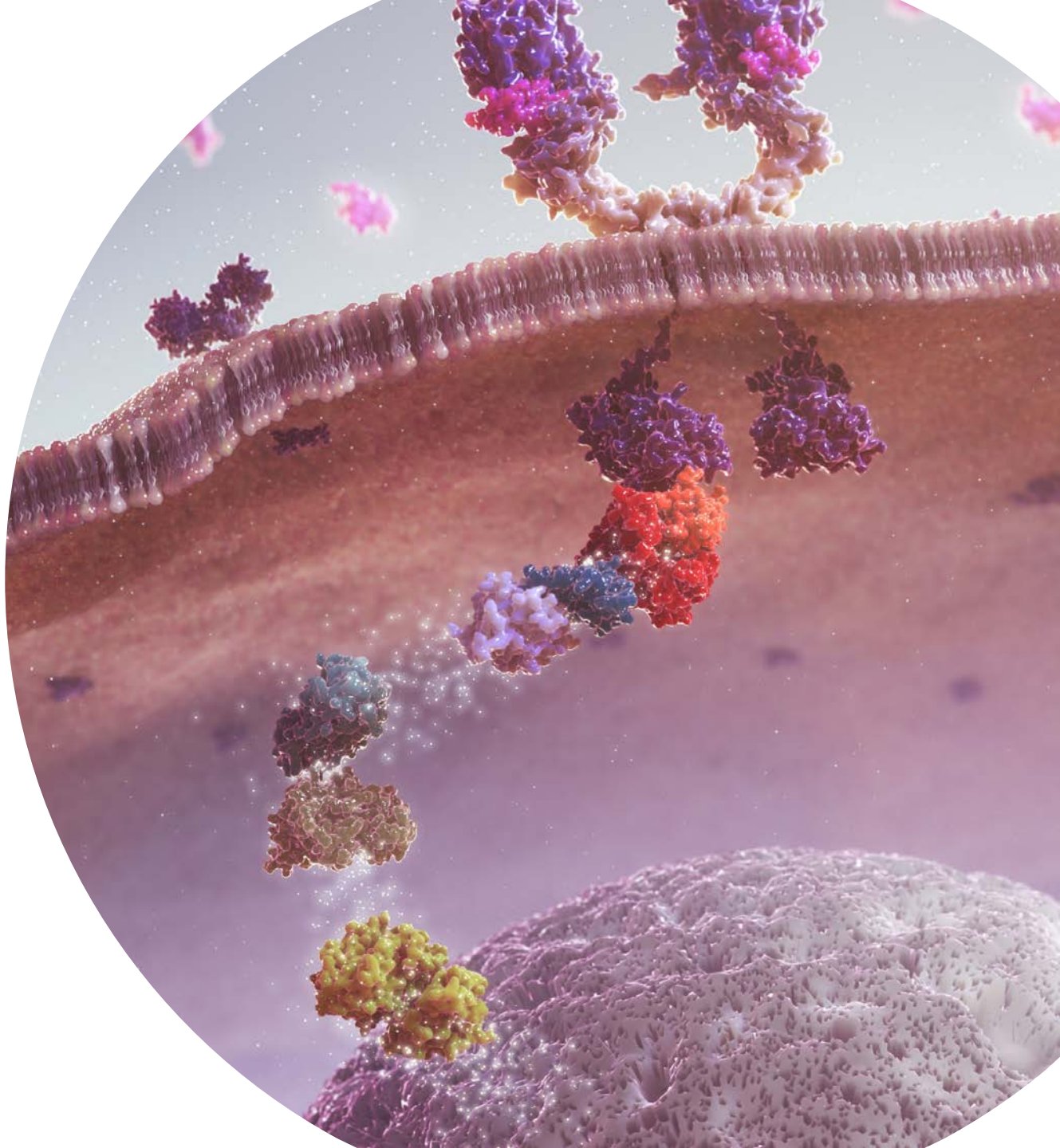
AstraZeneca

ESMO 2023

Meet AZN Management

For investors and analysts

23 October 2023



AstraZeneca @ ESMO 2023

Speakers and panelists

KEY EXTERNAL EXPERT
Dr Aaron Lisberg,
Thoracic Medical Oncologist, UCLA

Pascal Soriot,
Chief Executive Officer

Susan Galbraith,
Executive Vice President, Oncology R&D

Sunil Verma,
Global Head of Oncology, Medical

KEY EXTERNAL EXPERT
Dr Aditya Bardia,
Breast Medical Oncologist, MGH

Dave Fredrickson,
Executive Vice President, Oncology Business

Cristian Massacesi,
Chief Medical Officer & Oncology Chief Development Officer

SPECIALIST AREA LEADERSHIP

Niko Andre,
Global Franchise Head, Immuno-oncology

Matt Hellman,
VP, Head of Clinical Group, Early Oncology

Leora Horn,
Head of Clinical Development, Late Development Oncology, Global Clinical Strategy Head, Lung Cancer

Puja Sapra,
SVP, Biologics Engineering & Targeted Delivery

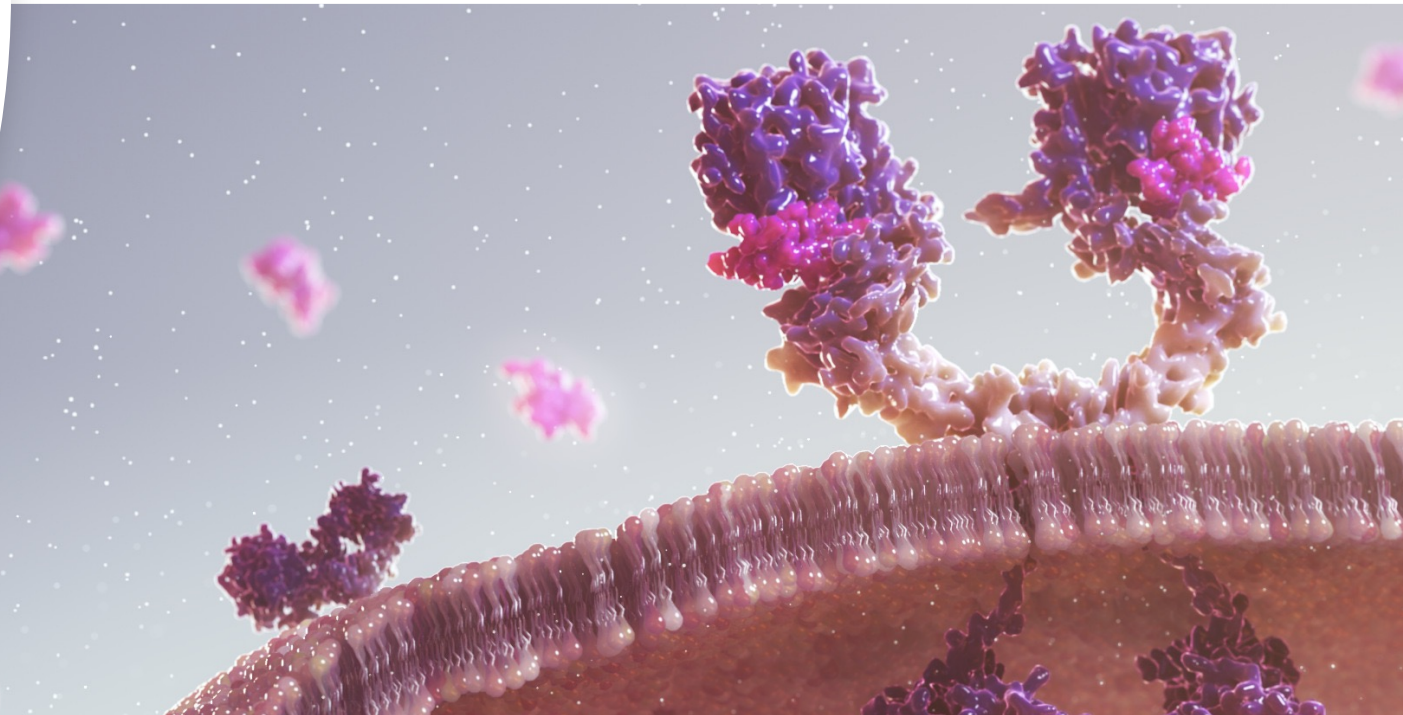
Vikram Chand,
VP, Global Franchise Head, Dato-DXd

Simon Hollingsworth,
Global Franchise Head, IO Bispecifics

Ingrid Mayer,
Global Clinical Strategy Head, Breast Cancer

Leading a revolution to redefine cancer care

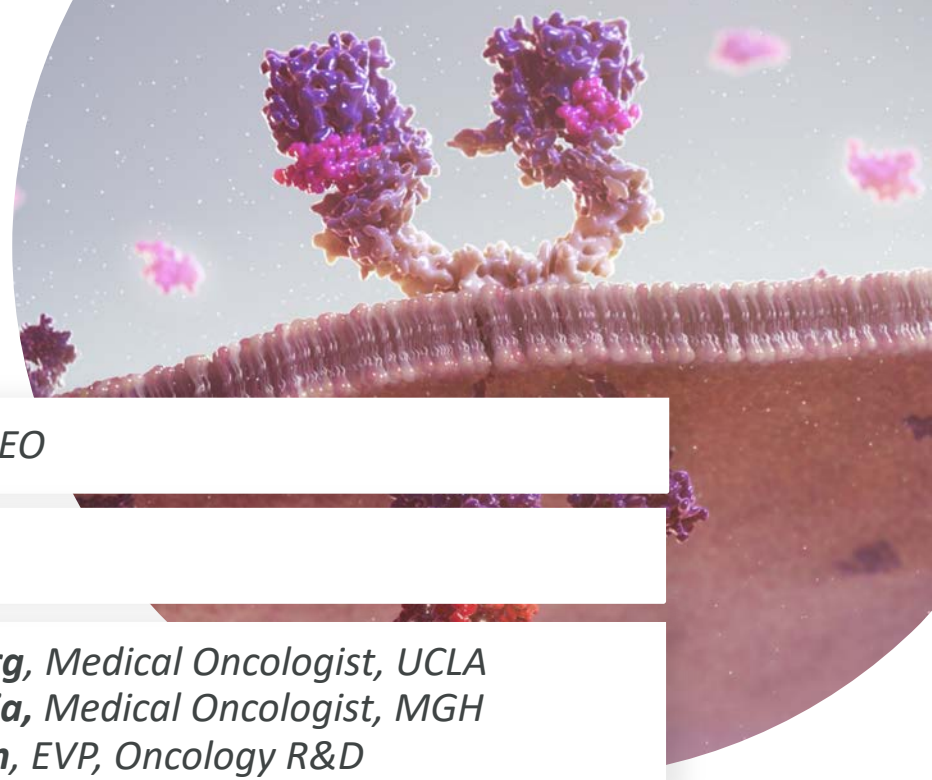
Pascal Soriot
CHIEF EXECUTIVE OFFICER



Forward-looking statements

In order, among other things, to utilise the 'safe harbour' provisions of the US Private Securities Litigation Reform Act of 1995, AstraZeneca (hereafter ‘the Group’) provides the following cautionary statement: This document contains certain forward-looking statements with respect to the operations, performance and financial condition of the Group, including, among other things, statements about expected revenues, margins, earnings per share or other financial or other measures. Although the Group believes its expectations are based on reasonable assumptions, any forward-looking statements, by their very nature, involve risks and uncertainties and may be influenced by factors that could cause actual outcomes and results to be materially different from those predicted. The forward-looking statements reflect knowledge and information available at the date of preparation of this document and the Group undertakes no obligation to update these forward-looking statements. The Group identifies the forward-looking statements by using the words 'anticipates', 'believes', 'expects', 'intends' and similar expressions in such statements. Important factors that could cause actual results to differ materially from those contained in forward-looking statements, certain of which are beyond the Group’s control, include, among other things: the risk of failure or delay in delivery of pipeline or launch of new medicines; the risk of failure to meet regulatory or ethical requirements for medicine development or approval; the risk of failures or delays in the quality or execution of the Group’s commercial strategies; the risk of pricing, affordability, access and competitive pressures; the risk of failure to maintain supply of compliant, quality medicines; the risk of illegal trade in the Group’s medicines; the impact of reliance on third-party goods and services; the risk of failure in information technology or cybersecurity; the risk of failure of critical processes; the risk of failure to collect and manage data in line with legal and regulatory requirements and strategic objectives; the risk of failure to attract, develop, engage and retain a diverse, talented and capable workforce; the risk of failure to meet regulatory or ethical expectations on environmental impact, including climate change; the risk of the safety and efficacy of marketed medicines being questioned; the risk of adverse outcome of litigation and/or governmental investigations; intellectual property-related risks to our products; the risk of failure to achieve strategic plans or meet targets or expectations; the risk of failure in financial control or the occurrence of fraud; the risk of unexpected deterioration in the Group’s financial position; the impact that global and/or geopolitical events such as the COVID-19 pandemic and the Russia-Ukraine war may have or continue to have on these risks, on the Group’s ability to continue to mitigate these risks, and on the Group’s operations, financial results or financial condition. Nothing in this document, or any related presentation/webcast, should be construed as a profit forecast.

