96)	25.9 (2.0)
▪ **Possibly treatment-related**	**298 (89)**	**269 (80)**	**245 (72)**
Maximum grade 3 or 4 AEs	113 (34)	90 (27)	56 (17)
▪ **Possibly treatment-related**	**71 (21)**	**52 (15)**	**13 (4)**
Serious AEs	108 (32)	82 (24)	63 (19)
▪ **Possibly treatment-related**	**45 (13)**	**38 (11)**	**13 (4)**
AEs leading to death	6 (2)	4 (1)	4 (1)
▪ **Possibly treatment-related**	**0**	**0**	**0**
AEs leading to discontinuation	105 (31)	65 (19)	68 (20)
▪ **Possibly related to durvalumab**	**54 (16)**	**44 (13)**	**1 (0.3)**
▪ **Possibly related to durvalumab**	**55 (16)**	**15 (4)**	**55 (16)**
Any-grade immune-mediated AEs	91 (27)	113 (34)	4 (1)
▪ **Maximum grade 3 or 4**	**27 (8)**	**27 (8)**	**0**
▪ **Leading to death**	**0**	**0**	**0**

1 year of Durvalumab + BCG induction and maintenance is a potential new treatment for patients with BCG-naïve, high-risk non-muscle-invasive bladder cancer

ESMO 2025:

GI/GU *Cancer*

Key Takeaways

Q&A

@SujithKalmadiMD

cornerstone specialty network

KEYNOTE-905: Perioperative enfortumab vedotin + pembrolizumab significantly improved EFS and OS vs cystectomy alone, with high pCR rates and should be a new perioperative standard of care option for cisplatin-ineligible muscle-invasive bladder cancer – *now approved!*

IMvigor011: In ctDNA-positive patients, adjuvant atezolizumab improved DFS and OS vs placebo, establishing ctDNA-guided MRD selection as a powerful tool to identify who benefits from adjuvant immunotherapy– *not yet approved*

PSMAddition: In first-line high-risk localized prostate cancer, adding dding enzalutamide to ADT + radiotherapy modestly improved PSA-PFS, but the overall benefit–risk profile was mixed – *not yet approved*

FORTITUDE-101: In first-line FGFR2b-overexpressing gastric/GEJ cancer, Bemarituzumab + chemotherapy demonstrated encouraging OS and PFS trends vs chemotherapy alone, supporting FGFR2b-targeting as a promising first-line strategy, confirmatory evidence still required – *not yet approved*

AGITG DYNAMIC-III: For patients with ctDNA- negative stage III colon cancer, ctDNA-guided de-escalation was feasible and reduced chemotherapy exposure by 53.8%, but non-inferiority for 3-yr RFS was not met (3-yr RFS 85.3% vs 88.1%) – *not yet approved*

RC48-C016: In first-line HER2-expressing locally advanced or metastatic urotherlial carcinoma, disitamab vedotin + toripalimab produced high ORR in HER2-overexpressing tumors (≈80%) and promising PFS signals in HER2-low tumors when combined with chemo– *not yet approved*

2025 ESMO Key Studies

Breast Cancer

- *DESTINY-Breast11
- *DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*

- evERA BC
- VIKTORIA
  - *Polling Question*

GU GI

- *KEYNOTE-905/EV-303
- *IMvigor-011
  - *Polling Question*
- *PSMAddition
  - *Rapid Review*: CAPItello-281
- *Polling Question*
- *FORTITUDE-101
- *AGITG-DYNAMIC-III
  - *Polling Question*
- *RC48-C016
  - *Rapid Review*: POTOMAC

Lung Cancer and Other Notable Studies

- *HARMONI-6
- FLAURA2
  - *Polling Question*
- *OptiTROP-Lung04
  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

cornerstone specialty network

*ESMO Presidential Session

CLINICAL QUESTION

HARMONI-6

* Presidential Symposium

Does adding ivonescimab to chemotherapy benefit patients in first-line treatment for advanced squamous non-small cell lung cancer?

KEY DATA

HARMONI-6: 1L Ivonescimab + chemo vs Tislelizumab + chemo

Study Design: Multicenter, randomized, double-blinded, parallel-controlled phase 3 study

- Pathologically confirmed squamous-NSCLC
- Stage IIIB-IV
- No prior systemic therapy
- No EGFR mutations or ALK rearrangements
- ECOG PS 0 or1

Stratified by stage (IIIB/IIIC vs IV), and PD-L1 TPS (≥1% vs <1%)

R 1:1

Ivonescimab (20 mg/kg, Q3W) + **Carboplatin** (AUC 5, Q3W) + **Paclitaxel** (175 mg/m^2, Q3W) up to 4 cycles → **Ivonescimab** (20mg/kg, Q3W) up to 24 months or unacceptable toxicity

Tislelizumab (200 mg, Q3W) + **Carboplatin** (AUC 5, Q3W) + **Paclitaxel** (175 mg/m^2, Q3W) up to 4 cycles → **Tislelizumab** (200 mg, Q3W) up to 24 months or unacceptable toxicity

Primary endpoint: Progression free survival (PFS) per independent radiology review committee (IRRC) per RECIST v1.1
Key Secondary endpoint: Overall survival (OS)
Secondary endpoints: PFS by investigator, ORR, DCR, DoR, TTR and safety

Data cutoff date: February 28, 2025

ESMO 2025. Abstr. LBA4
The Lancet Volume 406, Issue 10515p2078-2088November 01, 2025

KEY DATA

HARMONI-6 : 1L Ivonescimab + chemo vs Tislelizumab + chemo

Baseline characteristics

Characteristic, n (%)	Ivonescimab + chemo (n = 266)	Tislelizumab + chemo (n = 266)
Age		
• <65 yr	135 (50.8)	139 (52.3)
• ≥65 yr	131 (49.2)	127 (47.7)
Sex		
• Male	256 (96.2)	238 (89.5)
• Female	10 (3.8)	28 (10.5)
ECOG PS*		
• 0	42 (15.8)	42 (15.8)
• 1	224 (84.2)	222 (83.5)
Smoking history		
• Never	21 (7.9)	37 (13.9)
• Current/former	245 (92.1)	229 (86.1)
Disease stage		
• IIIB/IIIC	21 (7.9)	20 (7.5)
• IV	245 (92.1)	246 (92.5)

Characteristic, n (%)	Ivonescimab + chemo (n = 266)	Tislelizumab + chemo (n = 266)
Tumor characteristics		
• Central type	178 (66.9)	158 (59.4)
• Major blood vessel encasement	49 (18.4)	44 (16.5)
• With cavity	24 (9.0)	23 (8.6)
• With hemoptysis	86 (32.3)	79 (29.7)
PD-L1 TPS		
• <1%	105 (39.5)	105 (39.5)
• ≥1%	161 (60.5)	161 (60.5)
• 1-49%	112 (42.1)	99 (37.2)
• ≥50%	49 (18.4)	62 (23.3)
Metastases sites		
• ≥3 metastatic sites	42 (15.8)	39 (14.7)
• Liver metastases	28 (10.5)	45 (16.9)
• Brain metastases	9 (3.4)	17 (6.4)

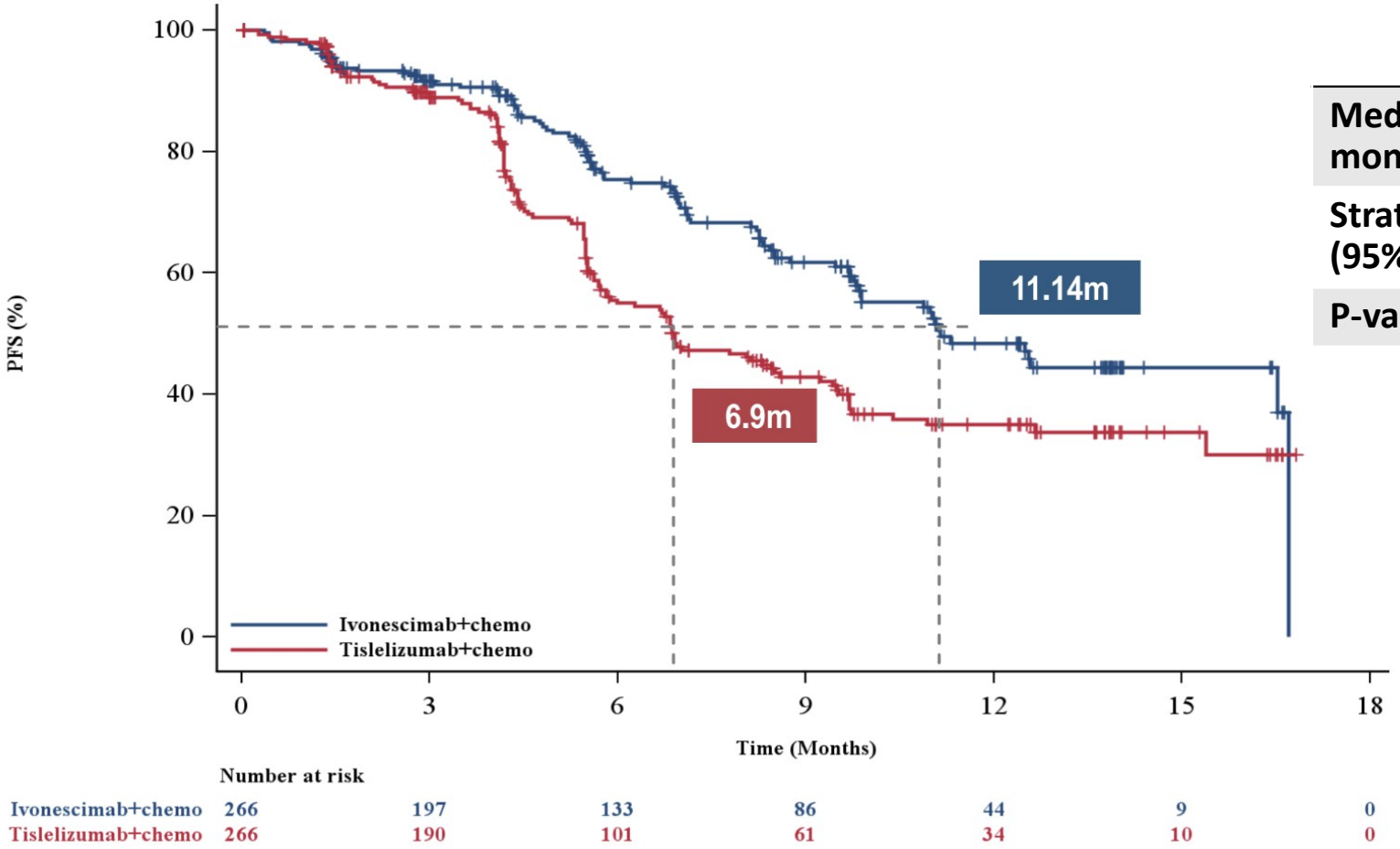
*Two patients ECOG PS were missing in the tislelizumab plus chemotherapy arm

ESMO 2025. Abstr. LBA4
The Lancet Volume 406, Issue 10515p2078-2088November 01, 2025

KEY DATA

HARMONI-6 : 1L Ivonescimab + chemo vs Tislelizumab + chemo

Primary Endpoint: PFS per IRRC per RECIST v1.1



	Ivonescimab + chemo (N=266)	Tislelizumab + chemo (N=266)
Median PFS, months (95% CI)	**11.14** (9.86, NE)	6.90 (5.82, 8.57)
Stratified HR (95% CI)	**0.60** (0.46, 0.78)	
P-value	**<0.0001**	

Median follow-up: 10.28 months

HR = **0.64**
(95% CI: 0.50, 0.84)

IRRC: independent radiology review committee

ESMO 2025. Abstr. LBA4
The Lancet Volume 406, Issue 10515p2078-2088November 01, 2025

KEY DATA

HARMONI-6: 1L Ivonescimab + chemo vs Tislelizumab + chemo

Select Subgroups: PFS by PD-L1 expression

Events/N	Ivonescimab + CT	Tislelizumab + CT	HR (95% CI)
PD-L1 TPS			
• <1%	42/105	58/105	**0.55** (0.37-0.82)
• ≥1%	52/161	69/161	**0.66** (0.46-0.95)
• 1%-49%	35/112	47/99	**0.63** (0.41-0.98)
• ≥50%	17/49	22/62	**0.71** (0.37-1.33)

Ivonescimab + CT improved PFS by IRRC vs tislelizumab + CT in all key subgroups

Median follow-up: 10.28 months

IRRC: independent radiology review committee

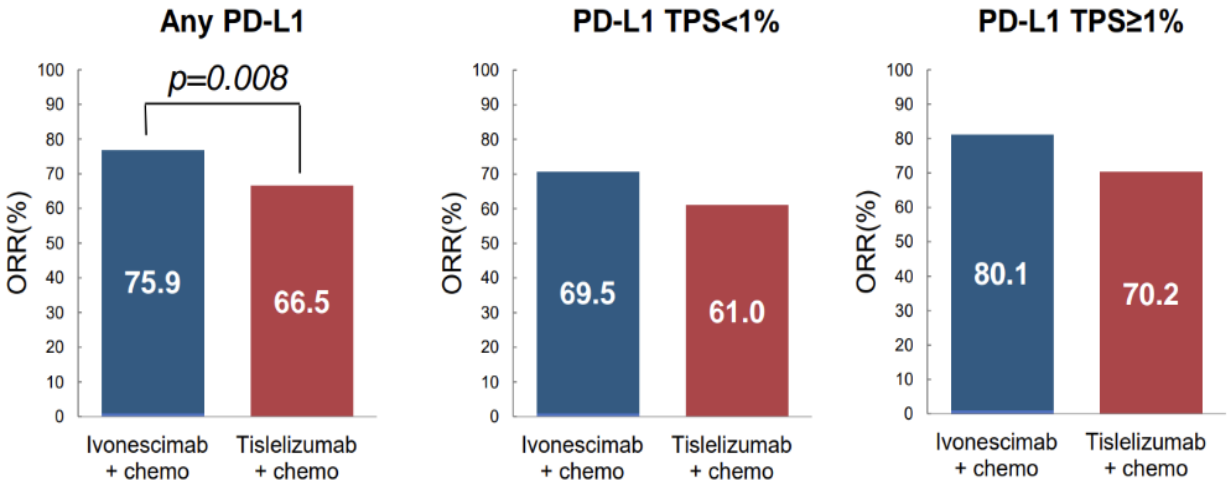
ESMO 2025. Abstr. LBA4
The Lancet Volume 406, Issue 10515p2078-2088November 01, 2025

KEY DATA

HARMONI-6: 1L Ivonescimab + chemo vs Tislelizumab + chemo

Secondary Endpoint: Overall Response Rate and Duration of Response

ORR by IRRC

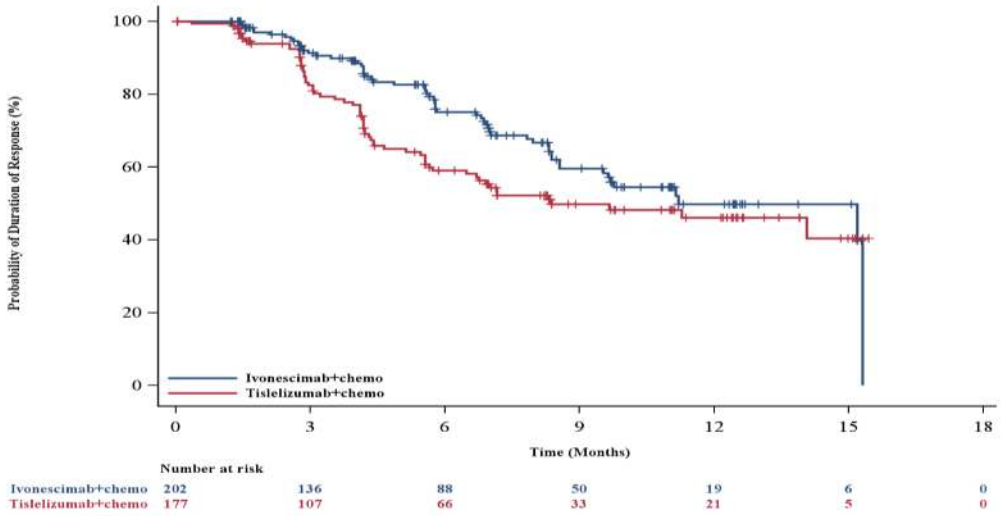


Best Overall Response, n (%)	Ivonescimab + chemo (N=266)	Tislelizumab + chemo (N=266)
• CR	1 (0.4)	0
• PR	201 (75.6)	177 (66.5)
• SD	39 (14.7)	60 (22.6)
• PD	6 (2.3)	15 (5.6)

IRRC: independent radiology review committee

DoR by IRRC

	Ivonescimab + chemo (N=266)	Tislelizumab + chemo (N=266)
Median DoR, months (95% CI)	**11.20** (8.54, NE)	8.38 (5.72, NE)
P-value	0.0219	



ESMO 2025. Abstr. LBA4
The Lancet Volume 406, Issue 10515p2078-2088November 01, 2025

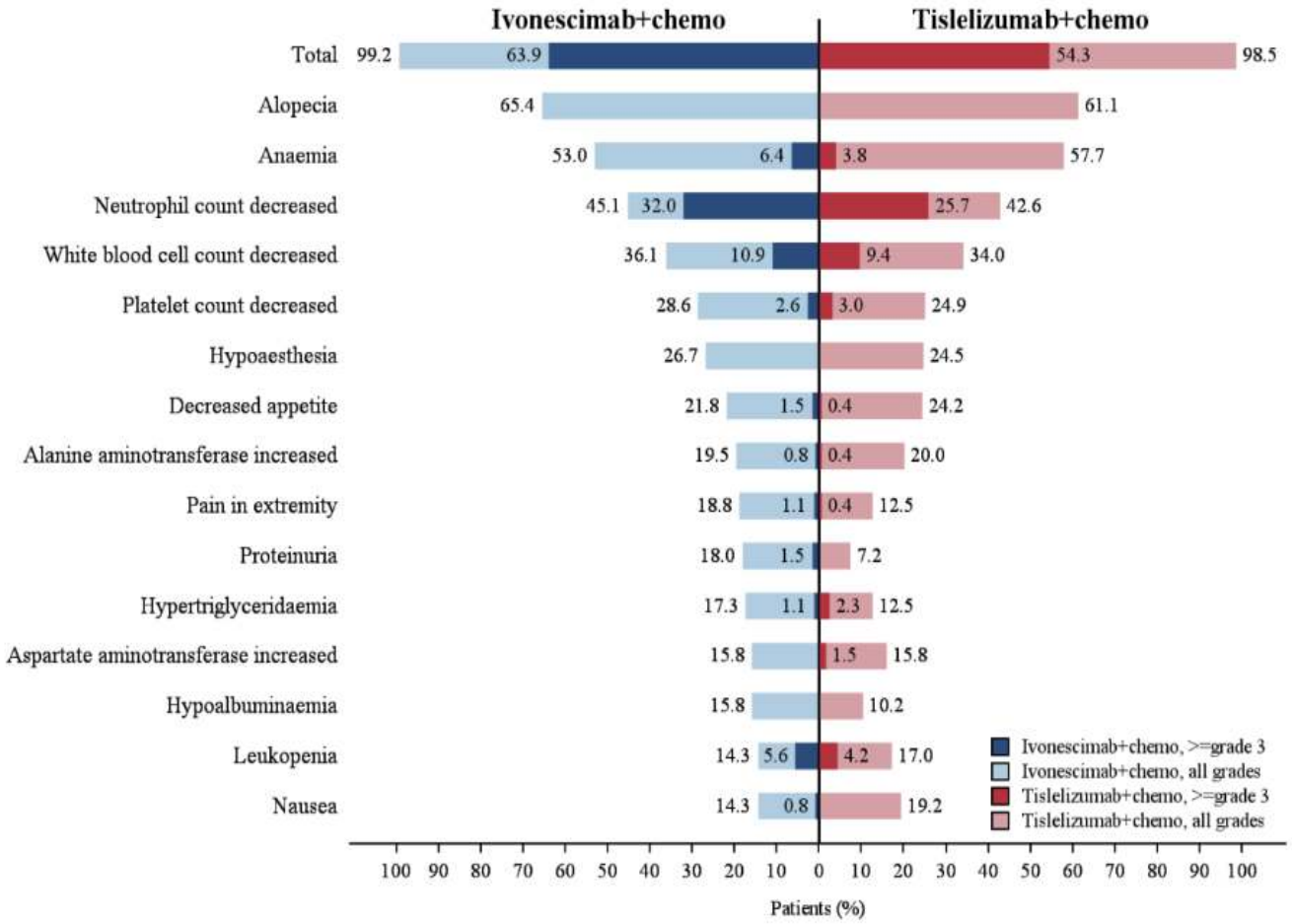
KEY DATA

HARMONI-6: 1L Ivonescimab + chemo vs Tislelizumab + chemo

Safety Summary

	Ivonescimab + chemo (N=266)	Tislelizumab + chemo (N=266)
TRAE	264 (99.2)	261 (98.5)
Grade ≥3 TRAE	170 (63.9)	144 (54.3)
Serious TRAE	86 (32.3)	80 (30.2)
Leading to ivonescimab or tislelizumab discontinuation	9 (3.4)	11 (4.2)
Leading to death	8 (3.0)	10 (3.8)

Most common TRAEs (incidence ≥15%)



ESMO 2025. Abstr. LBA4
The Lancet Volume 406, Issue 10515p2078-2088November 01, 2025

HARMONI-6

SUMMARY

- Ivonescimab added to chemotherapy improved PFS for advanced squamous-NSCLC first-line treatment
  - PFS benefit favored ivonescimab plus chemotherapy across all key subgroup
- Ivonescimab plus chemotherapy showed a manageable safety profile in squamous-NSCLC, consistent with pervious experience

IMPACT

Ivonescimab plus chemotherapy is a potential treatment option for patients for patients with advanced squamous cell non-small cell lung cancer

Not yet FDA approved

2025 ESMO Key Studies

Breast Cancer

- *DESTINY-Breast11
- *DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*

- evERA BC
- VIKTORIA
  - *Polling Question*

GU GI

- *KEYNOTE-905/EV-303
- *IMvigor-011
  - *Polling Question*
- *PSMAddition
  - *Rapid Review*: CAPItello-281
- *Polling Question*
- *FORTITUDE-101
- *AGITG-DYNAMIC-III
  - *Polling Question*
- *RC48-C016
  - *Rapid Review*: POTOMAC

Lung Cancer and Other Notable Studies

- *HARMONI-6
- FLAURA2
  - *Polling Question*
- *OptiTROP-Lung04
  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

cornerstone specialty network

*ESMO Presidential Session

Does osimertinib plus/minus platinum-pemetrexed benefit overall survival in patients with poor prognostic factors in first-line treatment for EGFR-mutated advanced NSCLC?

Exploratory overall survival analyses

KEY DATA

FLAURA2: 1L, Osi + plat-pem vs Osi mono

Study Design: Randomized, multicenter, open-label, phase 3 trial

- Aged ≥ 18 years
- Pathologically confirmed non-squamous NSCLC
- Ex19del/L858R (local/central test)
- WHO PS 0 or 1
- Stable CNS metastases were allowed
- Brain scans at baseline (MRI/ CT; mandatory)

Stratified by race (Asian Chinese/ Asian non-Chinese/ non-Asian), EGFRm test (local/central), and WHO PS (0/1)

R 1:1

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles for platinum-based treatments)

Maintenance osimertinib 80 mg (QD) + pemetrexed 500 mg/m² (Q3W)

Treatment beyond PD allowed per investigator discretion

Osimertinib 80 mg (QD)

Data cut-off: June 12, 2025

Primary endpoint: Progression-free survival (PFS) by investigator-assessment per RECIST v1.1
Key Secondary endpoints: Overall survival (OS)*

* For statistical significance of OS, a two-sided p-value of less than 0.04953, as determined by the O'Brien-Fleming spending rule was required.