AstraZeneca @ ESMO 2023



AGENDA

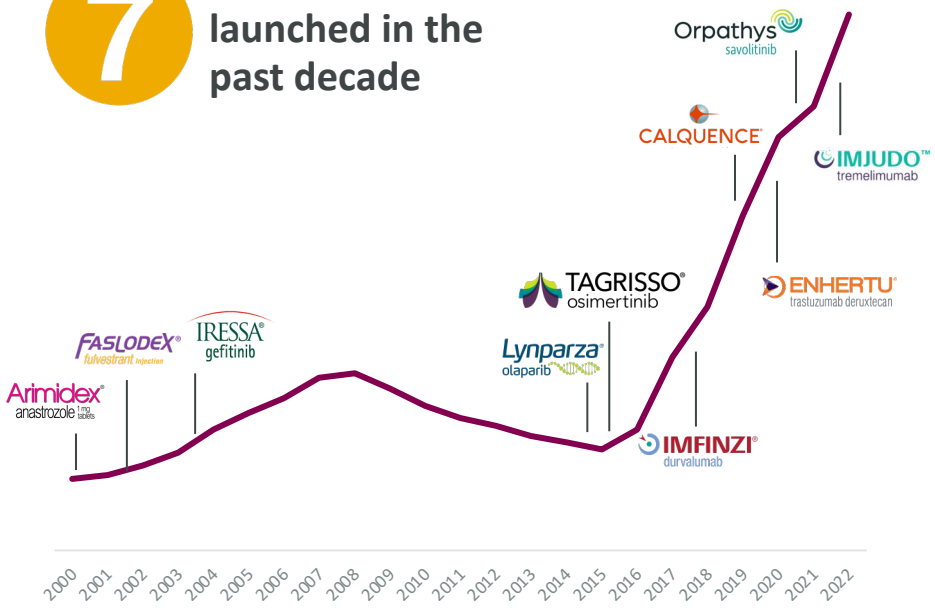
Leading a revolution to redefine cancer care	–	***Pascal Soriot**, CEO*
Placing AstraZeneca data from ESMO 2023 into context		
Realising the transformative potential of ADCs	–	***Dr Aaron Lisberg**, Medical Oncologist, UCLA* ***Dr Aditya Bardia,** Medical Oncologist, MGH* ***Susan Galbraith**, EVP, Oncology R&D*
Advancing our leadership in immuno-oncology	–	***Cristian Massacesi**, CMO, Oncology R&D* ***Dave Fredrickson**, EVP, Oncology Business*
Establishing *Tagrisso* as backbone TKI in EGFRm NSCLC	–	***Dave Fredrickson**, EVP, Oncology Business*
Q&A session	–	***AstraZeneca management***

AstraZeneca – leading a revolution to redefine cancer care

Proven track record, transforming the oncology landscape

Delivering treatments to patients with greatest unmet need

7 novel medicines launched in the past decade



Oncology Total Revenue ($'000m)

Establishing tumour area leadership

Organisational design promoting collaboration across R&D and commercial

Expanding next-wave pipeline

Diverse portfolio of novel modalities supporting potential combinations

Collaboration partners: Daiichi Sankyo (*Enhertu*, Dato-DXd), Merck & Co., Inc. (Lynparza).

GI = gastrointestinal; GYN = gynecological; GU = genitourinary; DNA = deoxyribonucleic acid; ADC = antibody-drug conjugate; RC = radio conjugate.

Establishing our tumour area leadership

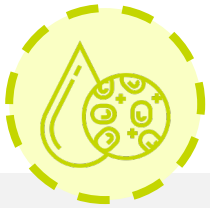
Lung

- TAGRISSO® osimertinib
- IMFINZI® durvalumab + IMJUDO® tremelimumab-actl
- ENHERTU® fam-trastuzumab deruxtecan-nxki
- Orpathys®
- Dato-DXd
- volrustomig (PD1/CTLA4)
- rilvegostomig (PD1/TIGIT)
- sabestomig (PD1/TIM3)
- ceralasertib
- AZD9592 (EGFR-cMET ADC)
- AZD5335 (FRα ADC)
- oleclumab
- monalizumab

Breast

- ENHERTU® fam-trastuzumab deruxtecan-nxki
- Lynparza® olaparib
- IMFINZI® durvalumab
- Dato-DXd
- capivasertib
- camizestrant
- AZD8205 (B7H4 ADC)

Haematology



- CALQUENCE® (acalabrutinib)
- AZD0486 (CD3xCD19 TCE)
- sabestomig (PD1/TIM3)
- LM-305 (GPRC5D ADC)

GI

- IMFINZI® durvalumab
- IMFINZI® durvalumab + IMJUDO® tremelimumab-actl
- Lynparza® olaparib
- ENHERTU® fam-trastuzumab deruxtecan-nxki
- IMFINZI® durvalumab + Orpathys®
- Orpathys®
- AZD5851 (GPC3 CAR-T)
- AZD8205 (B7H4 ADC)
- AZD0901 (anti-Cl18.2 ADC)

GYN/GU

- Lynparza® olaparib
- IMFINZI® durvalumab
- IMFINZI® durvalumab + IMJUDO® tremelimumab-actl
- ENHERTU® fam-trastuzumab deruxtecan-nxki
- capivasertib
- AZD8205 (B7H4 ADC)
- AZD5335 (FRα ADC)

Dato-DXd = datopotamab deruxtecan; EGFR = epidermal growth factor receptor; c-MET = mesenchymal-epithelial transition factor; ADC = antibody-drug conjugate; CD3xCD19 = cluster of differentiation 3 and cluster of differentiation 19 bispecific; TCE = T cell engager; AKTi = protein kinase B inhibitor; BCL2-xL = B-cell lymphoma-extra large; PD1 = programmed cell death protein 1; TIM3 = T-cell immunoglobulin and mucin domain-containing protein 3; GPC3 = glypican 3 protein; CAR-T = chimeric antigen receptor t-cell; CLDN18.2 = Claudin-18.2; EGFR-cMET = epidermal growth factor receptor mutation and mesenchymal-epithelial transition factor; FRα = folate receptor α; GPRC5D = G protein-coupled receptor family C group 5 member D.Collaboration partners: Daiichi Sankyo (*Enhertu*, Dato-DXd), Merck & Co., Inc. (*Lynparza*); Compugen (rilvegostomig).

AstraZeneca exceptional momentum in oncology this year

9 **positive data read-outs to-date in 2023**

TROPION-Breast01 | **positive Phase III HLR** since H1 2023

Plenaries at four key Oncology congresses

AACR	ASCO	IASLC	ESMO
AEGEAN	ADAURA	FLAURA2	TL01 TB01

Key data highlights at ESMO 2023

>90 accepted abstracts

26 oral presentations incl.

- DUO-E (LBA41)
- MATTERHORN (LBA73)
- DESTINY-PanTumor02 (LBA34)
- TROPION-Lung05 (1314MO)

2 Presidential plenaries

- TROPION-Lung01 (LBA12)
- TROPION-Breast01 (LBA11)

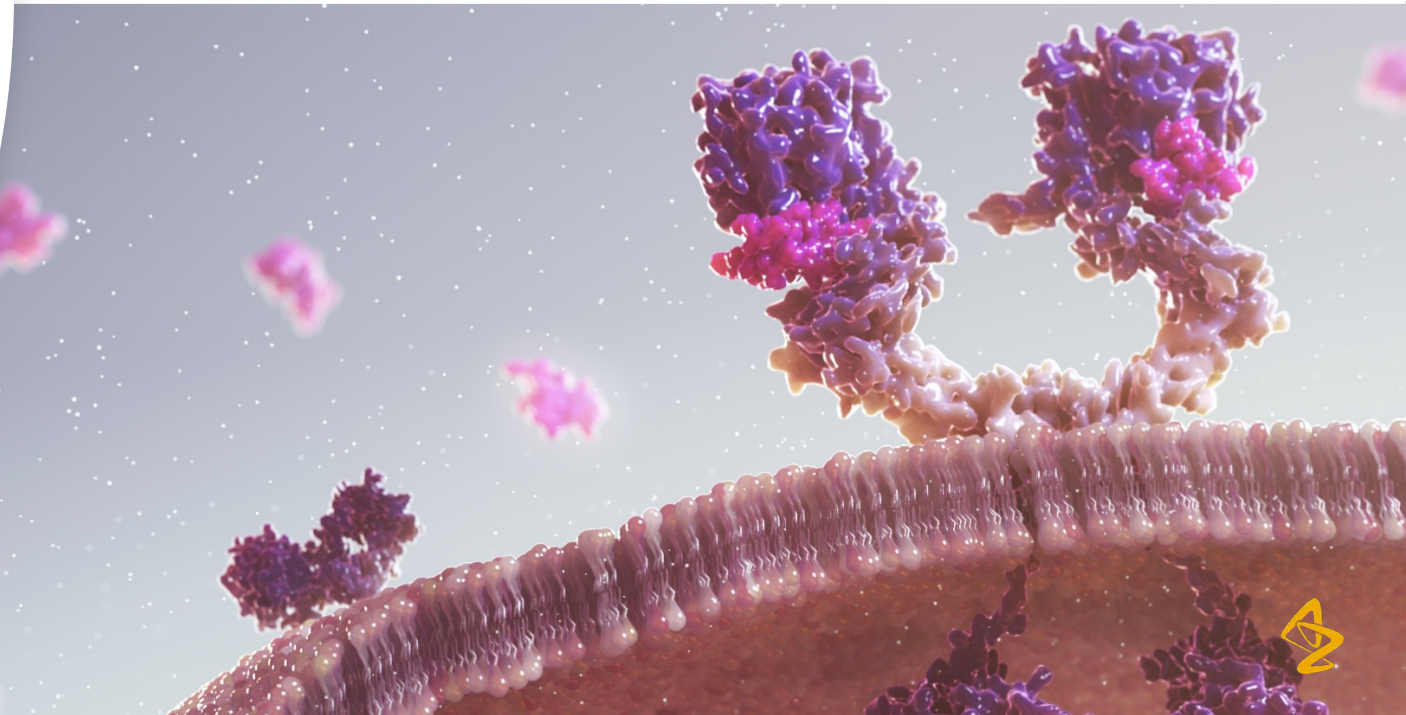
Collaboration partner: Daiichi Sankyo (*Enhertu*, Dato-DXd).

HLR = high-level results; TL01 = TROPION-Lung01; TB01 = TROPION-Breast01; ESMO = European Society for Medical Oncology; LBA = late-breaking abstract; MO = mini-oral.