KEY DATA

FLAURA2: 1L, Osi + plat-pem vs Osi mono

Previously reported PFS and OS

Primary Endpoint: Progression Free Survival

	Osi + plat-pem (n=279)	Osi mono (n=278)
Median PFS, mo (95% CI)	**25.5** (24.7, NC)	16.7 (14.1,21.3)
HR (95% CI)	**0.62 (0.49, 0.79); p<0.001**	

Key Secondary Endpoint: Overall Survival (OS)

	Osi + plat-pem (n=279)	Osi mono (n=278)
Median OS, mo (95% CI)	**47.5** (41.0, NC)	37.6 (33.2, 43.2)
HR (95% CI)	**0.77 (0.61, 0.96); p=0.02**	

Data cut-off: June 12, 2025

Planchard. NEJM. 2023;389:1935.
Planchard. WCLC 2025. Abstract PL02.04

KEY DATA

FLAURA2: 1L, Osi + plat-pem vs Osi mono

Exploratory Overall Survival based on baseline prognostic factors

Baseline Subgroup	Osimertinib + Platinum/Pemetrexed			Osimertinib			HR for OS (95% CI)
	N	Median OS, Mo	3-Yr OS, %	N	Median OS, Mo	3-Yr OS, %	
All patients	279	47.5	63	278	36.7	51	0.77 (0.61-0.96)
CNS metastases							
• Yes	116	40.9	57	110	29.7	40	0.72 (0.52-0.99)
• No	163	NR	67	168	43.9	58	0.77 (0.57-1.05)
EGFR mutation							
• L858R	106	38.1	54	107	32.4	42	0.76 (0.55-1.07)
• Ex19del	172	NR	69	169	43.0	57	0.76 (0.56-1.02)
Plasma EGFRm							
• Detected	148	38.4	53	161	32.5	42	0.79 (0.60-1.03)
• Not detected	65	NR	83	48	NR	77	0.79 (0.44-1.44)
Liver metastases							
• Yes	43	36.6	54	66	28.0	35	0.66 (0.41-1.05)
• No	236	49.6	65	212	41.8	56	0.83 (0.64-1.07)
Bone metastases							
• Yes	132	40.2	55	142	32.3	42	0.76 (0.56-1.02)
• No	147	NR	71	136	44.5	60	0.79 (0.57-1.10)
Tissue TP53							
• Altered	46	51.1	65	40	43.1	58	0.71 (0.40-1.27)
• Wild type	33	NR	85	34	NR	76	0.70 (0.32-1.54)

Data cut-off: June 12, 2025

SUMMARY

FLAURA2

- Osimertinib plus platinum-pemetrexed demonstrated the longest global phase 3 study OS (47.5 months), showing OS benefit in patients with EGFRm advanced NSCLC
- OS benefit consistent with the overall population across key molecular and clinical prognostic subgroups

IMPACT

Osimertinib plus platinum-pemetrexed is an effective treatment option for patients with EGFRm advanced non-small cell lung cancer in the first-line setting and should be considered a standard of care

FDA Approved

Polling question

What is your preferred first-line treatment for EGFR-mutated advanced NSCLC?

1. Osimertinib
2. Osimertinib + chemotherapy
3. Amivantamab + Lazertinib
4. Other

2025 ESMO Key Studies

Breast Cancer

- *DESTINY-Breast11
- *DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*

- evERA BC
- VIKTORIA
  - *Polling Question*

GU GI

- *KEYNOTE-905/EV-303
- *IMvigor-011
  - *Polling Question*
- *PSMAddition
  - *Rapid Review*: CAPItello-281
- *Polling Question*
- *FORTITUDE-101
- *AGITG-DYNAMIC-III
  - *Polling Question*
- *RC48-C016
  - *Rapid Review*: POTOMAC

Lung Cancer and Other Notable Studies

- *HARMONI-6
- FLAURA2
  - *Polling Question*
- *OptiTROP-Lung04
  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

cornerstone specialty network

*ESMO Presidential Session

CLINICAL QUESTION

OptiTROP-Lung04

* Presidential Symposium

Does Sacituzumab tirumotecan in EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC) benefit patients following progression on EGFR-TKIs?

KEY DATA

OptiTROP-Lung04: Sac-TMT vs Chemotherapy in EGFRm NSCLC following progression on EGFR-TKIs

Study Design: Randomized, multicenter, open-label, phase 3 trial

- ECOG score 0 or1
- Non-squamous-NSCLC (stage IIIB/IIIC or stage IV)
- EGFR-sensitive mutation
- Progression after 3rd gen TKI therapy or progression after 1st or 2nd gen TKIs with negative T790M

Stratified by prior EGDR-TKI therapy (3rd gen TKI in 1L vs in 2L vs no 3rd gen TKI) and brain metastases (yes vs no)

R 1:1

Sacituzumab tirumotecan (Sac-TMT) 5 mg/kg IV, Q2W

- **Pemetrexed 500 mg/m² + Carboplatin AUC 5 or Cisplatin 75 mg/m² Q3W for up to 4 cycles**
- **Pemetrexed 500 mg/m² maintenance, Q3W**

Primary endpoint*: Progression-free survival (PFS) assessed by BICR

Key Secondary endpoints: Overall survival (OS), PFS by INV, ORR, DCR, DoR and safety

*Tumor response was assessed using RECIST version 1.1
INV: investigator

KEY DATA

OptiTROP-Lung04: Sac-TMT vs Chemotherapy in EGFRm NSCLC following progression on EGFR-TKIs

Baseline Characteristics

Characteristic, n (%)	Sac-TMT (n = 188)	Chemotherapy (n = 188)
Median age (range), years	60 (31-75)	59 (33-75)
▪ ≥65 yrs	58 (30.9)	51 (27.1)
Male	66 (35.1)	83 (44.1)
ECOG PS 1	153 (81.4)	145 (77.1)
Smoking history		
▪ Never	145 (77.1)	135 (71.8)
▪ Current/former	43 (22.9)	53 (28.2)
Disease stage		
▪ IIIB/IIIC	6 (3.2)	3 (1.6)
▪ IV	182 (96.8)	185 (98.4)
≥3 metastatic sites	128 (68.1)	126 (67.0)
Brain metastases	33 (17.6)	36 (19.1)
Liver metastases	25 (13.3)	33 (17.6)

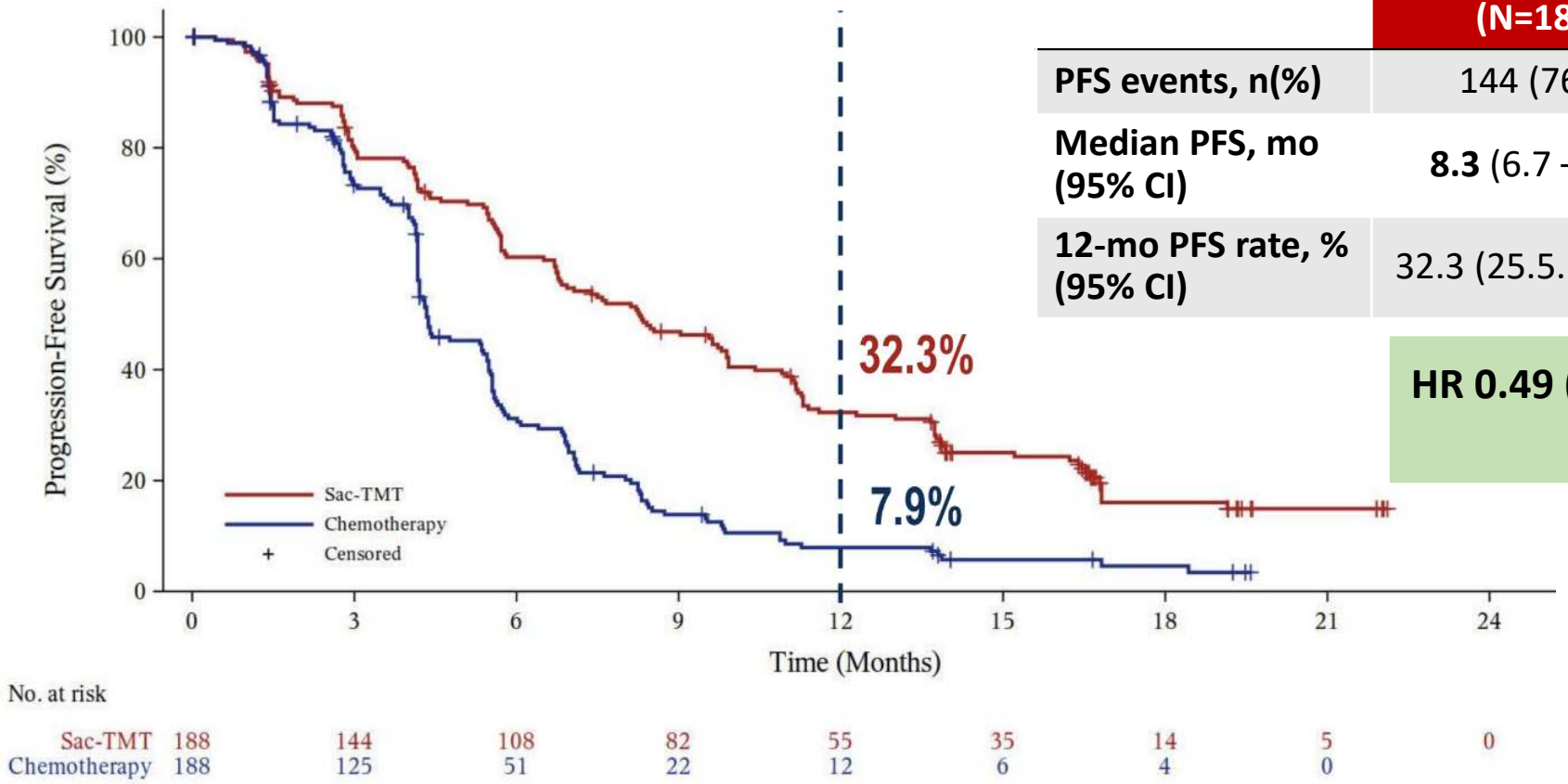
Characteristic, n (%)	Sac-TMT (n = 188)	Chemotherapy (n = 188)
EGFR mutation subtype*		
▪ Exon 19 deletion	106 (56.4)	118 (62.8)
▪ Exon 21 L858R	84 (44.7)	71 (37.8)
T790M mutation status		
▪ Positive	29 (15.4)	36 (19.1)
▪ Negative	48 (25.5)	40 (21.3)
▪ Unknown	111 (59.0)	112 (59.6)
Prior 3rd generation EGFR-TKI		
▪ 1st line	118 (62.8)	117 (62.2)
▪ 2nd line	60 (31.9)	60 (31.9)

*Including overlapping mutations in some patients. Other EGFR mutations co-occurring with exon 21 L858R or exon 19 deletion were included in the subcategory "Other" (sac-TMT: 4.3%; chemotherapy: 3.7%).

KEY DATA

OptiTROP-Lung04: Sac-TMT vs Chemotherapy in EGFRm NSCLC following progression on EGFR-TKIs

Primary Endpoint: Progression-Free Survival by BICR



	Sac-TMT (N=188)	Chemotherapy (N=188)
PFS events, n(%)	144 (76.6)	159 (84.6)
Median PFS, mo (95% CI)	**8.3** (6.7 – 9.9)	**4.3** (4.2 – 5.5)
12-mo PFS rate, % (95% CI)	32.3 (25.5. – 39.2)	7.9 (4.4 – 12.8)

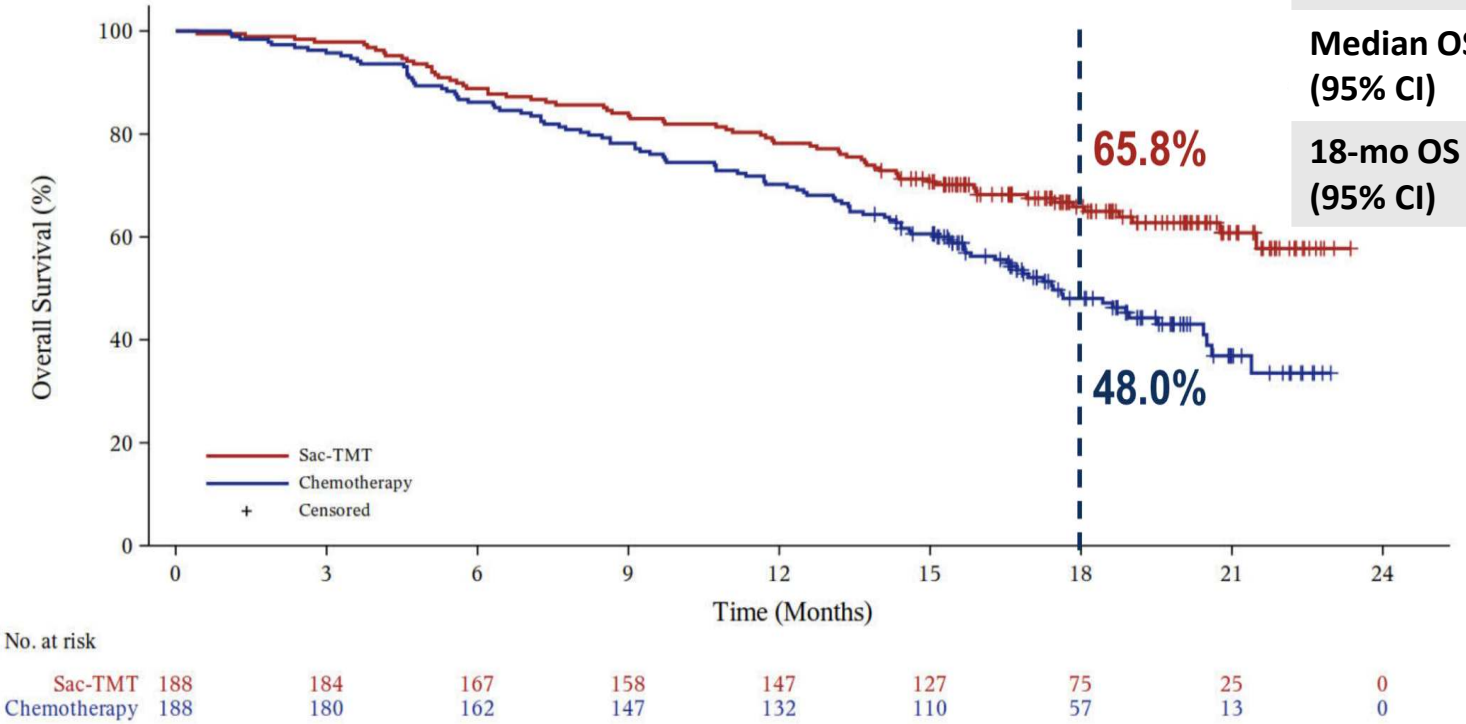
HR 0.49 (95% CI: 0.39 – 0.62)
***P* < 0.0001**

Data cutoff: June 6, 2025; the final analysis of PFS

KEY DATA

OptiTROP-Lung04: Sac-TMT vs Chemotherapy in EGFRm NSCLC following progression on EGFR-TKIs

Secondary Endpoints: Overall Survival (OS)



	Sac-TMT (N=188)	Chemotherapy (N=188)
OS events, n(%)	67 (76.6)	101 (53.7)
Median OS, mo (95% CI)	**NR** (21.5 – NE)	**17.4** (15.7 – 20.4)
18-mo OS rate, % (95% CI)	**65.8** (58.3 – 72.3)	**48.0** (40.2 – 55.4)

HR 0.60 (95% CI: 0.44 – 0.82)
P* < 0.001

Data cutoff: June 6, 2025; the pre-specified IA of OS

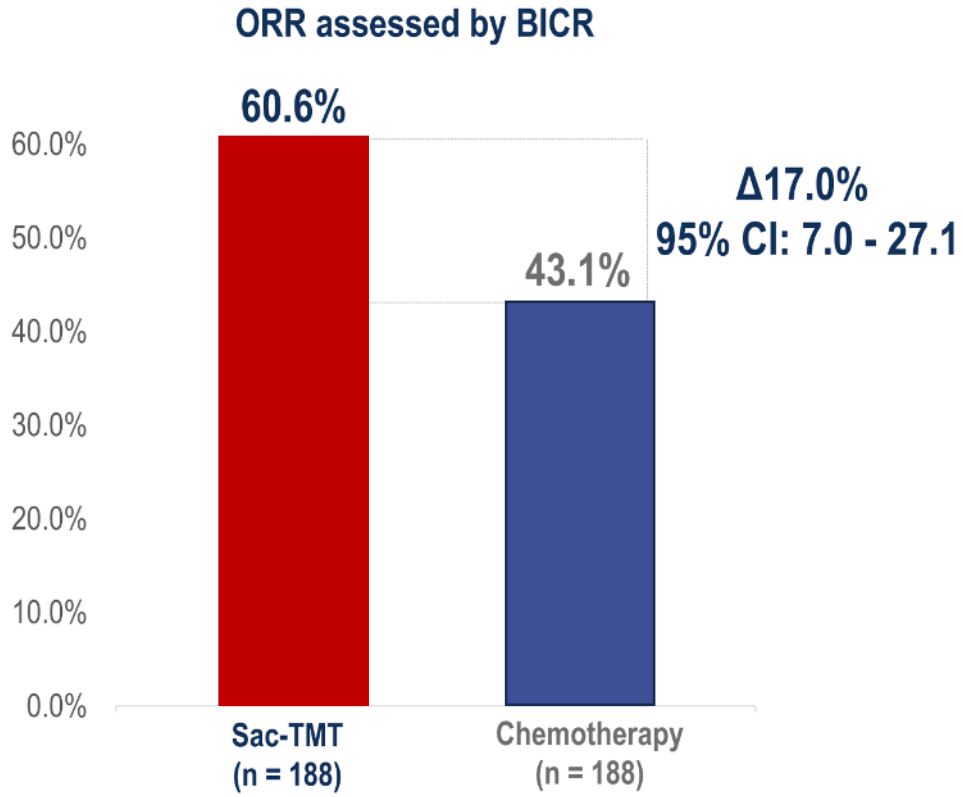
*Based on pre-specified OS IA, two-sided P value was less than the pre-specified efficacy boundary to achieve statistically significant improvement (two-sided alpha value of 0.0124 determined by the O'Brien-Fleming alpha spending function).

KEY DATA

OptiTROP-Lung04: Sac-TMT vs Chemotherapy in EGFRm NSCLC following progression on EGFR-TKIs

Secondary Endpoints: ORR, DCR and DOR by BICR

	Sac-TMT (N=188)	Chemotherapy (N=188)
ORR, % (95% CI)	**60.6** (53.3 – 67.7)	**43.1** (35.9 – 50.5)
Difference* (95% CI)	**17.0** (7.0 – 27.1)	
DCR, % (95% CI)	87.2 (81.6 – 91.6)	80.3 (73.9 – 85.7)
Median DOR, mo (95% CI)	**8.3** (6.2 – 10.0)	**4.2** (3.0 – 4.4)
12-mo DOR rate, % (95% CI)	36.3 (27.3 – 45.3)	8.1 (3.3 – 15.8)



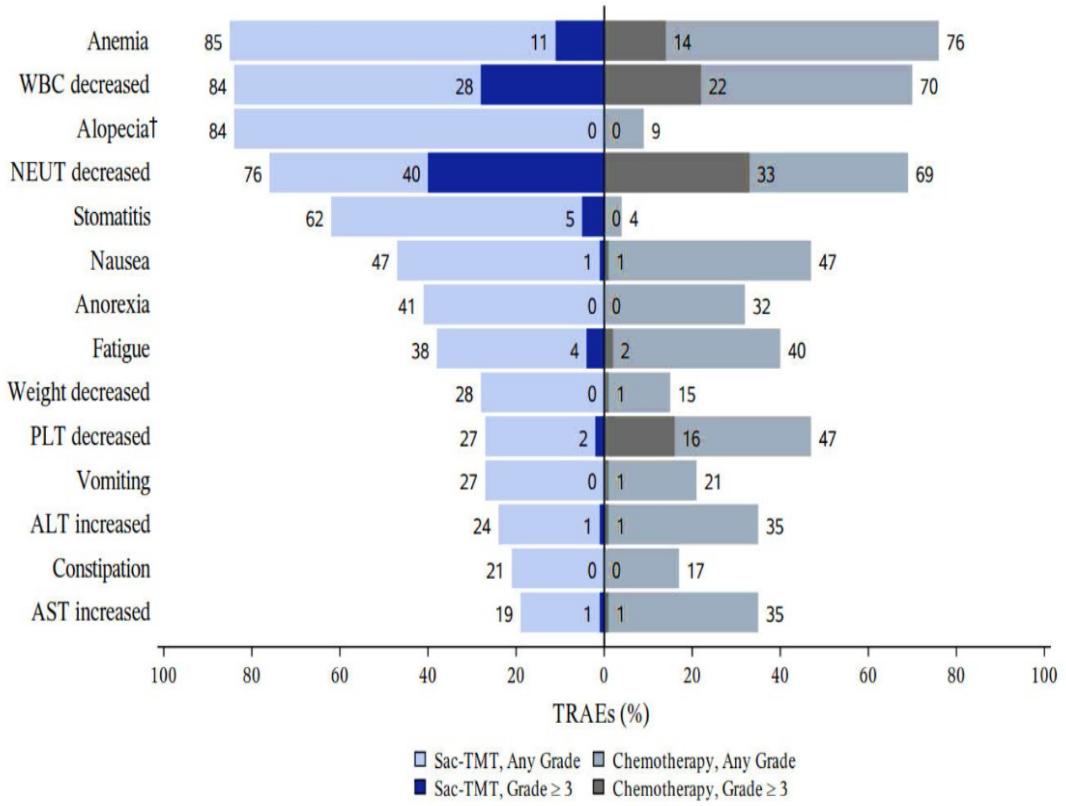
KEY DATA

OptiTROP-Lung04: Sac-TMT vs Chemotherapy in EGFRm NSCLC following progression on EGFR-TKIs

Summary of Safety, As-Treated Population

	Sac-TMT (N=188)	Chemotherapy (N=188)
TRAEs	188 (100%)	179 (98.4)
Grade ≥3	109 (58.0%)	98 (53.8%)
Serious TRAEs	17 (9.0%)	32 (17.6%)
Led to dose reduction	57 (30.3%)	41 (22.5%)
Led to dose interruption	69 (36.7%)	60 (33.0%)
Led to discontinuation	0	1 (0.5)
Led to death	0	1 (0.5)*

Common TRAEs



*One patient (0.5%) in the chemotherapy group died from a treatment-related adverse event (cardiorespiratory arrest).

Data cutoff date: 25 July 2024

OptiTROP-Lung04

SUMMARY

- Sac-TMT demonstrates statistically significant and clinically meaningful improvements in PFS and OS compared to platinum-based chemotherapy
- Sac-TMT showed a manageable safety profile, with no unexpected safety signals identified
- Several global phase 3 studies of sac-TMT monotherapy and combination study with Osimertinib in EGFR-mutant are ongoing

IMPACT

Sacituzumab tirumotecan is a promising new treatment option for patients with EGFRm NSCLC with EGFR-TKI resistance

Potential new treatment option, not yet FDA approved

Polling question

With the approval of Dato-DXd for metastatic EGFRm NSCLC after prior EGFR-directed therapy and platinum-based chemotherapy, how would OptiTROP-Lung04 if approved influence your treatment decision?

1. Prefer Dato-DXd first
2. Would consider both equally depending on toxicity and patient factors
3. Unsure, need more data

*On **June 23, 2025**, the FDA granted accelerated approval to **datopotamab deruxtecan-dlnk** (Datroway, Daiichi Sankyo, Inc.) for adults with locally advanced or metastatic EGFR-mutated NSCLC who have received prior EGFR-directed therapy and platinum-based chemotherapy.*

cornerstone specialty network

2025 ESMO Key Studies

Breast Cancer

- *DESTINY-Breast11
- *DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*

- evERA BC
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GU GI

- *KEYNOTE-905/EV-303
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  - *Polling Question*
- *PSMAddition
  - *Rapid Review*: CAPItello-281
- *Polling Question*
- *FORTITUDE-101
- *AGITG-DYNAMIC-III
  - *Polling Question*
- *RC48-C016
  - *Rapid Review*: POTOMAC

Lung Cancer and Other Notable Studies

- *HARMONI-6
- FLAURA2
  - *Polling Question*
- *OptiTROP-Lung04
  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

cornerstone specialty network

*ESMO Presidential Session

ALEX

Does alectinib benefit patients with previously untreated, advanced ALK-positive (ALK+) non-small cell lung cancer?

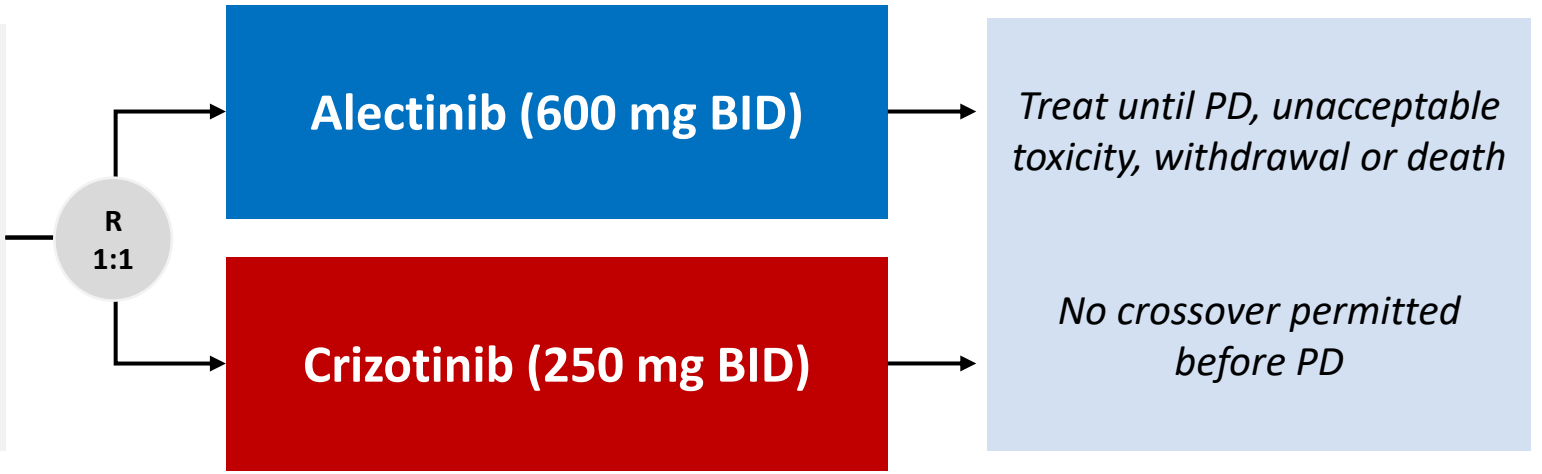
Final overall survival

KEY DATA

ALEX: Alectinib vs Crizotinib, 1L ALK+ NSCLC

Study Design: Randomized, open-label, phase 3 mulitcenter study

- Histologically/ cytologically confirmed advanced *ALK*-positive NSCLC (by Ventana IHC)
- Aged ≥18 years
- ECOG PS 0 – 2
- No prior systemic therapy for advanced disease