Transforming treatment with antibody drug conjugates

TROPION-Lung01

Dr Aaron Lisberg
THORACIC MEDICAL ONCOLOGIST, UCLA



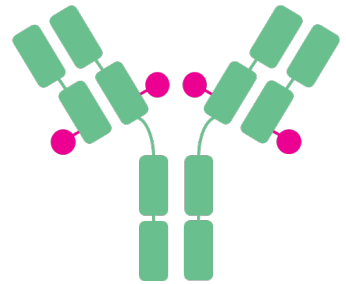
Background

Unmet need in 2L NSCLC

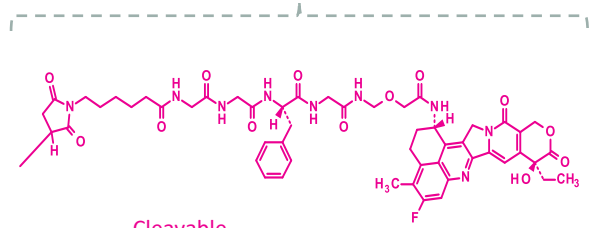
- Standard-of-care, **second-line chemotherapy** for metastatic NSCLC is associated with a **modest benefit and substantial toxicity**
- **Dato-DXd** is a **TROP2-directed ADC** that selectively delivers a potent topoisomerase I inhibitor payload directly into tumour cells[1]
- **Promising antitumor activity** was seen with Dato-DXd in patients with adv/met NSCLC in the phase 1 TROPION-PanTumor01 trial (26% ORR)[1]

Dato-DXd

Humanised anti-TROP2 IgG1 mAb[2-5]



Deruxtecan



Cleavable tetrapeptide-based linker

Topo-I inhibitor payload (DXd)

Image is for illustrative purposes only; actual drug positions may vary. 1. Shimizu T, et al. J Clin Oncol. 2023;41:4678-4687. 2. Okajima D, et al. Mol Cancer Ther. 2021;20:2329-2340. 3. Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67:173-185. 4. Ogitani Y, et al. Clin Cancer Res. 2016;22:5097-5108. 5. Ogitani Y, et al. Cancer Sci. 2016;107:1039-1046.

2L = 2nd-line; NSCLC = non-small cell lung cancer; TROP2 = trophoblast cell-surface antigen 2; ADC = antibody drug conjugate; DatpDXd = datopotomab deruxtecan; adv = advanced; met = metastaticl ORR = objective response rate; IgG1 = immunoglobulin G1; mAB = monoclonal antibody.

Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Lung01 Phase III trial in 2L+ NSCLC

Randomised Phase III open-label global trial

- NSCLC (Stg. IIIB, IIIC, or IV)
- ECOG PS 0 or 1
- No prior docetaxel

Without AGA[1]

- 1-2 prior lines, including platinum CTx and anti-PD-(L)1

With AGA

- Positive for EGFR, ALK, NTRK, BRAF, ROS1, MET exon 14 skipping, or RET
- 1-2 lines prior approved therapies + platinum based CTx and ≤1 anti-PD-(L)1 +/- cytotoxic agent

Stratified by:

- Histology (squamous vs. non-squamous)
- AGA (presence vs absence)
- Anti-PD-(L)1 mAb included in most recent prior therapy (yes vs no)
- Geography (US/Japan/Western Europe vs RoW)

Endpoints

Dual primary endpoints:

- PFS (BICR)
- OS

Secondary endpoints:

- ORR (BICR)
- DOR (BICR)
- Safety

Enrolment period: 19 February 2021 to 7 November 2022. 1. Patients with KRAS mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations
2L = 2nd-line; NSCLC = non-small cell lung cancer; Stg. = stage; ECOG PS = Eastern Cooperative Oncology Group performance scale; AGA = actionable genomic alteration; CTx = chemotherapy; PD-(L)1 = programmed cell death protein 1 or programmed cell death protein 1 ligand 1; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; NTRK = neurotrophic tropomyosin receptor kinase; BRAF = v-raf murine sarcoma viral oncogene homolog B1; MET = mesenchymal-epithelial transition factor; RET = rearranged during transfection; R = randomised; Dato-DXd = datopotamab deruxtecan; q3w = every three weeks; RoW = rest of world; PFS = progression-free survival; BICR = blinded independent centralised review; OS = overall survival; ORR = objective response rate; DOR = duration of response. Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Lung01 – Baseline features

Characteristic		Dato-DXd N=299	Docetaxel N=305
Age, median (range), years		63 (26, 84)	64 (24, 88)
Male, n (%)		183 (61)	210 (69)
Race, n (%)	Asian	119 (40)	120 (39)
	White	123 (41)	126 (41)
	Black or African American	6 (2)	4 (1)
	Other[1]	51 (17)	55 (18)
ECOG, n (%)	0	89 (30)	94 (31)
	1	210 (70)	211 (69)
Histology, n (%)	Non-Squamous	234 (78)	234 (77)
	Squamous	65 (22)	71 (23)

Characteristic		Dato-DXd N=299	Docetaxel N=305
Current or former smoker, n (%)		238 (80)	251 (82)
Actionable genomic alterations, n (%)	Present	50 (17)	51 (17)
	EGFR mutation	39 (13)	45 (15)
Brain metastasis at baseline, n (%)[2]		50 (17)	47 (15)
Prior lines, n (%)	1	167 (56)	174 (57)
	2	108 (36)	102 (33)
	≥3	22 (7)	28 (9)
Previous systemic therapy, n (%)[3]	Platinum containing	297 (99)	305 (100)
	Anti–PD-(L)1	263 (88)	268 (88)
	Targeted	46 (15)	50 (16)

1. Race data was missing for 8 participants in each arm. 2. Patients who are no longer symptomatic and who require no treatment with corticosteroids and anticonvulsants and have recovered from acute toxic effects of radiation are eligible. 3. In the Dato-DXd arm, 2 patients did not receive prior treatment with a platinum-containing therapy and 1 patient with actionable genomic alterations did not receive previous targeted therapy, deviating from the protocol. Dato-DXd = datopotamab deruxtecan; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; PD-(L)1, programmed cell death protein 1 or programmed cell death protein 1 ligand 1. Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Lung01 – Patient disposition

Disposition	Dato-DXd N=297	Docetaxel N=290
Treatment status, n (%)		
Ongoing on study treatment	52 (18)	17 (6)
Discontinued from study treatment	245 (83)	273 (94)
Treatment duration, n (%)		
0-3 months	118 (40)	168 (58)
3-6 months	73 (25)	66 (23)
3-9 months	47 (16)	34 (12)
>9 months	59 (20)	22 (8)
Primary reason for treatment discontinuation, n (%)		
Adverse event	39 (13)	46 (16)
Progressive disease	173 (58)	180 (62)
Clinical progression	9 (3)	11 (4)
Withdrawal/physician decision	12 (4)	23 (8)
Death	10 (3)	10 (3)
Other	2 (1)	3 (1)

Median study follow-up:

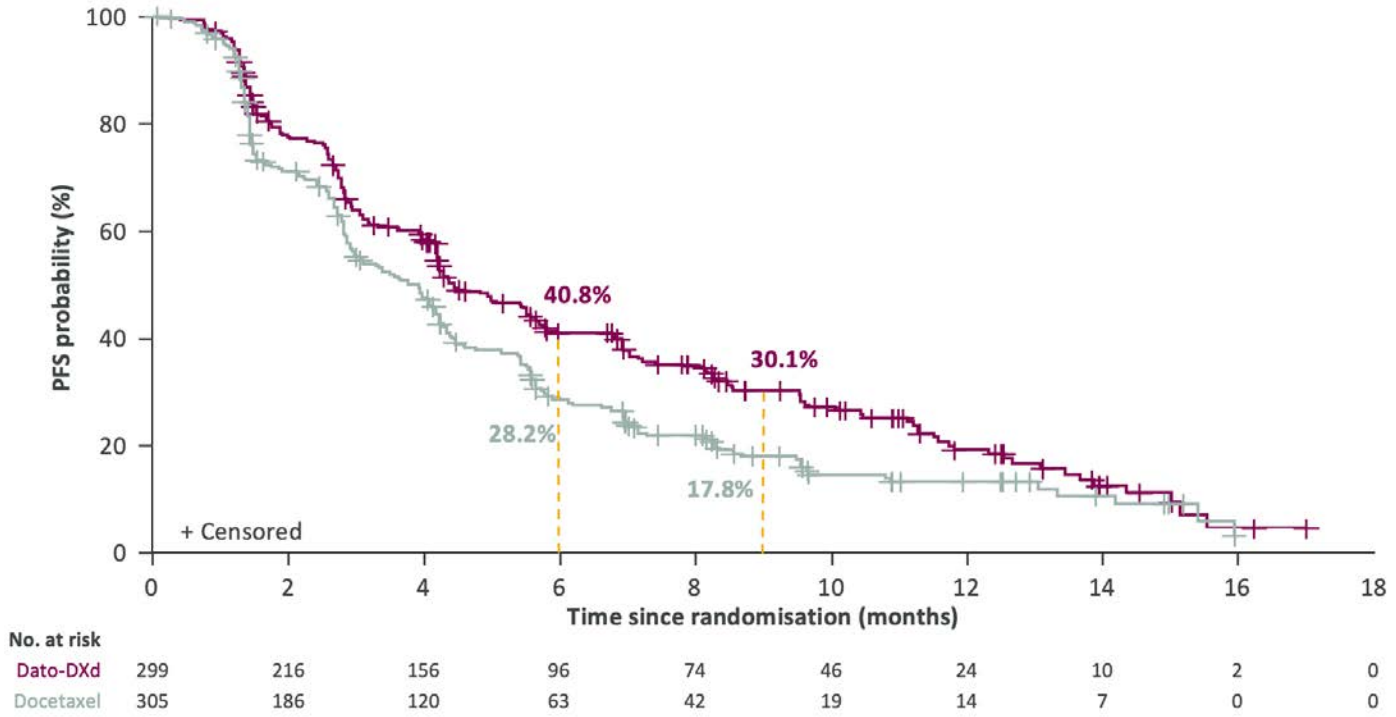
Dato-DXd – **13.1** months

docetaxel – **13.0** months

Dato-DXd = datopotamab deruxtecan.

Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Lung01 – Progression-free survival in ITT



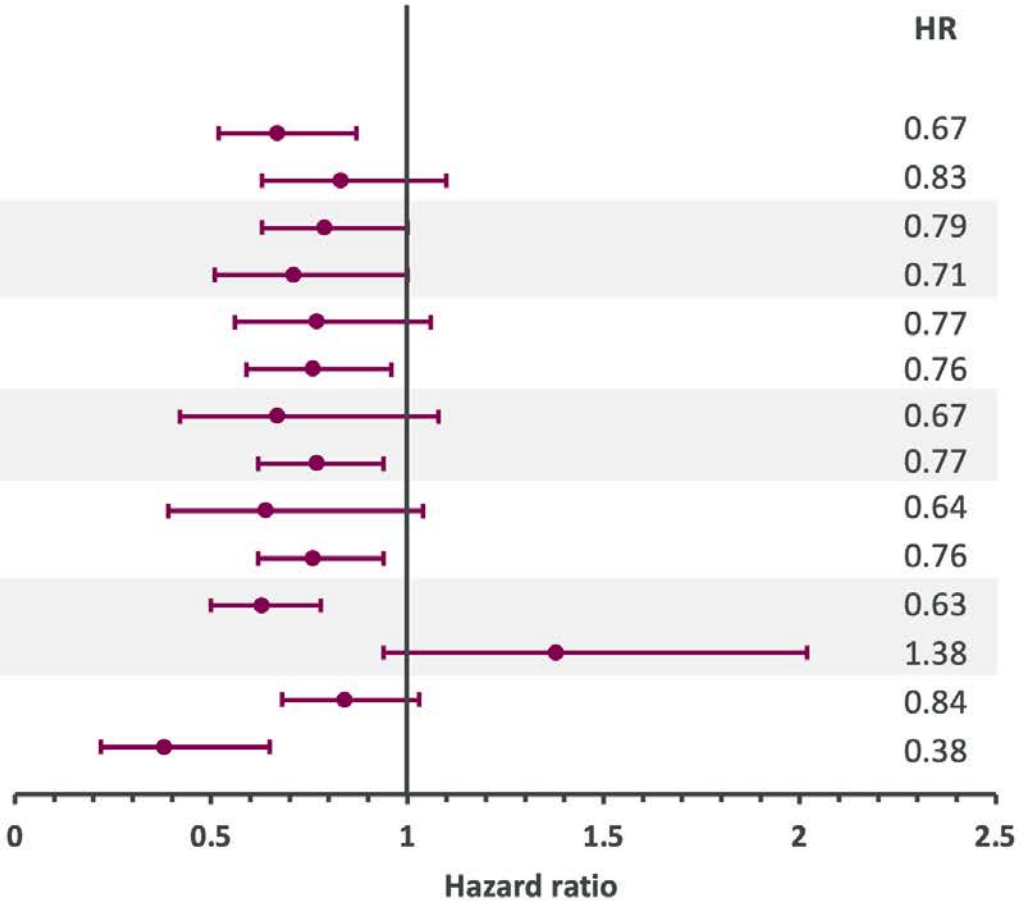
	Dato-DXd	Docetaxel
Median PFS, months (95% CI)[1]	4.4 (4.2, 5.6)	3.7 (2.9,4.2)
HR (95% CI)	**0.75** (0.62, 0.91)	
P-value	0.004	
Prespecified boundary (2-sided)	0.008	