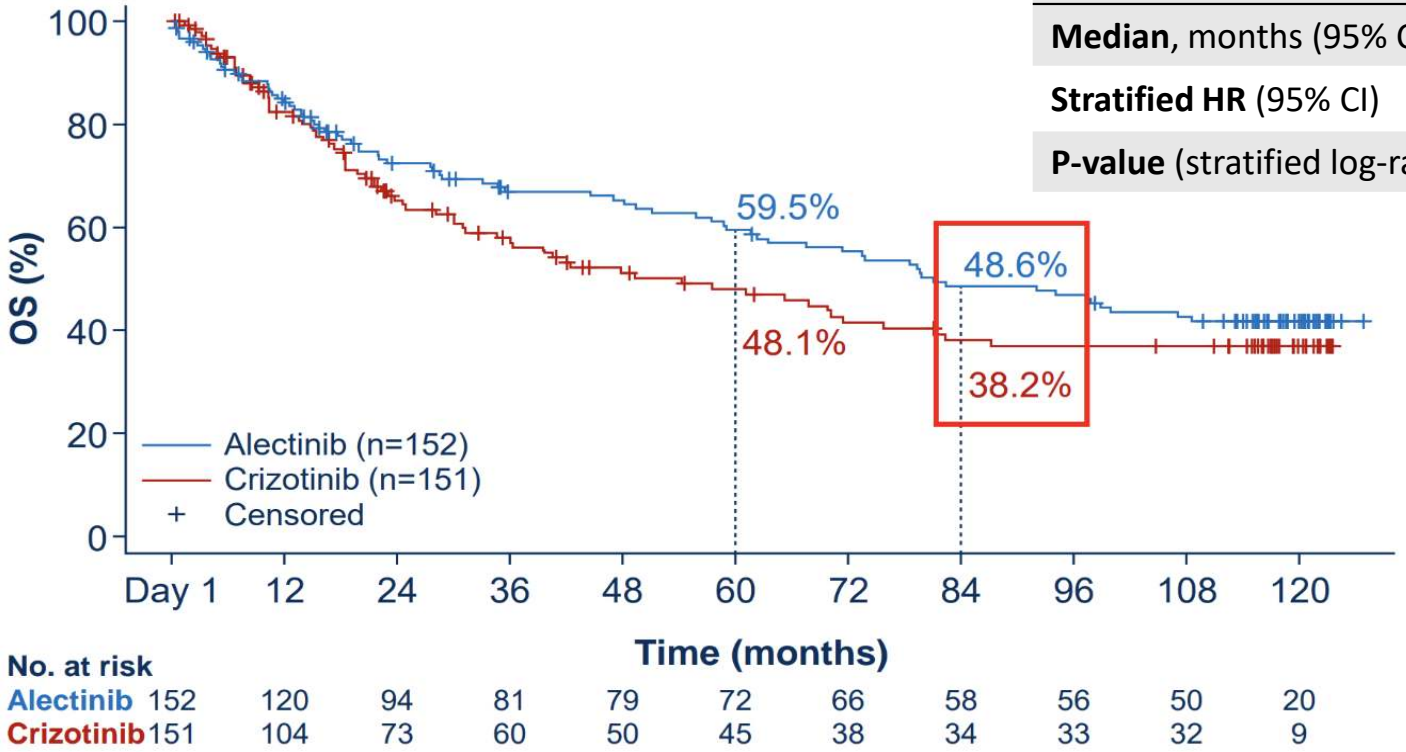
Stratified by ECOG PS (0 or 1 vs 2), race (Asian vs non-Asian), and baseline CNS metastases (yes vs no)

Primary endpoint: Progression free survival (PFS) per investigator using RECIST v1.1
Key Secondary endpoint: PFS by IRC, Time to CNS progression, ORR, DoR, OS and safety

ALEX: Alectinib vs Crizotinib, 1L ALK+ NSCLC

Secondary Endpoint: Overall Survival (OS) in ITT population

	Alectinib (n=152)	Crizotinib (n=151)
Patients with event, n (%)	76 (**50.0**)	73 (**48.3**)
Median, months (95% CI)	**81.1** (9.86, NE)	**54.2** (34.6-75.6)
Stratified HR (95% CI)	**0.78** (0.56-1.08)	
P-value (stratified log-rank)	0.1320	



Data cutoff: April 28, 2025

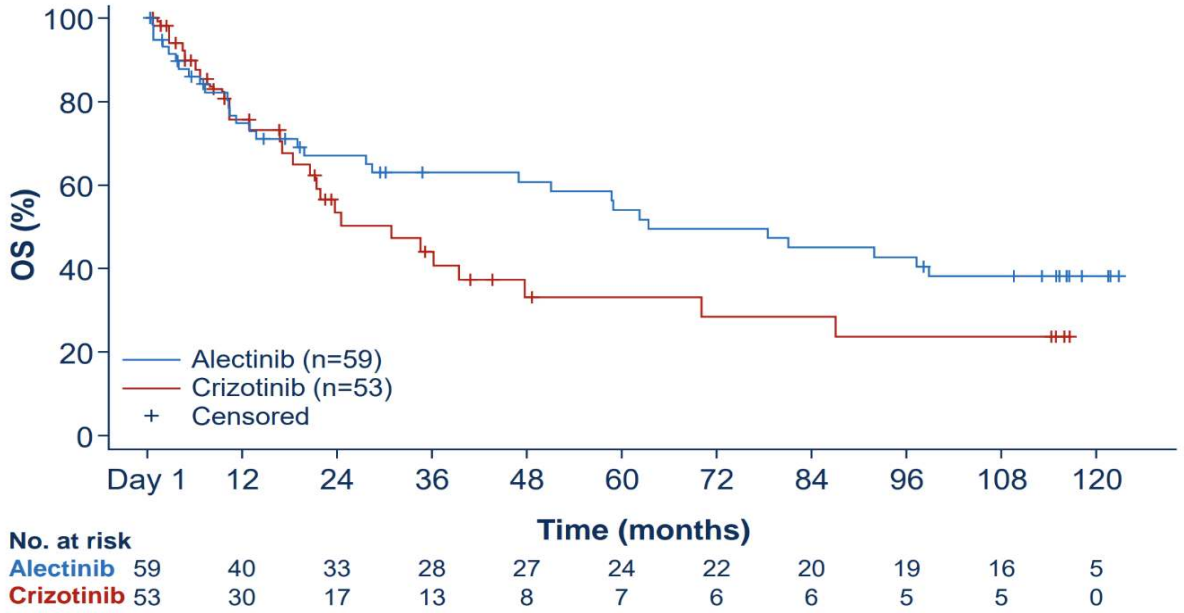
KEY DATA

ALEX: Alectinib vs Crizotinib, 1L ALK+ NSCLC

OS by CNS metastases* at baseline

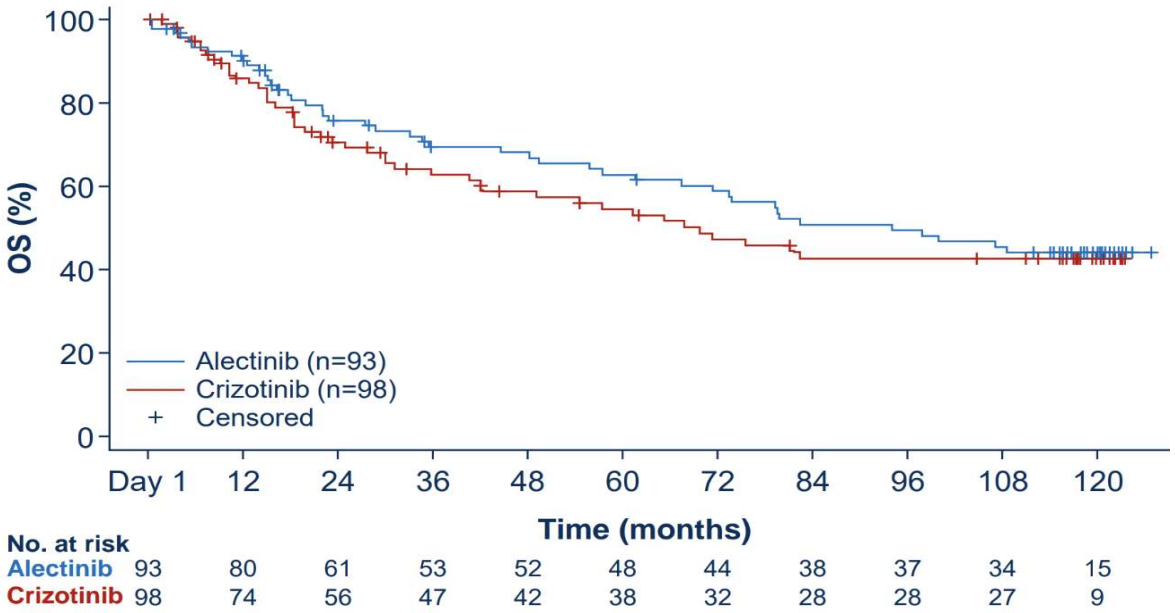
With CSN metastases at baseline

Median OS: **63.4** months with alectinib vs 30.9 months with crizotinib (HR 0.68; 95% CI 0.40-1.15)



Without CNS metastases at baseline

Median OS: **94.0** months with alectinib vs 69.8 months with crizotinib (HR 0.87; 95% CI 0.58-1.32)



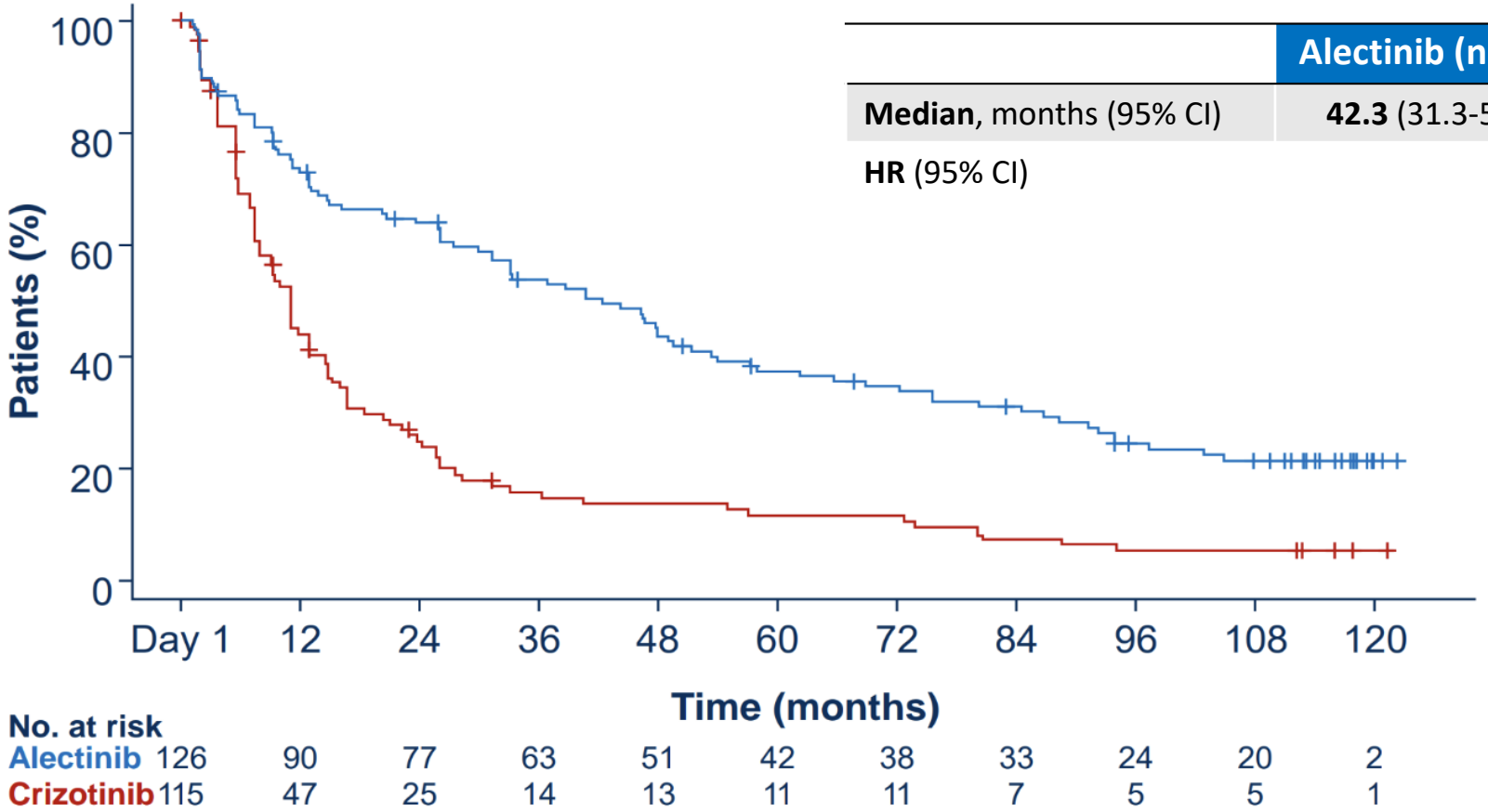
Median OS with prior brain radiation: 92.0 mo with alectinib (n=25) vs 39.5 mo with crizotinib(n=18) HR 0.62; 95% CI 0.24–1.60
Median OS without prior radiation: 46.9 months with alectinib (n=34) vs 23.7months with crizotinib (n=35) HR 0.73; 95% CI 0.38–1.3

Data cutoff: April 28, 2025
*Assessed by investigator.

KEY DATA

ALEX: Alectinib vs Crizotinib, 1L ALK+ NSCLC

Investigator-assessed DoR in responders*



	Alectinib (n=126)	Crizotinib (n=115)
Median, months (95% CI)	**42.3** (31.3-51.3)	**11.1** (7.9-13.0)
HR (95% CI)	**0.41** (0.30-0.56)	

Data cutoff: April 28, 2025

*Responders were defined as patients with investigator-assessed measurable disease at baseline.

ALEX: Alectinib vs Crizotinib, 1L ALK+ NSCLC

Safety Summary

- Median duration of treatment was 28.1 months (range 0–127) with alectinib and 10.8 months (range 0–123) with crizotinib
- The most common AE leading to dose reduction and discontinuation of alectinib was increased blood bilirubin (5.3% and 3.3% of patients, respectively), while for crizotinib it was increased ALT (8.6% and 6.6%, respectively)

n (%)	Alectinib (n=152)	Crizotinib (n=151)
All-grade AEs	147 (96.7)	148 (98.0)
Grade 3-5 AEs	88 (57.9)	87 (57.6)
Serious AEs	70 (46.1)	48 (31.8)
TRAEs	125 (82.2)	135 (89.4)
AEs leading to death	10 (6.6)*	7 (4.6)
AEs leading to treatment discontinuation	27 (17.8)	22 (14.6)
AEs leading to dose reduction	35 (23.0)	30 (19.9)
AEs leading to dose interruption	49 (32.2)	43 (28.5)

Data cutoff: April 28, 2025

*COVID-19 (n=1), pneumonia (n=1), blood creatine increased (n=1), acute myeloid leukaemia (n=1), ovarian cyst ruptured (n=1), cardiac arrest (n=1), all considered unrelated to alectinib, and death with unknown cause and no autopsy performed (n=3), suspected to be related to other causes than alectinib treatment

SUMMARY

ALEX

IMPACT

- Alectinib induced a clinically meaningful median OS of 81.1 months and median DoR of 42.3 months in patients with previously untreated, advanced ALK+ NSCLC
  - 22% lower risk of death with alectinib than with crizotinib (HR 0.78; 95% CI 0.56-1.08)
  - OS benefit with alectinib was observed across several pre-specified patient subgroups, including patients with CNS metastases at baseline
  - Prolonged median DoR with alectinib (42.3 months vs 11.1 months)

- No new safety concerns were reported

Alectinib is an effective treatment option in the first – line setting for previously untreated, advanced ALK+ NSCLC non-small cell lung cancer regardless of brain metastases

Testing for ALK drives best treatment decision

ALEX Alectinib		CROWN Lorlatinib	
FDA approved			
• **Histologically/ cytologically confirmed advanced ALK-positive NSCLC (by Ventana IHC)** • **Aged ≥18 years** • **ECOG PS 0 – 2** • **No prior systemic therapy for advanced disease**		• **Stage IIIB/IV ALK+ NSCLC** • **≥1 extracranial measurable target lesion (RECIST v1.1) with no prior radiation required** • **Asymptomatic treated or untreated CNS metastases were permitted** • **ECOG PS 0-2** • **No prior systemic therapy for metastatic disease**	
Alectinib (n=152)	Crizotinib (n=151)	**Lorlatinib** (n=149)	Crizotinib (n=147)
Medium follow-up: **53.5 months**		Medium follow-up: **60.2 months**	
mPFS: **34.8 months**	10.9 months	**NR (64.3-NR)**	9.1 (7.4-10.9)
mOS: **81.1 months** **7-year OS rate: 48.6%** vs	54.2 months 38.2 %	*Not calculable* (*OS immature*)	*Not calculable*

Polling question

What is your preferred treatment in the frontline setting for ALK-positive metastatic NSCLC?

1. Alectinib
2. Lorlatinib
3. Other

2025 ESMO Key Studies

Breast Cancer

- *DESTINY-Breast11
- *DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*

- evERA BC
- VIKTORIA
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- *AGITG-DYNAMIC-III
  - *Polling Question*
- *RC48-C016
  - *Rapid Review*: POTOMAC

Lung Cancer and Other Notable Studies

- *HARMONI-6
- FLAURA2
  - *Polling Question*
- *OptiTROP-Lung04
  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

*ESMO Presidential Session

CLINICAL QUESTION

ENGOT-ov65/KEYNOTE-B96

* Presidential Symposium

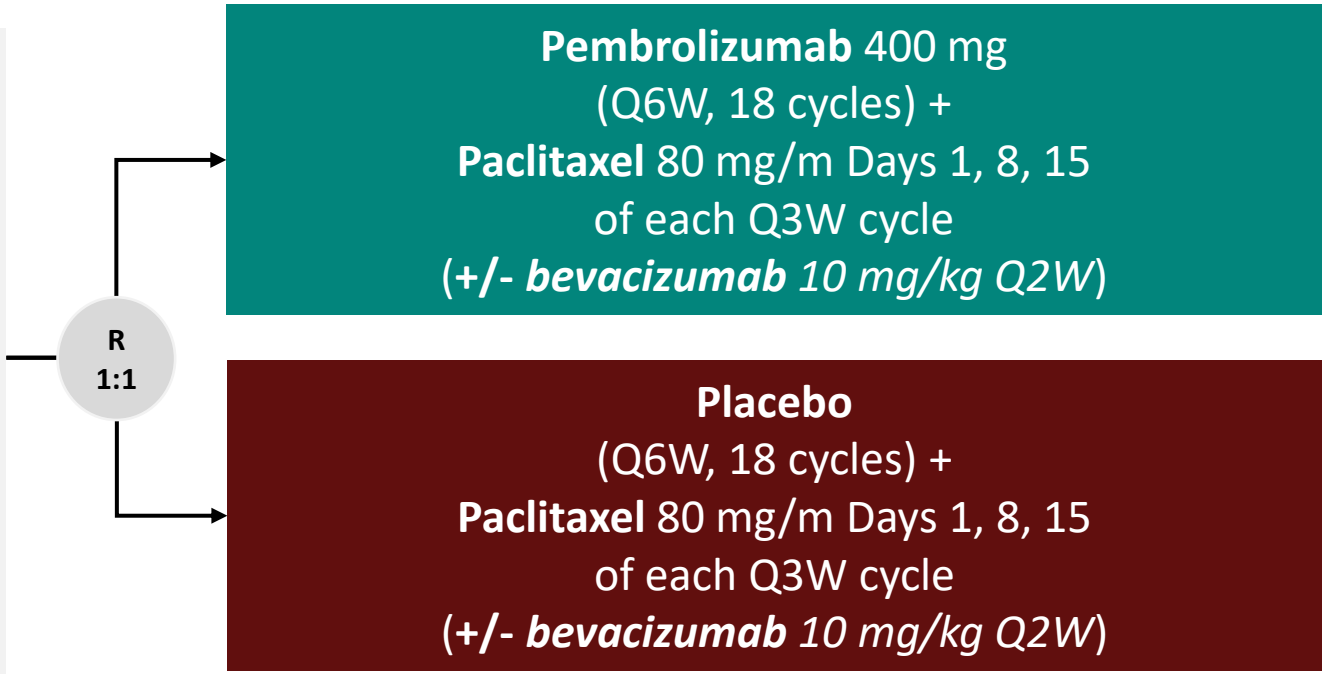
Does Pembrolizumab Plus Weekly Paclitaxel With or Without Bevacizumab provide benefits for patients with Platinum-Resistant Recurrent Ovarian Cancer?

KEY DATA

ENGOT-ov65/KEYNOTE-B96: Pembrolizumab + weekly paclitaxel ± bevacizumab in platinum-resistant ovarian cancer

Study Design: Randomized, double-blind, phase 3

- Histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma
- 1 or 2 prior lines of therapy at least 1 platinum-based chemotherapy
  - Prior anti-PD-1 or anti-PD-L1, PARPi and bevacizumab permitted
- Radiographic progression within 6 months after the last dose of platinum-based chemotherapy
- ECOG PS 0 or 1



Stratified by planned bevacizumab use (yes vs no), region (US vs EU vs ROW), PL-D1 CPS (>1 vs 1 to <10 vs ≥10)

Primary endpoint: Progression-free survival (PFS) per RECIST v1.1 by investigator

Key Secondary endpoint: Overall survival (OS)

KEY DATA

ENGOT-ov65/KEYNOTE-B96: Pembrolizumab + weekly paclitaxel ± bevacizumab in platinum-resistant ovarian cancer

Baseline characteristics

Characteristic, n (%)	Pembro Arm (n = 322)	Placebo Arm (n = 321)
Age, median (range)	62 y (37-85)	61 y (37-82)
PD-L1 CPS		
▪ <1	88 (27.3)	89 (27.7)
▪ 1 to <10	133 (41.3)	132 (41.1)
▪ ≥10	101 (31.4)	100 (31.2)
Stage at diagnosis (FIGO		
▪ IA-IIB	25 (7.8)	89 (27.7)
▪ III-IIIC	183 (56.8)	132 (41.1)
▪ IVA-IVB	114 (35.4)	100 (31.2)
EGOG PS 1	142 (44.1)	144 (44.9)
High-grade serous histology	278 (86.3)	275 (85.7)

Characteristic, n (%)	Pembro Arm (n = 322)	Placebo Arm (n = 321)
Bevacizumab use	235 (73.0)	236 (73.5)
Prior lines of therapy		
▪ 1 line	121 (37.6)	113 (35.2)
▪ 2 lines	200 (62.1)	207 (64.5)
Prior anticancer therapy		
▪ Anti-PD-1 or PD-L1	7 (2.2)	7 (2.2)
▪ Bevacizumab	149 (46.3)	146 (45.5)
▪ PARP inhibitor	112 (34.8)	123 (38.3)
Platinum-free interval		
▪ <3 mo	137 (42.5)	162 (50.5)
▪ ≥3 to <6mo	183 (56.8)	154 (48.0)
▪ >6 mo	2 (0.6)	4 (1.2)