	Dato-DXd	Docetaxel
ORR, % (95% CI)[2]	26.4 (21.5, 31.8)	12.8 (9.3, 17.1)
DOR, mo. (95% CI)	7.1 (5.6, 10.9)	5.6 (5.4, 8.1)

1. Median PFS follow-up time was 10.9 months (95% CI: 9.8, 12.5) and 9.6 months (95% CI: 8.2, 11.9) for Dato-DXd and docetaxel, respectively. 2. Included four CRs and 75 PRs for Dato-DXd and 39 PRs for docetaxel.
PFS = progression-free survival; no. = number; Dato-DXd = datopotamab deruxtecan; HR = hazard ratio; CI = confidence interval; ORR = objective response rate; DOR = duration of response, mo. = months.
Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Lung01 – PFS in key subgroups

		Events/n		HR
		Dato-DXd	Docetaxel	
Age at randomisation	<65 years	118/162	115/155	0.67
	≥65 years	95/137	103/150	0.83
Sex	Male	136/183	158/210	0.79
	Female	77/116	60/95	0.71
Race	Asian	76/119	82/120	0.77
	Non-Asian	131/172	129/177	0.76
Smoking status	Never	36/61	33/52	0.67
	Former/current	177/238	184/251	0.77
Brain metastasis at baseline	With	33/50	31/47	0.64
	Without	180/249	187/258	0.76
Histology	Non-squamous	156/229	168/232	0.63
	Squamous	57/70	50/73	1.38
Actionable genomic alterations[1]	Absent	189/252	184/255	0.84
	Present	24/47	34/50	0.38



1. Regardless of histology.

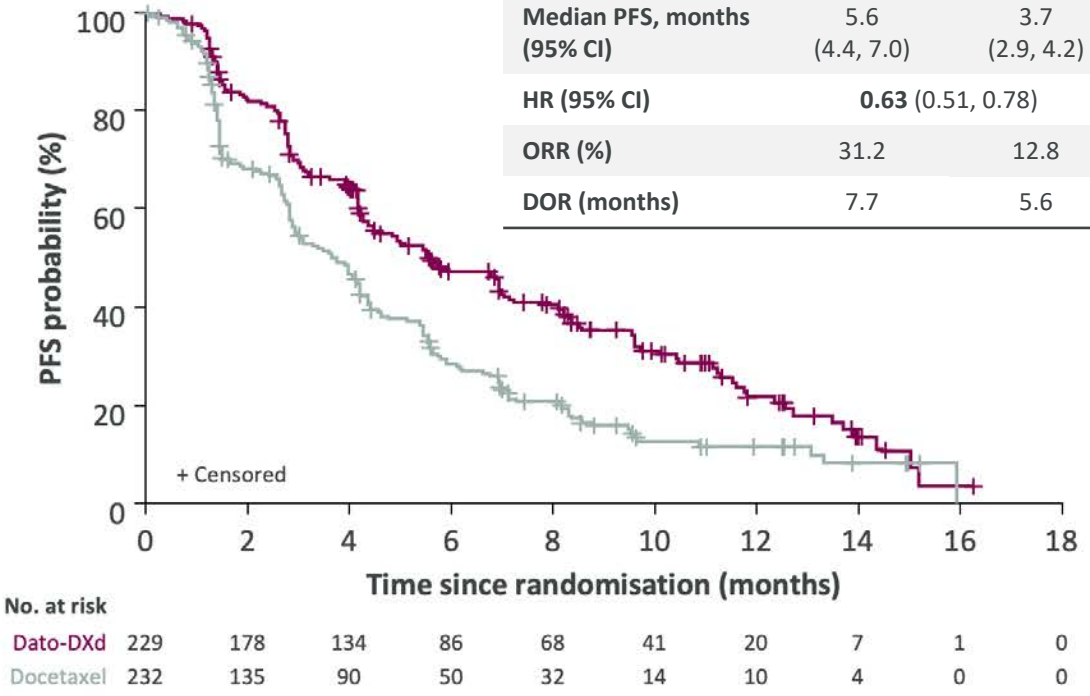
PFS = progression-free survival; Dato-DXd = datopotamab deruxtecan; HR = hazard ratio.
Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Lung01 – PFS by histology

With and without AGAs

Non-squamous
(with and without AGA)

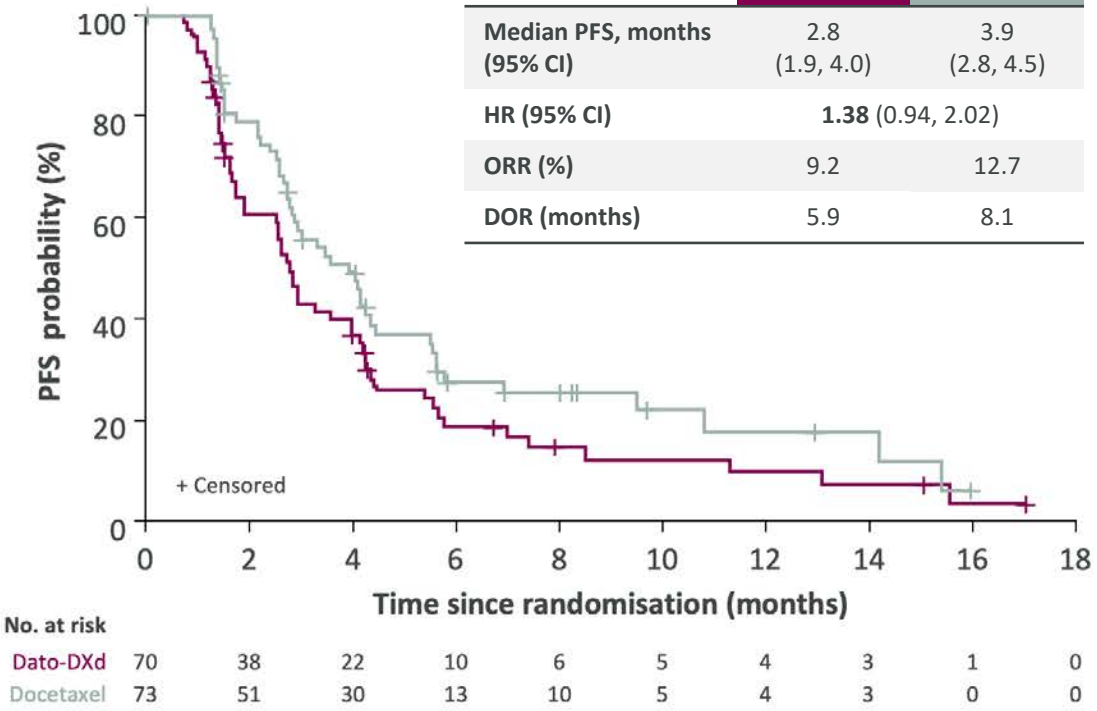
	Dato-DXd	Docetaxel
Median PFS, months (95% CI)	5.6 (4.4, 7.0)	3.7 (2.9, 4.2)
HR (95% CI)	**0.63** (0.51, 0.78)	
ORR (%)	31.2	12.8
DOR (months)	7.7	5.6



PFS HR for non-squamous without AGA: 0.71 (0.56, 0.91)

Squamous
(with and without AGA)

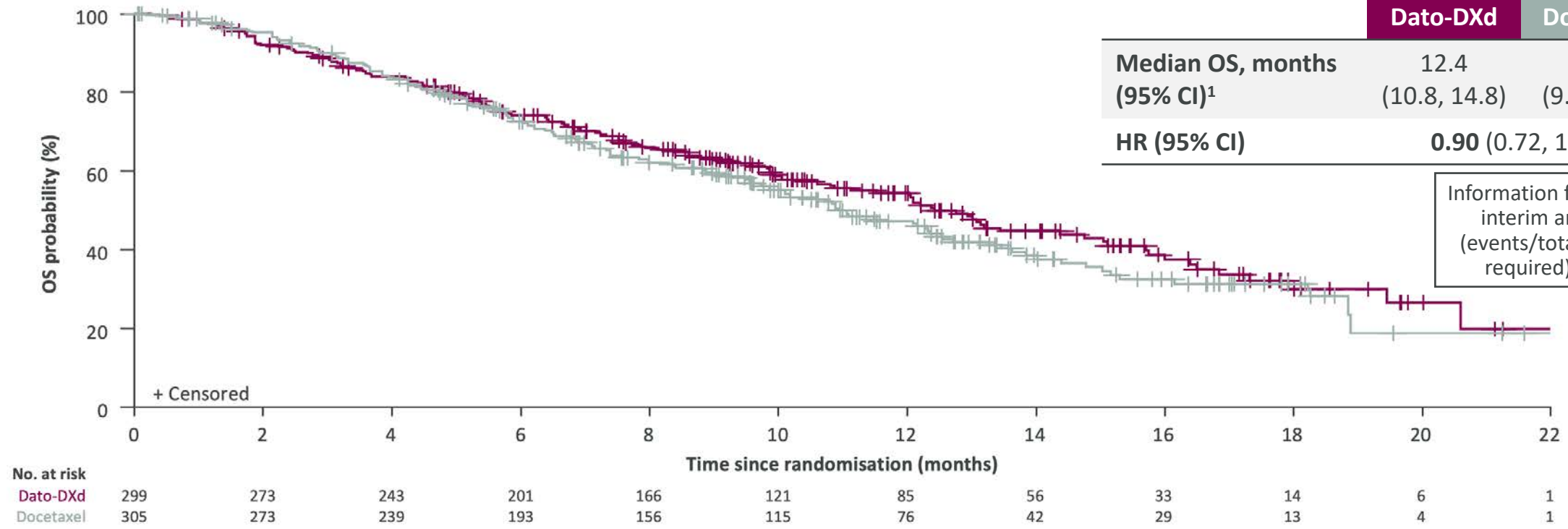
	Dato-DXd	Docetaxel
Median PFS, months (95% CI)	2.8 (1.9, 4.0)	3.9 (2.8, 4.5)
HR (95% CI)	**1.38** (0.94, 2.02)	
ORR (%)	9.2	12.7
DOR (months)	5.9	8.1



Squamous subset included 3 patients with AGAs.

PFS = progression-free survival; AGA = actionable genomic alterations; Dato-DXd = datopotamab deruxtecan; HR = hazard ratio; CI = confidence interval; ORR = objective response rate; DOR = duration of response; no. = number.
Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Lung01 – Interim overall survival – ITT



	Dato-DXd	Docetaxel
Median OS, months (95% CI)[1]	12.4 (10.8, 14.8)	11.0 (9.8, 12.5)
HR (95% CI)	**0.90** (0.72, 1.13)	

Information fraction at interim analysis (events/total events required): **74%**

Non-squamous HR (95% CI): **0.77** (0.59, 1.01); **Squamous HR** (95% CI): **1.32** (0.87, 2.00)

Trial is continuing to final OS analysis

1. Median OS follow-up time was 11.8 months (95% CI: 11.3, 12.7) and 11.7 months (95% CI: 10.9, 12.9) for Dato-DXd and docetaxel, respectively.

ITT = intent-to-treat; OS = overall survival; CI = confidence interval; HR = hazard ratio; Dato-DXd = datopotamab deruxtecan; no. = number.

Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Lung01 – Overall safety summary

TRAEs, n (%)	Dato-DXd N=297	Docetaxel N=290
All grades	257 (87)	252 (87)
Grade ≥3	73 (25)	120 (41)
Associated with dose reduction	58 (20)	85 (29)
Associated with dose delay	49 (17)	31 (11)
Associated with discontinuation	23 (8)	34 (12)
Associated with death[1]	3 (1)	2 (1)
Serious TRAEs	30 (10)	36 (12)
Grade ≥3	25 (8)	33 (11)

Median treatment durations for Dato-DXd and docetaxel were **4.2** and **2.8** months, respectively

Fewer Grade ≥3 TRAEs were observed with Dato-DXd compared with docetaxel

Fewer TRAEs leading to dose reductions or discontinuations were seen with Dato-DXd compared with docetaxel

1. Investigator assessed. Dato-DXd: 2 cases of ILD/pneumonitis and 1 case of sepsis; docetaxel: 1 case of ILD/pneumonitis and 1 case of septic shock. The safety analysis set included all randomized patients who received ≥1 dose of the study drug.