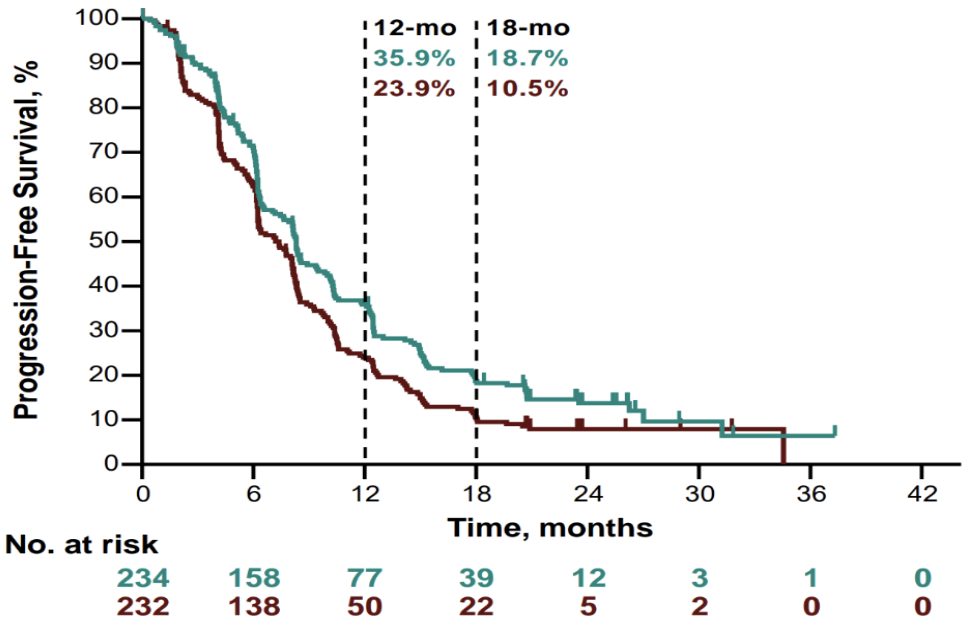
KEY DATA

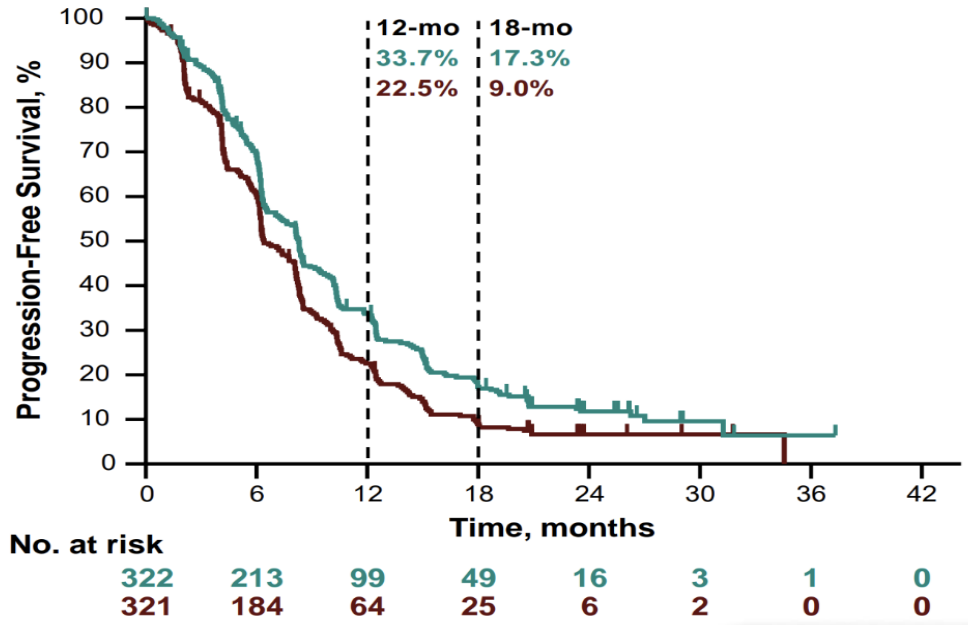
ENGOT-ov65/KEYNOTE-B96: Pembrolizumab + weekly paclitaxel ± bevacizumab in platinum-resistant ovarian cancer

Primary Endpoint: Progression Free Survival (PFS) in the CPS ≥1 and ITT Population at IA1

CPS ≥1	Pembro Arm	Placebo Arm
Median, mos	8.3	7.2
Events	81.6%	86.6%
HR (95% CI)	0.75 (0.61-0.91)	

ITT	Pembro Arm	Placebo Arm
Median, mos	8.3	6.4
Events	83.2%	87.2%
HR (95% CI)	0.73 (0.62-0.86)	



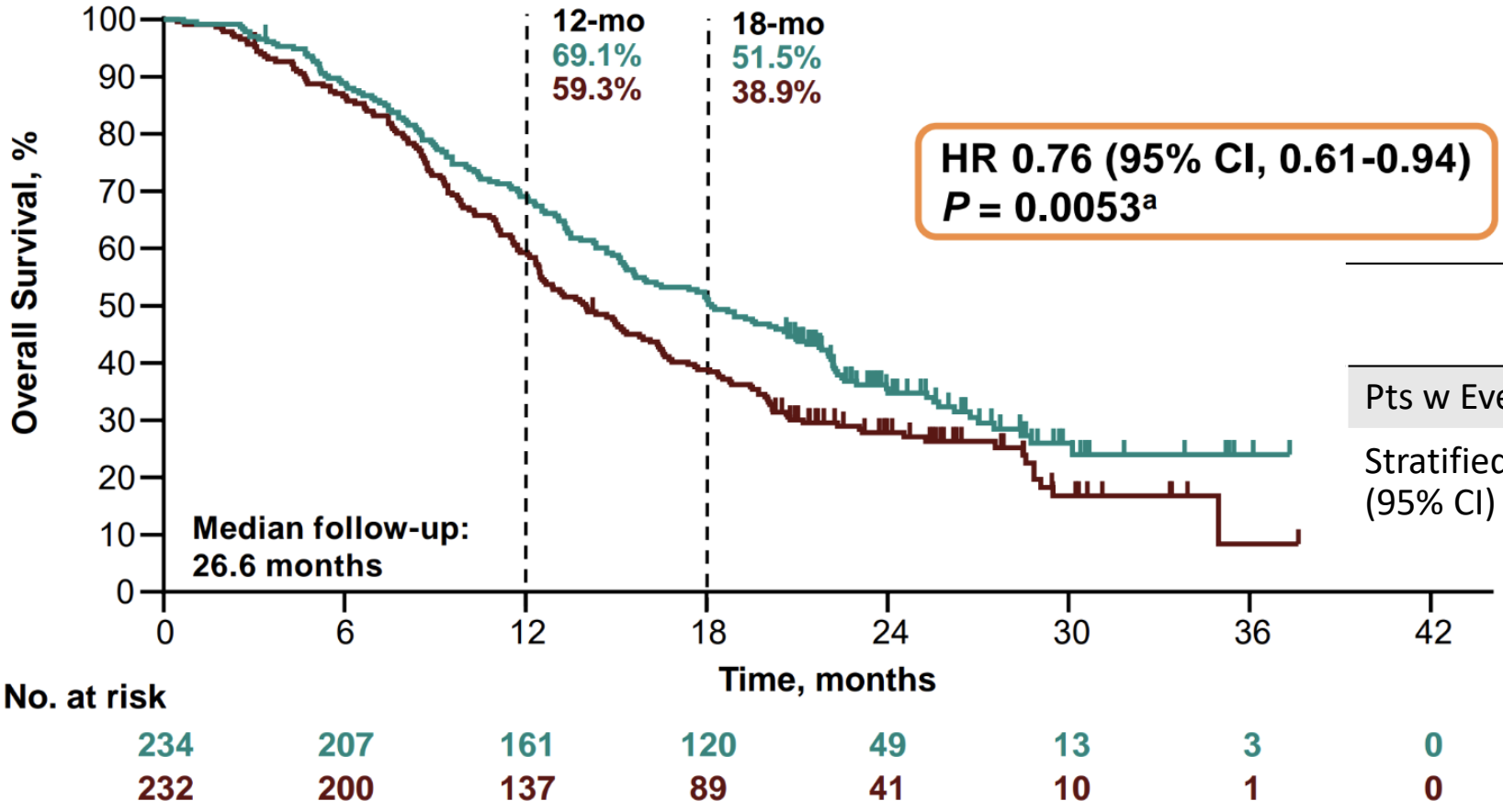


Median Follow-up: 2.6 months

KEY DATA

ENGOT-ov65/KEYNOTE-B96: Pembrolizumab + weekly paclitaxel ± bevacizumab in platinum-resistant ovarian cancer

Secondary Endpoint: Overall Survival (OS) in the CPS ≥1 Population at IA2



	Pembro Arm	Placebo Arm
Pts w Event	67.1%	75.4%
Stratified HR (95% CI)	18.2 (15.3-21.0)	14.0 (12.5-16.1)

KEY DATA

ENGOT-ov65/KEYNOTE-B96: Pembrolizumab + weekly paclitaxel ± bevacizumab in platinum-resistant ovarian cancer

Safety Summary

n (%)	All-Cause AEs		Treatment-Related AEs		Immune-Mediated AEs	
	Pembro Arm (N=320)	Placebo Arm (N=318)	Pembro Arm (N=320)	Placebo Arm (N=318)	Pembro Arm (N=320)	Placebo Arm (N=318)
Any grade	318 (99.7)	316 (99.4)	313 (97.8)	303 (95.3)	125 (39.1)	60 (18.9)
Grade ≥3	264 (82.5)	225 (70.8)	216 (67.5)	176 (55.3)	37 (11.6)	11 (3.5)
Serious	178 (55.6)	122 (38.4)	106 (33.1)	62 (19.5)	35 (10.9)	7 (2.2)
Leading to death	15 (4.7)	14 (4.4)	3 (0.9)	5 (1.6)	2 (0.6)	0
Leading to discontinuation of any treatment	132 (41.3)	108 (34.0)	115 (35.9)	89 (28.0)	22 (6.9)	8 (2.5)

SUMMARY

ENGOT-ov65/ KEYNOTE-B96

- Pembrolizumab in combination with weekly paclitaxel, with or without bevacizumab, demonstrated improvements in PFS regardless of PD-L1 status and in OS in participants with PD-L1-expressing tumor
- This phase 3 study is the first to show a statistically significant OS benefit with an immune checkpoint inhibitor in ovarian cancer also reports one of the longest OS outcomes seen in PRROC
- The safety profile was consistent with the known profile of the individual therapies, with no new safety signals

IMPACT

Pembrolizumab plus weekly paclitaxel, with or without bevacizumab, may be a new treatment option for patients with platinum-resistant recurrent ovarian cancer

Potential new treatment option, not yet FDA approved
PDUFA date: Feb 20, 2026

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2025 ESMO Key Studies

Breast Cancer

- *DESTINY-Breast11
- *DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*

- evERA BC
- VIKTORIA
  - *Polling Question*

GU GI

- *KEYNOTE-905/EV-303
- *IMvigor-011
  - *Polling Question*
- *PSMAddition
  - *Rapid Review*: CAPItello-281
- *Polling Question*
- *FORTITUDE-101
- *AGITG-DYNAMIC-III
  - *Polling Question*
- *RC48-C016
  - *Rapid Review*: POTOMAC

Lung Cancer and Other Notable Studies

- *HARMONI-6
- FLAURA2
  - *Polling Question*
- *OptiTROP-Lung04
  - *Polling Question*
- ALEX
  - *Polling Question*

- *KEYNOTE-B96
- REJOICE-Ovarian01
  - *Polling Question*

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*ESMO Presidential Session

REJOICE-Ovarian01

Does raludotatug deruxtecan (R-DXd) benefit patients with platinum-resistant ovarian cancer?

KEY DATA

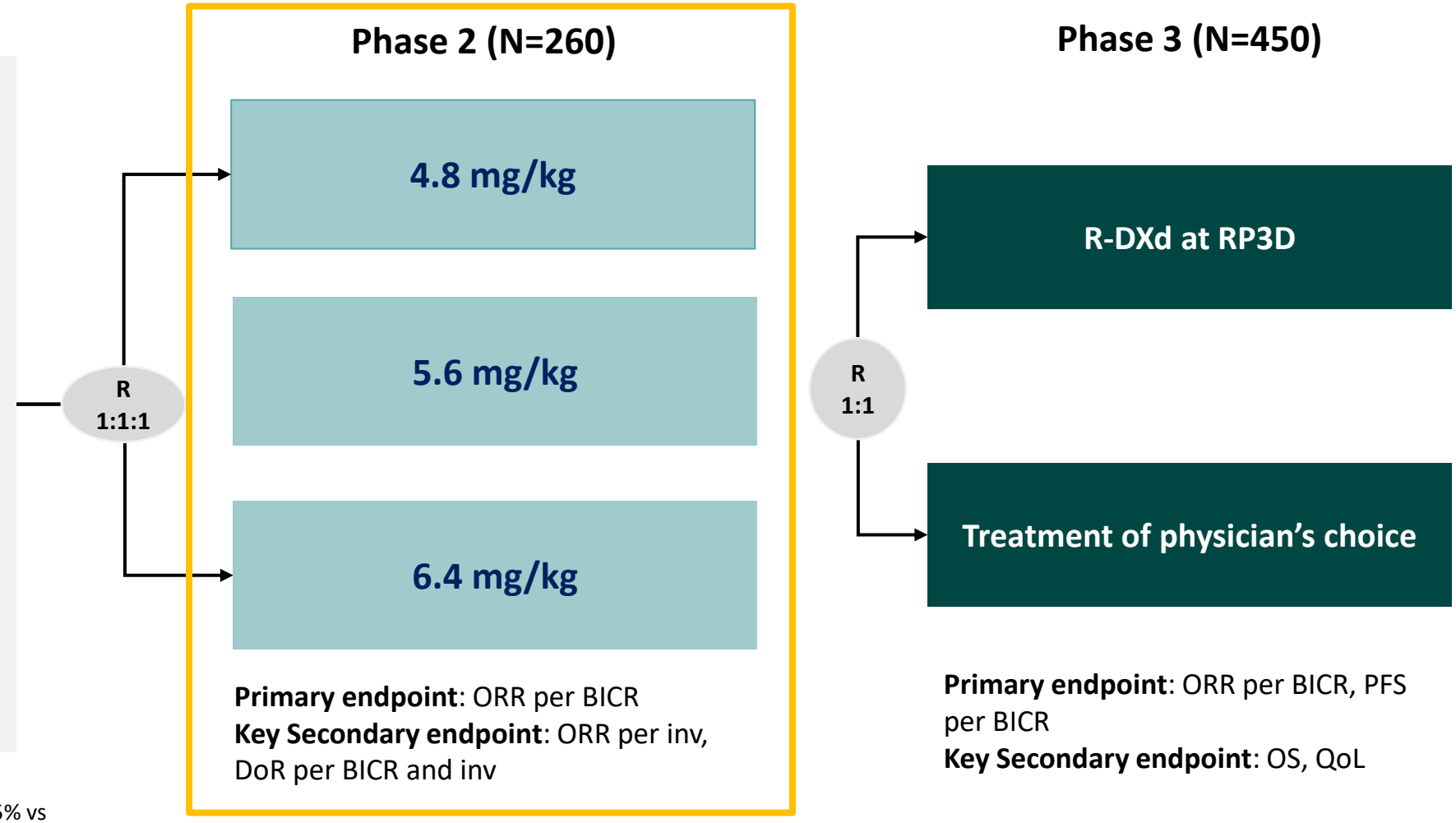
REJOICE-Ovarian01: R-DXd, Platinum-Resistant Ovarian Cancer