TRAE, treatment-related adverse event; Dato-DXd = datopotamab deruxtecan.
Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Lung01 – Adverse Events of Special Interest

AESI	Dato-DXd N=297	Docetaxel N=290
Stomatitis/oral mucositis, n (%)[1]		
All grades	160 (54)	59 (20)
Grade ≥3	19 (6)	4 (1)
Ocular events, n (%)[2]		
All grades	57 (19)	27 (9)
Grade ≥3	5 (2)[3]	0 (0)
Adjudicated drug-related ILD, n (%)[4]		
All grades	25 (8)	12 (4)
Grades ≥3	10 (3)	4 (1)
Grade 5	7 (2)	1 (0.3)

Stomatitis/oral mucositis associated with Dato-DXd resulted in a low rate of discontinuation (0.7%)

Dry eye was the most common ocular event seen with Dato-DXd (6.1%; primarily Grade ≤2), followed by increased lacrimation (5.4%)

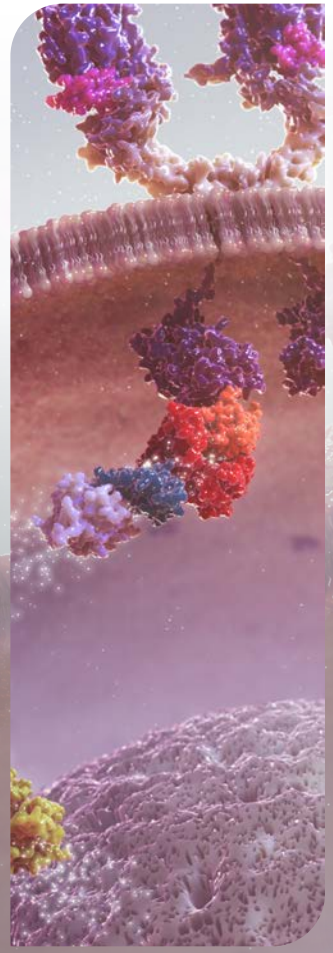
Seven adjudicated drug-related Grade 5 ILD events

- Primary cause of death in 4 out of 7 was attributed to disease progression by investigator
- Non-squamous: 4 of 232 patients (1.7%); squamous: 3 of 65 patients (4.6%)[5]

IRRs were observed in 8% patients in each arm, all were Grade ≤2 with the exception of 1 Grade 3 event with Dato-DXd

AESIs listed in this slide are treatment emergent and include all PTs that define the medical concept. 1. Events included the selected PTs: Oral mucositis/stomatitis, oropharyngeal pain, mouth ulceration, odynophagia, dysphagia, oral pain, glossitis, pharyngeal inflammation, aphthous ulcer, and oral mucosa erosion. 2. Ocular events included selected preferred terms from Corneal Disorder SMQ and select relevant preferred terms from Eye Disorder SOC. 3. Included four cases of keratitis and one case of ulcerative keratitis. 4. Interstitial lung disease includes events that were adjudicated as ILD and related to use of Dato-DXd or docetaxel (includes cases of potential ILD/pneumonitis, based on MedDRA v26.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure); 5. Among treated patients, histology information per the case report form. AESI = adverse event of special interest; Dato-DXd, = datopotamab deruxtecan; ILD = interstitial lung disease; IRR = infusion-related reaction; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SMQ = standard MedDRA queries; SOC = System Organ Class. Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Lung01 – Summary



- Dato-DXd is the first ADC to demonstrate a statistically significant improvement in PFS over docetaxel in patients with previously treated, locally advanced or metastatic NSCLC
- PFS benefit was primarily driven by patients with non-squamous histology
- Fewer Grade ≥3 TRAEs and no new safety signals were observed with Dato-DXd
- Grade ≥3 ILD was seen, highlighting the need for careful monitoring and adherence to ILD management guidelines
- The interim OS findings favour Dato-DXd, and the trial is continuing to final analysis

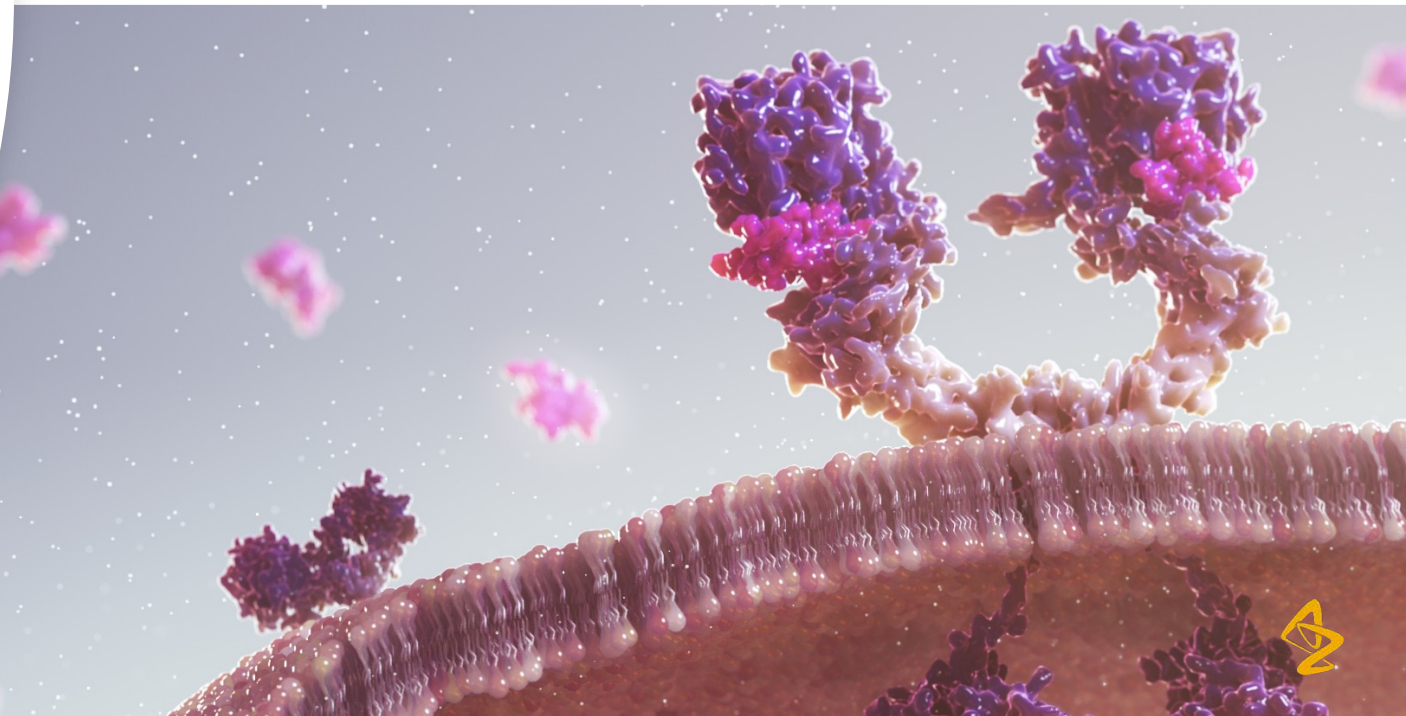
Dato-DXd is a potential new meaningful therapy for patients with previously treated non-squamous NSCLC

Dato-DXd = datopotamab deruxtecan; ADC = antibody-drug conjugate; PFS = progression-free survival; NSCLC = non-small cell lung cancer; TRAE = treatment-related adverse event; ILD = interstitial lung disease; OS = overall survival.
Collaboration partner: Daiichi Sankyo (Dato-DXd).

Transforming treatment with antibody drug conjugates

TROPION-Breast01

Dr Aditya Bardia
DIRECTOR OF BREAST CANCER RESEARCH PROGRAM, MASSACHUSETTS GENERAL HOSPITAL



Background

Unmet need in HR+/HER2 – mBC

- **HR+/HER2– breast cancer** is the **most common subtype** of breast cancer, accounting for 60–70% of all cases[1]
- Despite new therapeutic options becoming available, there remains an **unmet need** after **endocrine therapy** and **one line of systemic therapy** for patients with HR+/HER2– mBC[2–5]
- Chemotherapy is utilised widely for management of endocrine-resistant HR+/HER2 – mBC, but is associated with low response rate, poor prognosis, and significant toxicity including myelosuppression and peripheral neuropathy[6]
- **TROP2-directed ADCs** can have **significant toxicities** including diarrhoea, neutropenia and thrombocytopenia[7,8]

1. Sung H et al. CA Cancer J Clin 2021;71:209–49; 2. Gennari A, et al. Ann Oncol 2021;32:1475-1495; 3. Wolff AC, et al. J Clin Oncol 2023;41:3867–72; 4. Moy B, et al. J Clin Oncol 2023;41:1318–20; 5. Moy B, et al. J Clin Oncol; 2022;40:3088–90; 6. Kuderer NM, et al. Nat Rev Clin Oncol 2022;19:681–97; 7. Rugo HS, et al. J Clin Oncol 2022;40:3365–76; 8. Yin Y et al. Mini Oral at ESMO 2023; presentation 380MO.

HR+ = hormone receptor-positive; HER2- = human epidermal growth factor 2; mBC – metastatic breast cancer; TROP2 = trophoblast cell-surface antigen 2.

Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Breast01

Randomised, Phase III open-label global trial

- HR+/HER2- breast cancer[1]
- 1-2 prior lines of CTx in inoperable/metastatic setting
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

R
1:1

Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

Dato-DXd
6mg/kg IV Day 1 Q3W
n=365

ICC
Q3W per protocol[2]
eribulin mesylate / vinorelbine / capecitabine / gemcitabine
n=376

Randomisation stratified by:

— Lines of chemotherapy in unresectable/metastatic setting (1 vs 2)
— Geographic location (US/Canada/EU vs RoW)
— Previous CDK4/6i use (yes vs no)

Endpoints

Dual primary endpoints

- PFS (BICR)
- OS

Key secondary endpoints

- ORR
- PFS (inv)
- Safety

1. Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, 2. ICC was administered as follows: eribulin mesylate, 1.4 mg/m² IV on Days 1 and 8, Q3W; capcetabine 1000 or 1250 mg/m² orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice); vinorelbine 25 mg/m² IV on Days 1 and 8, Q3W; gemcitabine 1000 mg/m² IV on Days 1 and 8 Q3W
HR = hormone receptor; HER2 = human epidermal growth factor 2; CTx = chemotherapy; ET = endocrine therapy, ECOG PS = Eastern Cooperative Oncology Group performance status; R = randomised; PD = progressive disease; q3w = once every 3 weeks; IV = intravenous; Dato-DXd = datopotamab deruxtecan; ICC = investigator's choice of chemotherapy; RoW = rest of world; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; PFS = progression-free survival; BICR = blinded independent central review; ORR = objective response rate; inv = investigator-assessed. Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Breast01 – Baseline features

Demographics and baseline characteristics were generally well balanced

		Dato-DXd (n=365)	ICC (n=367)
Age, median (range), years		56 (29–86)	54 (28–86)
Female, n (%)		360 (99)	363 (99)
Race, n (%)	Black or African American / Asian / White / Other[1]	4 (1) / 146 (40) / 180 (49) / 35 (10)	7 (2) / 152 (41) / 170 (46) / 38 (10)
Ethnicity, n (%)	Hispanic or Latino / Not Hispanic or Latino[2]	40 (11) / 322 (88)	43 (12) / 318 (87)
Prior lines of chemotherapy,[3] n (%)	1 / 2	229 (63) / 135 (37)	225 (61) / 141 (38)
Prior CDK4/6 inhibitor, n (%)	Yes / No	299 (82) / 66 (18)	286 (78) / 81 (22)
Prior taxane and/or anthracycline, n (%)	Taxane and/or anthracycline	330 (90)	339 (92)
	Neither	35 (10)	28 (8)

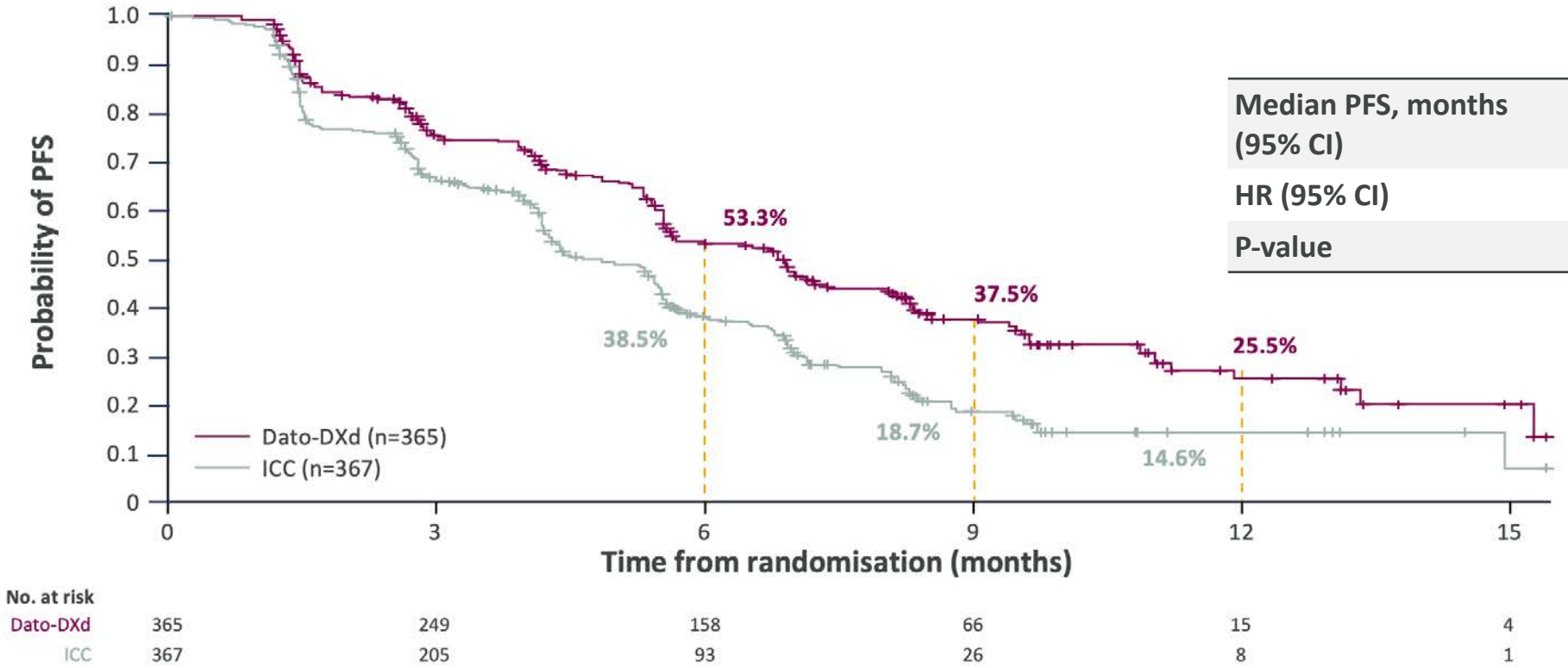
1. Including not reported. 2. Ethnicity missing: 3 patients in Dato-DXd group; 6 patients in ICC group; 3. In the inoperable/metastatic setting; one patient in the Dato-DXd group had 3 prior lines of chemotherapy; one patient in the ICC group had 4 prior lines.

Dato-DXd = datopotamab deruxtecan; ICC = investigator's choice of chemotherapy; CDK4/6i = cyclin-dependent kinase 4 and 6.

Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Breast01 – PFS by BICR (primary endpoint)

Dato-DXd demonstrated statistically significant and clinically meaningful difference vs. ICC



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7–7.4)	4.9 (4.2–5.5)
HR (95% CI)	**0.63** (0.52–0.76)	
P-value	<0.0001	

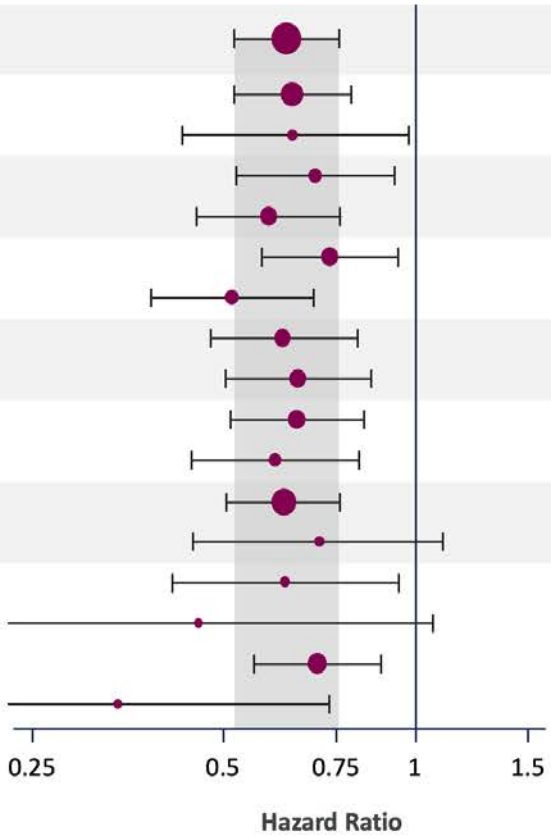
PFS by investigator assessment: median 6.9 vs 4.5 months; HR 0.64 (95% CI 0.53-0.76)

PFS = progression-free survival; BICR = blinded independent centralised review; Dato-DXd = datopotamab deruxtecan; ICC = investigator's choice of chemotherapy; CI = confidence interval; HR = hazard ratio; no. = number.
Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Breast01 – PFS by BICR across subgroups

Consistent benefit across key subgroups

		Events/n		Hazard ratio
		Dato-DXd	ICC	
All patients		212/365	235/367	0.63
Age at randomisation	<65 years	163/274	190/295	0.64
	≥65 years	49/91	45/72	0.65
Race	Asian	88/146	101/152	0.70
	Non-Asian	109/187	119/183	0.59
ECOG performance status	0	119/197	136/220	0.73
	1	91/165	98/145	0.52
Geographic region	US, Canada, Europe	110/186	112/182	0.62
	Rest of World [1]	102/179	123/185	0.66
Number of previous lines of chemotherapy	1	128/229	145/225	0.65
	2	84/135	90/141	0.60
Prior use of CDK4/6 inhibitor	Yes	177/299	190/286	0.62
	No	35/66	45/81	0.70
Prior use of taxane and/or anthracycline	Taxane alone	48/80	47/71	0.62
	Anthracycline alone	9/14	16/21	0.46
	Both taxane and anthracycline	141/236	155/247	0.70
	Neither taxane nor anthracycline	14/35	17/28	0.34

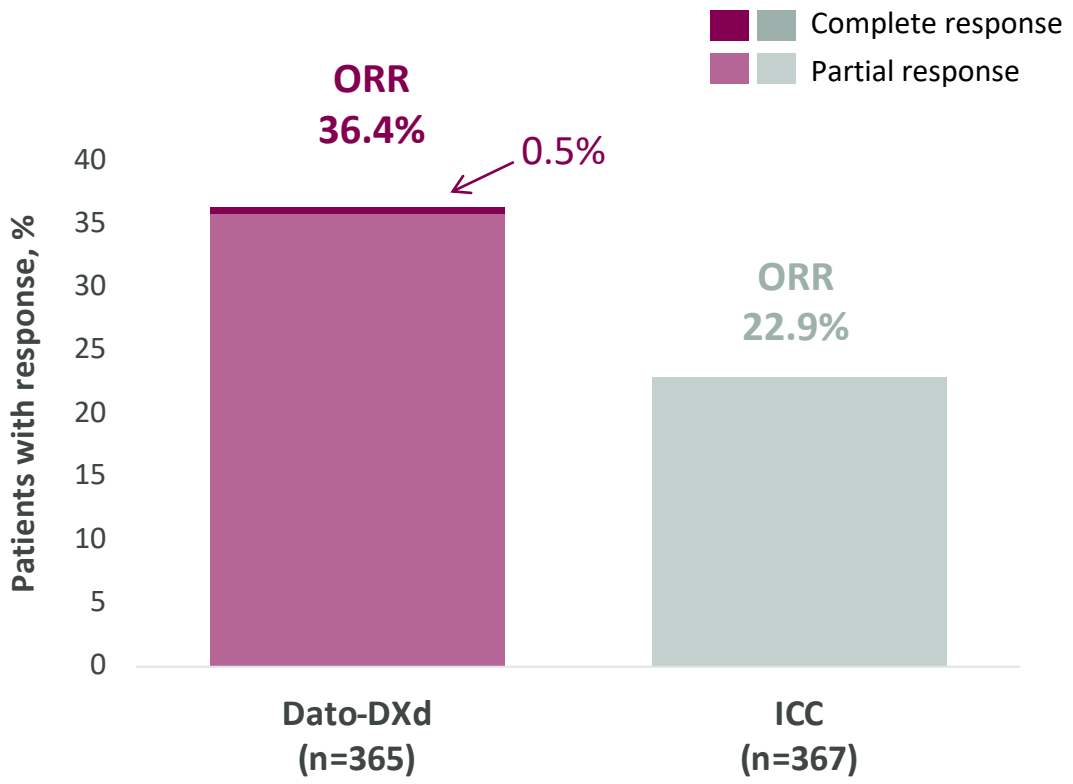


Data cut-off: 17 July 2023. Size of circle is proportional to the number of events across both treatment groups. 1. Three patients from Canada were incorrectly stratified to Rest of World.
PFS = progression-free survival; BICR = blinded independent centralised review; Dato-DXd = datopotamab deruxtecan; ICC = investigator's choice of chemotherapy; ECOG = Eastern Cooperative Oncology Group; CDK4/6i = cyclin-dependent kinase 4 and 6.
Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Breast01 – Response rate and interim OS

50% greater response rate with Dato-DXd vs. ICC

Response rate



Overall survival: dual primary endpoint

OS data were not mature:[1]
- Median follow-up 9.7 months

A trend favouring Dato-DXd was observed:
- HR 0.84 (95% CI 0.62–1.14)

The study is continuing to the next planned analysis for OS

1. Information fraction: 39%. ORR by BICR.

Dato-DXd = datopotamab deruxtecan; ICC = investigator's choice of chemotherapy; ORR = objective response rate; OS = overall survival; HR = hazard ratio; CI = confidence interval; BICR = blinded independent centralised review.
Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Breast01 – Overall safety summary

Favourable and manageable safety profile

TRAEs, n (%)	Dato-DXd (n=360)	ICC (n=351)
All grades	337 (94)	303 (86)
Grade ≥3	75 (21)	157 (45)
Associated with dose reduction	75 (21)	106 (30)
Associated with dose interruption	43 (12)	86 (25)
Associated with discontinuation	9 (3)	9 (3)
Associated with death	0	1 (0.3)
Serious TRAEs	21 (6)	32 (9)
Grade ≥3	17 (5)	31 (8)

Median treatment duration was **6.7 months** with Dato-DXd and **4.1 months** with ICC

Rate of Grade ≥3 TRAEs in the Dato-DXd group was less than half that in the ICC group

Fewer TRAEs leading to dose reductions or interruptions with Dato-DXd compared with ICC

No grade 4 or 5 events.

TRAEs = treatment-related adverse events; Dato-DXd = datopotamab deruxtecan; ICC = investigator's choice of chemotherapy.

Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Breast01 – TRAEs in ≥15% of Patients

No new safety signals observed

System Organ Class Preferred term, n (%)	Dato-DXd (n=360)		ICC (n=351)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system disorders				
Anaemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia[1]	39 (11)	4 (1)	149 (42)	108 (31)
Eye disorders				
Dry eye	78 (22)	2 (1)	27 (8)	0
Gastrointestinal disorders				
Nausea	184 (51)	5 (1)	83 (24)	2 (1)
Stomatitis	180 (50)	23 (6)	46 (13)	9 (3)
Vomiting	71 (20)	4 (1)	27 (8)	2 (1)
Constipation	65 (18)	0	32 (9)	0
General disorders				
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Skin and subcutaneous disorders				
Alopecia	131 (36)	0	72 (21)	0
Adjudicated drug-related ILD	9 (3)	2 (1)†	0	0

Most TRAEs were Grade 1-2 and manageable

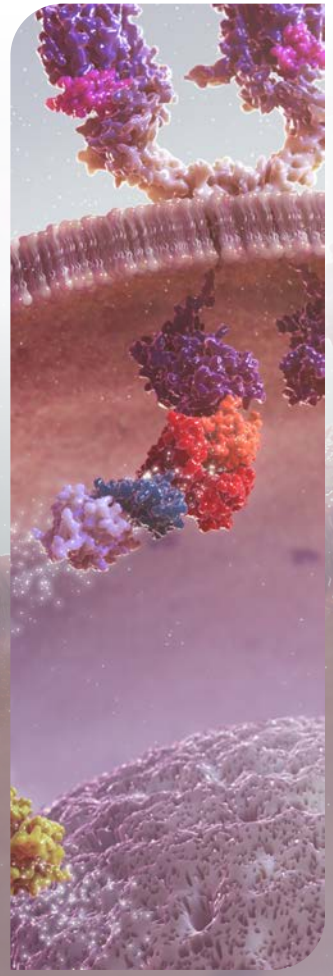
AESIs

- Oral mucositis/stomatitis:[2] led to treatment discontinuation in one patient in the Dato-DXd group
- Ocular events:[3] most were dry eye; one patient discontinued treatment in the Dato-DXd group
- Adjudicated drug-related ILD:[4] rate was low; mainly Grade 1/2

Adjudicated drug-related ILD	Dato-DXd	ICC
All grades, n (%)	9 (3)	0
Grade ≥3, n (%)	2 (1)[5]	0

1. Neutropenia includes the PTs neutropenia and neutrophil count decreased. 2. Oral stomatitis/mucositis events included PTs of aphthous ulcer, dysphagia, glossitis, mouth ulceration, odynophagia, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, stomatitis, tongue ulceration; all grade: 59% with Dato-DXd, 17% with ICC; grade 3: 7% with Dato-DXd, 3% with ICC. 3. Ophthalmologic assessments were required at screening, and then every 3 cycles from C1D1 and at end of therapy; ocular events included selected PTs from Corneal Disorder SMQ and select relevant PTs from Eye Disorder SOC; all grade: 49% with Dato-DXd, 23% with ICC; grade 3: 1% with Dato-DXd (one patient with dry eye, one patient with punctate keratitis, and one patient with dry eye and ulcerative keratitis), 0% with ICC. 4. ILD includes events that were adjudicated as ILD and related to use of Dato-DXd or ICC (includes cases of potential ILD/pneumonitis, based on MedDRA v23.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure). 5. One adjudicated drug-related grade 5 ILD event: attributed to disease progression by investigator. TRAEs = treatment-related adverse events; Dato-DXd = datopotamab deruxtecan; ICC = investigator's choice of chemotherapy; ILD = interstitial lung disease. Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Breast01 – Summary



- TROPION Breast01 demonstrated that Dato-DXd provides both improved efficacy and safety compared with ICC for patients with HR+/HER2– disease
- **TROPION-Breast01 met its dual primary PFS endpoint, demonstrating statistically significant and clinically meaningful improvement in PFS with Dato-DXd compared with ICC**
  - Consistent PFS benefit observed across subgroups
  - Higher ORR with Dato-DXd and a trend at interim OS favouring Dato-DXd
- **Overall, Dato-DXd demonstrated a favourable and manageable safety profile, with no new safety signals**
  - Most AESIs were Grade 1-2
  - Patients receiving Dato-DXd had fewer Grade ≥3 TRAEs (less than half that with ICC), as well as fewer TRAEs leading to dose interruption/reduction compared with ICC

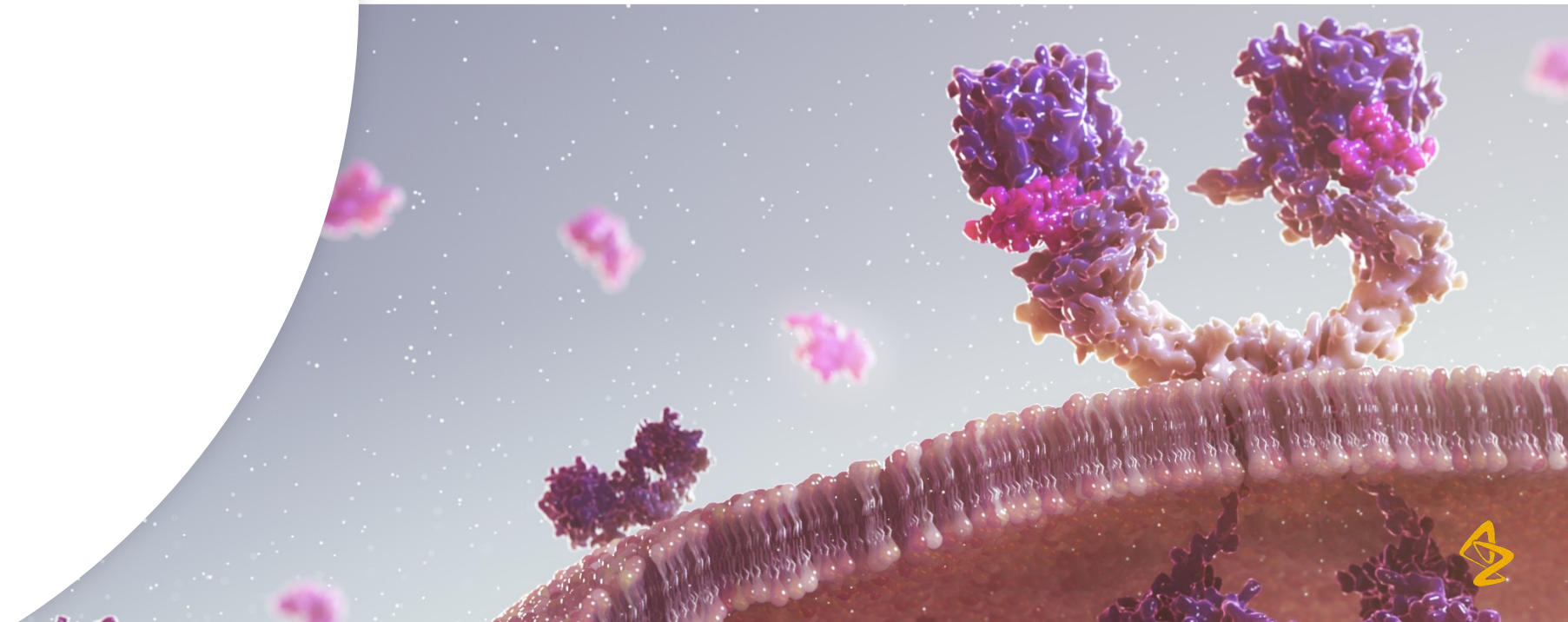
Results support Dato-DXd as potential new therapeutic option for patients with metastatic HR+/HER2– breast cancer

Dato-DXd = datopotamab deruxtecan; HR+ = hormone receptor-positive; HER2- = human epidermal growth factor receptor 2-negative; ICC = investigator's choice of chemotherapy; PFS = progression-free survival; ORR = objective response rate; OS = overall survival; TRAEs = treatment-related adverse events; AESIs = adverse events of special interest.
Collaboration partner: Daiichi Sankyo (Dato-DXd).

Realising the transformative potential of ADCs

Future ambition for Dato-DXd

Susan Galbraith
ONCOLOGY R&D



Unlocking the increasing value of Dato-DXd

1

Beats conventional monotherapy CTx

- TROPION-Lung01
- TROPION-Breast01

2

Best-in-class profile supports IO combo

- TROPION-Lung02
- TROPION-Lung04
- BEGONIA

3

Broad potential in earlier lines and other tumour types

- TROPION-Lung07
- TROPION-Lung08
- AVANZAR
- TROPION-Breast02
- TROPION-Breast03
- TROPION-Breast04
- TROPION-Breast05
- TROPION-PanTumor01
- TROPION-PanTumor03

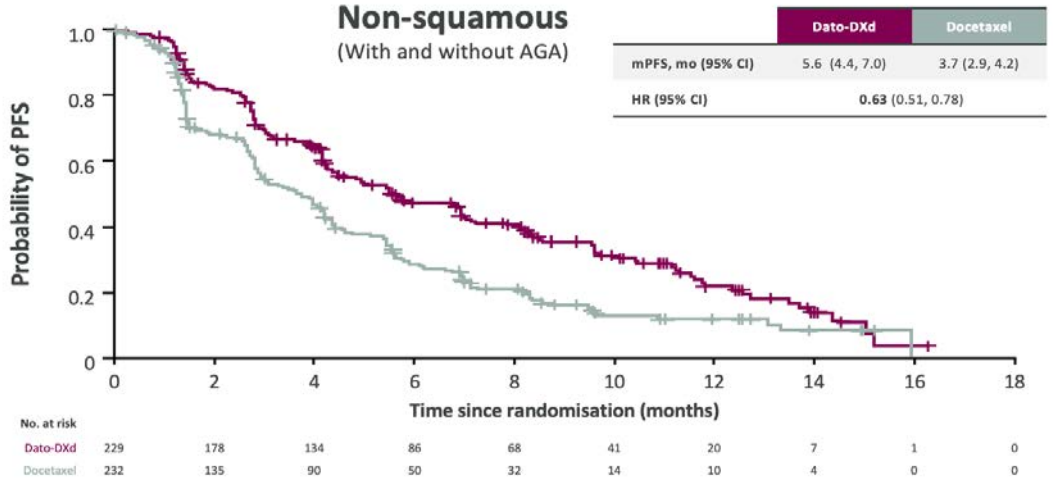
*TROPION-Breast04 and TROPION-Breast05 have not begun enrollment as of 23 October 2023. Dato-DXd = datopotamab deruxtecan; Ctx = chemotherapy; IO = immunotherapy.
Collaboration partner: Daiichi Sankyo (Dato-DXd).

1. Dato-DXd beats conventional monotherapy CTx

TROPION-Lung01 filing underway[1], TROPION-Breast01 data shared with regulators

TROPION-Lung01 | 2L+ NSCLC

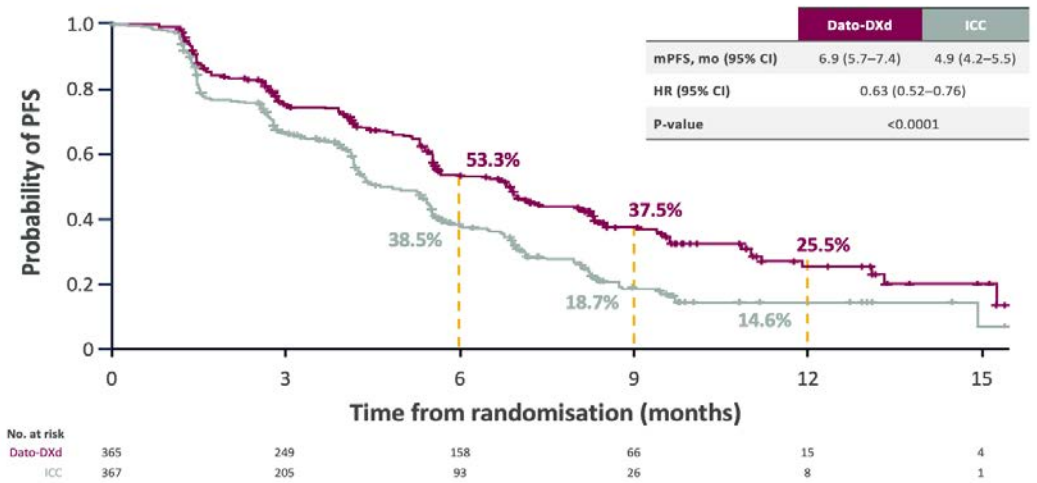
Clear benefit in easily identifiable non-squamous patients



- Fewer Grade ≥ 3 TRAEs observed with Dato-DXd (25% vs 41%), manageable stomatitis, 1.7% Grade 5 ILD rate in non-squamous[2]
- Docetaxel high rate of haematologic toxicities contributing to shorter duration of treatment
- Fewer TRAEs leading to discontinuation with Dato-DXd (8% vs 11%)

TROPION-Breast01 | 2L+ HR+ mBC

Benefit across ITT



- Lower rate of Grade ≥3 TRAEs with Dato-DXd (21% vs 45%), only 1% Grade ≥3 ILD
- Low-grade (Grade 1/2) dry eye/ocular events[3] in both arms likely due to frequency of monitoring
- Low discontinuation rate (3%)

1. Disclosed plans to file with US FDA (July 2023); 2. Grade 5 ILD was 4.6% [n=3] for squamous vs 1.7% [n=3] for non-squamous; 3. ocular events with Dato-DXd were low grade and most were dry eye (24%), only one Grade 3 event was observed. Dato-DXd = datopotamab deruxtecan; CTx = chemotherapy; NSCLC = non-small cell lung cancer; AGA = actionable genomic alteration; mPFS = median progression-free survival; HR = hazard ratio; CI = confidence interval; No. = number; TRAEs = treatment related adverse events; ILD = interstitial lung disease; HR+ = hormone receptor positive; mBC = metastatic breast cancer; ITT = intent to treat; ICC = investigator's choice chemotherapy.. Collaboration partner: Daiichi Sankyo (Dato-DXd).