Study Design: Phase 2/3 multicenter, randomized study

- High-grade serious or high-grade endometroid ovarian, primary peritoneal, or fallopian tube cancer
- 1-3 prior lines of therapy including bevacizumab
- Platinum-resistant disease (primary platinum-refractory disease is exclusionary)
- Prior mirvetuximab soravtansine (for tumors with high FRα expression)
- ECOG PS 0 or 1
- No prior CDH6*-targeting agents or ADCs with a linked DXd
- No selection by tumor CDH6 expression

Stratified by number of prior LOT (1 vs 2-3), CDH6 membrane expression by IHC (≥75% vs <75%), and TPC (paclitaxel vs other; phase 3 only)

*CDH6: cadherin 6



REJOICE-Ovarian01: R-DXd, Platinum-Resistant Ovarian Cancer

Baseline characteristics

Characteristic, n (%)	R-DXd 4.8-6.4 mg/kg (n = 107)
Age, median (range), yrs	60 (34-81)
• Age >70 yr	17 (15.9)
Region	
• Asia	45 (42.1)
• Europe	61 (57.0)
• Australia	1 (0.9)
ECOG PS	
• 0	61 (57.0)
• 1	46 (43.0)
Cancer type	
• Ovarian	91 (85.0)
• Peritoneal	4 (3.7)
• Fallopian tube	12 (11.2)
Tumor FIGO stage at initial diagnosis	
• I-II	11 (10.3)
• III	53 (49.5)
• IV	39 (36.4)
• Unknown	4 (3.7)

Characteristic, n (%)	R-DXd 4.8-6.4 mg/kg (n = 107)
Number of prior lines of system therapy	
• 1	10 (9.3)
• 2	42 (39.3)
• 3	55 (51.4)
Received prior therapy	
• Bevacizumab	89 (83.2)
• PARP inhibitor	75 (70.1)
• Mirvetuximab soravtansine	3 (2.8)
Last platinum-free interval	
• <3 months	39 (14.7)
• 3-6 months	45 (16.9)
Tumor CDH6 membrane positive at any intensity at baseline	n=101
• Any positive	95 (94.1)
• <75% positive	41 (40.6)
• ≥75% positive	60 (59.4)

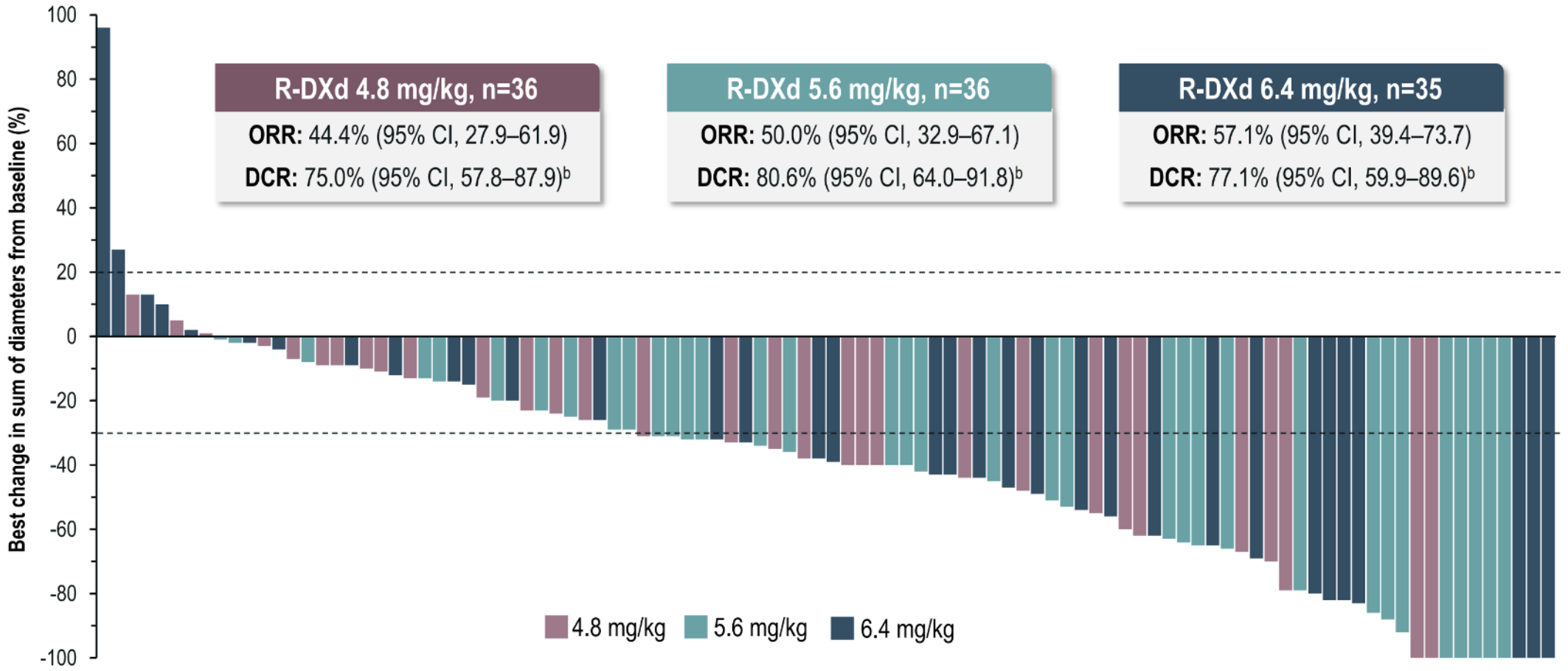
REJOICE-Ovarian01: R-DXd, Platinum-Resistant Ovarian Cancer

Primary Endpoint: Confirmed Response by BICR

	R-DXd 4.8 mg/kg N=36	R-DXd 5.6 mg/kg N=36	R-DXd 6.4 mg/kg N=35	R-DXd 4.8-6.4 mg/kg N=107
Ojective Response Rate, % (95% CI)	44.4 (27.9-61.9)	50.0 (32.9-67.1)	57.1 (39.4-73.7)	50.5 (40.6-60.3)
Best Overall Response, n (%)				
• CR	1 (2.8)	2 (5.6)	0	3 (2.8)
• PR	15 (41.7)	16 (44.4)	20 (57.1)	51 (47.7)
• SD	17 (47.2)	15 (41.7)	10 (28.6)	42 (39.3)
• PD	2 (5.6)	2 (5.6)	4 (11/4)	8 (7.5)
• Not evaluated	1 (2.8)	1 (2.8)	1 (2.9)	3 (2.8)
Disease Control Rate, % (95% CI)	75.0 (57.8-87.9)	80.6 (64.0-91.8)	77.1 (59.9-89.6)	77.6 (68.5-85.1)
TRR, median (range), weeks	7.1 (5.4-18.7)	6.6 (5.1-18.3)	7.2 (53.19.1)	7.1 (5.1-19.1)

REJOICE-Ovarian01: R-DXd, Platinum-Resistant Ovarian Cancer

Tumor response



REJOICE-Ovarian01: R-DXd, Platinum-Resistant Ovarian Cancer

Safety Summary

	R-DXd 4.8 mg/kg N=36	R-DXd 5.6 mg/kg N=36	R-DXd 6.4 mg/kg N=35	R-DXd 4.8-6.4 mg/kg N=107
Any TEAE, n (%)	35 (97.2)	36 (100)	36 (100)	106 (99.1)
• Grade ≥3	16 (44.4)	20 (55.6)	20 (57.1)	56 (52.3)
Any treatment-related TEAE, n (%)	31 (88.9)	34 (94.4)	34 (97.1)	100 (93.5)
• Grade ≥3	10 (27.8)	11 (30.6)	17 (48.6)	38 (35.5)
• Grade 5	0	0	0	0
Any treatment-related SAE, n (%)	14 (38.9)	12 (33.3)	14 (40.0)	40 (37.4)
• Grade ≥3	13 (36.1)	10 (27.8)	11 (31.4)	34 (31.8)
• Grade 5	3 (8.3)	2 (5.6)	1 (2.9)	6 (5.6)
Dose modifications associated with treatment-related TEAEs, n (%)				
• Drug discontinuation	3 (8.3)	0	3 (8.6)	6 (5.6)
• Dose reduction	5 (13.9)	4 (11.1)	11 (31.4)	20 (18.7)
• Dose delay	8 (22.2)	7 (19.4)	10 (28.6)	25 (23.4)
ILD/ pneumonitis adjudicated as treatment related, n (%)				
Any grade	1 (2.8)	1 (2.8)	2 (5.7)	4 (3.7)
Grade ≥3	1 (2.8)	0	0	1 (0.9)
Grade 5	0	0	0	0

SUMMARY

REJOICE-Ovarian01

- R-DXd showed promising activity in platinum-resistant ovarian cancer, with a 50.5% ORR (including 3 CRs) across doses (4.8–6.4 mg/kg) and responses observed regardless of CDH6 expression level
- Safety was manageable, consistent with prior findings, with one Grade ≥3 treatment-related ILD event, supporting a positive benefit–risk profile for the 5.6 mg/kg dose
- R-DXd 5.6 mg/kg was selected as the optimal dose, and will be evaluated in the Phase 3 part of the REJOICE-Ovarian01 trial vs treatment of physician's choice

IMPACT

Raludotatug deruxtecan (at 5.6 mg/kg) is a potential new treatment option for patients with platinum-resistant ovarian cancer

Received Breakthrough Therapy Designation Sept 2025, not yet FDA approved

Polling question

*Based on the presented **Keynote-B96** and **REJOICE-Ovarian01** data, and if approved by the FDA: would you recommend immunotherapy-based combinations or ADC therapy first for platinum-resistant ovarian cancer in the majority of cases?*

1. Immunotherapy based combinations (KEYNOTE-B896)
2. ADC therapy (R-DXd, REJOICE-Ovarian01)
3. Unsure, need more data

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ESMO 2025:

Lung and Ovarian Cancers

Key Takeaways

Q&A

@EricSchaeferMD

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HARMONI-6: In first-line advanced squamous NSCLC, Ivonescimab + platinum-taxane improved mPFS 11.14 (vs 6.90 months with tislelizumab) and may become a standard of care in the curative intent setting for advanced squamous NSCLC – *not yet approved*

FLAURA2: In first-line EGFRm advanced NSCLC, osimertinib plus platinum-pemetrexed achieved a median OS of 47.5 months (vs 37.6 months with osimertinib monotherapy) and consistent benefits across key subgroups (CNS, mutation type, TP53 status) – *FDA approved Feb 16, 2024*

OptiTROP-Lung04: In EGFRm NSCLC following post-EGFR-TKIs, sac-TMT improved PFS (8.3 vs 4.3 months, HR 0.49; P<0.0001) and ORR (60.6% vs 43.1%) versus chemotherapy – *not yet approved*

ALEX: In first-line ALK-positive advanced NSCLC, alectinib achieved durable overall-survival and long-term CNS control versus crizotinib, reinforcing alectinib's long-standing role as first-line standard of care for ALK-positive advanced NSCLC – *FDA approved Nov 6, 2017*

ENGOT-ov65/KEYNOTE-B96: In platinum-resistant recurrent ovarian cancer with up to 2 prior lines of therapy, pembrolizumab plus weekly paclitaxel, with or without bevacizumab demonstrated overall-survival benefit versus placebo – *not yet approved*

REJOICE-Ovarian01: In pretreated, platinum-resistant high-grade ovarian cancer, R-DXd achieved confirmed ORR (~50–51% across tested doses) and the 5.6 mg/kg dose was favored for risk/benefit – *FDA Breakthrough Therapy Sept 2025, not yet approved*