2. Dato-DXd best-in-class profile supports IO combo

AE profile enables combination with both IO and chemotherapy

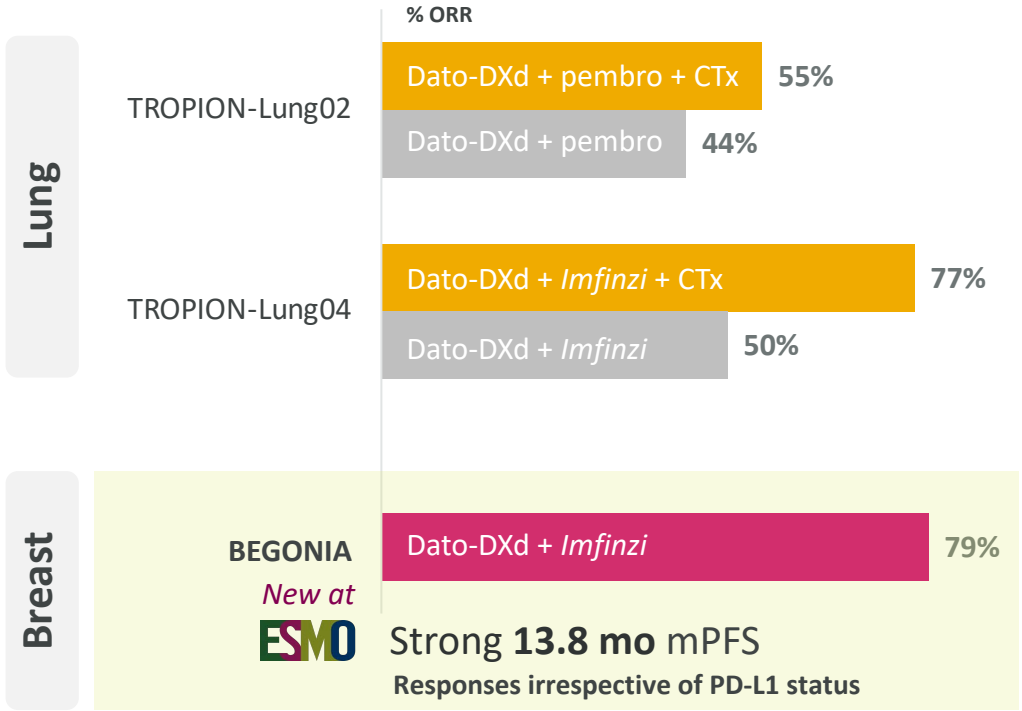
Lower bone marrow toxicity confers better combinability with platinum chemotherapy

Convenient dosing aligns with chemotherapy – one i.v. infusion per cycle

Encouraging Dato-DXd treatment duration

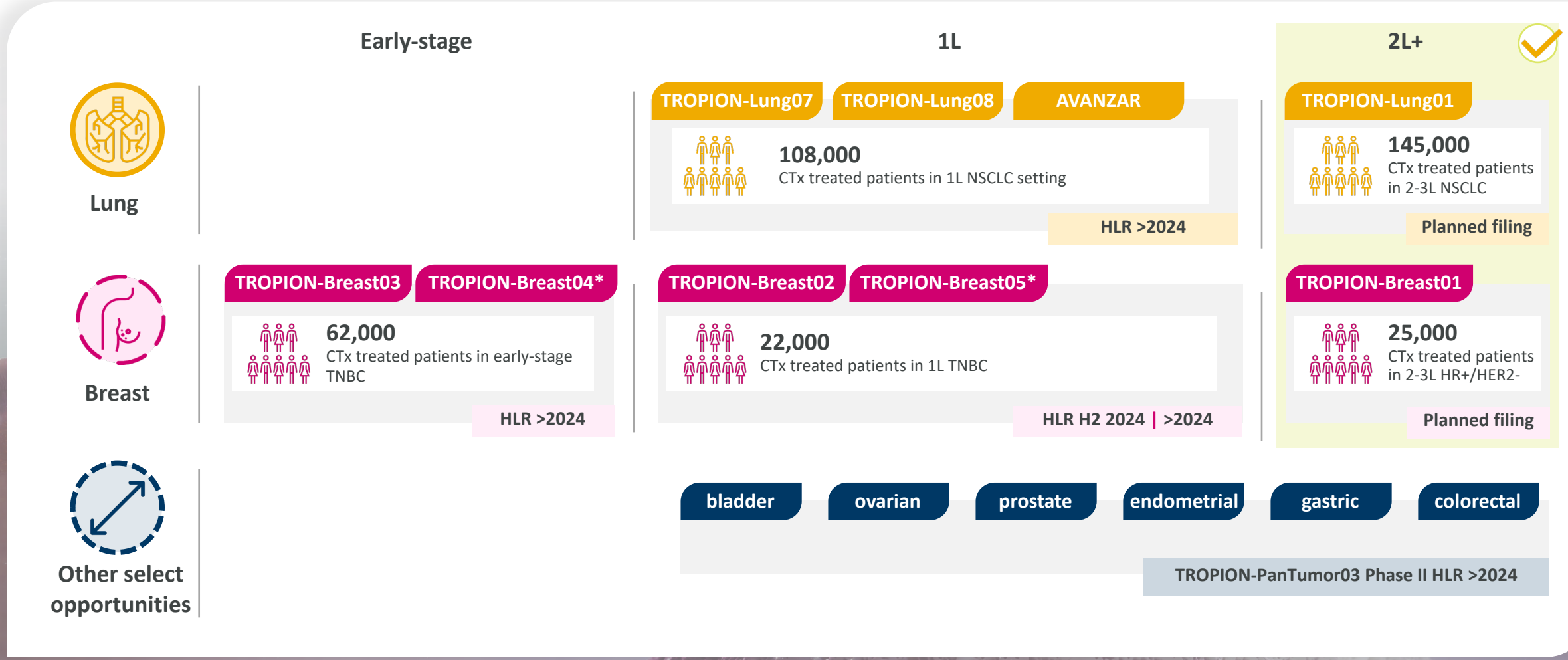
Treated large number of patients in 1L in combination with acceptable tolerability

Early efficacy data reinforces potential in Phase III combination trials



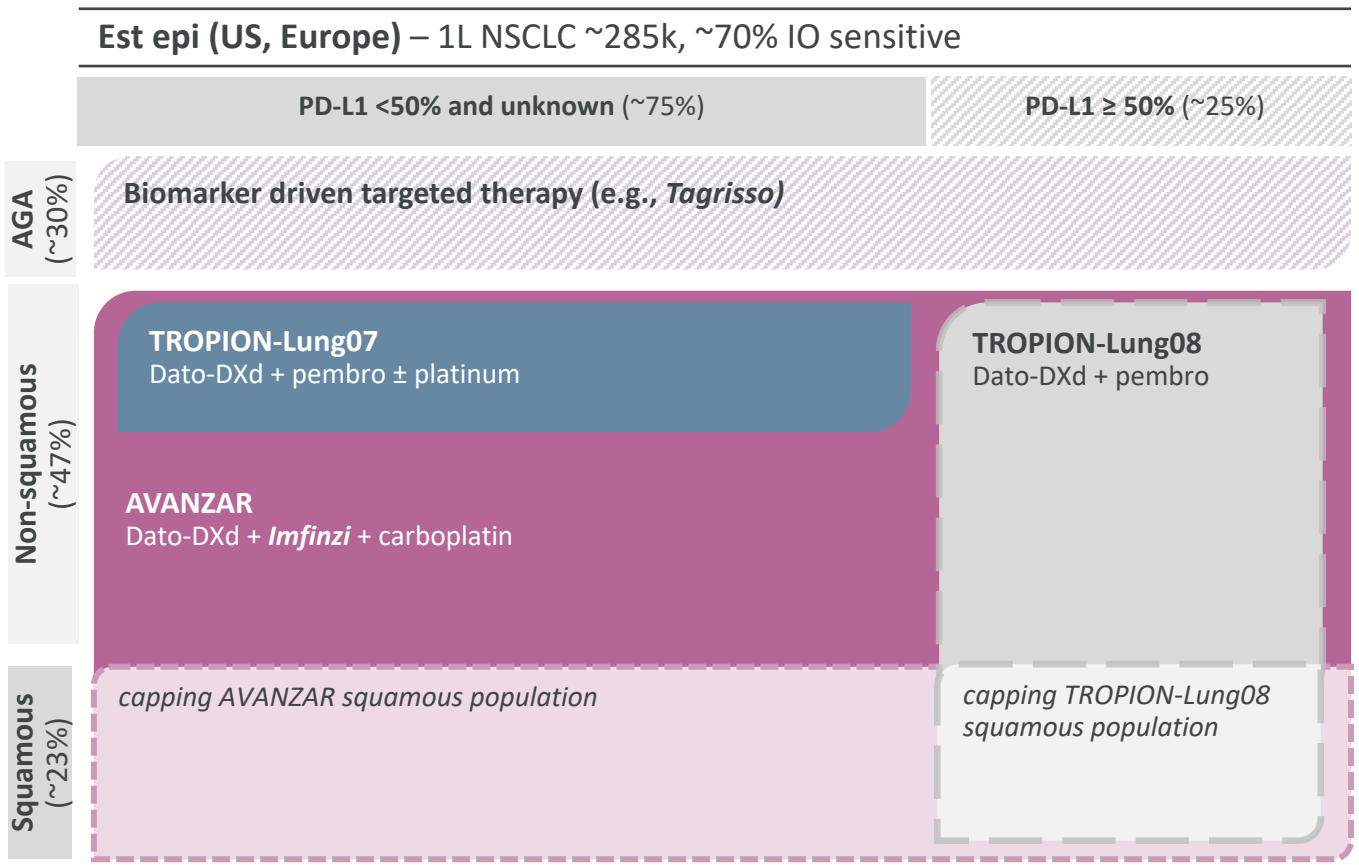
Dato-DXd = datopotamab deruxtecan; IO = immunotherapy; combo = combination; i.v. = intravenous; ORR = overall response rate; mo = months; mPFS = median progression free survival; PD-L1 = programmed cell death ligand 1; ESMO = European society for medical oncology.
Collaboration partner: Daiichi Sankyo (Dato-DXd).

3. Broad potential of Dato-DXd in earlier lines and other tumour types



*TROPION-Breast04 and TROPION-Breast05 have not begun enrollment as of 23 October 2023. Dato-DXd = datopotamab deruxtecan; CTx = chemotherapy; TNBC = triple negative breast cancer; HLR = high-level results; NSCLC = non-small cell lung cancer; HR+ = hormone receptor positive; HER2- = human epidermal growth factor receptor negative.
Collaboration partner: Daiichi Sankyo (Dato-DXd).

Dato-DXd 1L NSCLC development programme strengthened by TROPION-Lung01 learnings



Programme to be enriched for non-squamous population

AVANZAR trial includes TROP2 biomarker approach

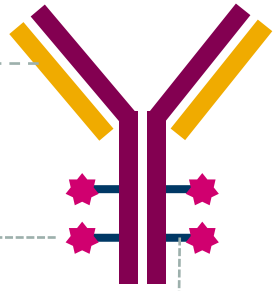
Consideration for use of TROP2 biomarker in other trials

Note: AVANZAR Phase III trial sits outside the collaboration with Daiichi Sankyo, while TROPION-Lung08 development is led by Daiichi Sankyo under the existing collaboration. Dato-DXd = datopotamab deruxtecan; NSCLC = non-small cell lung cancer; est = estimated; epi = epidemiology; IO = immunotherapy; PD-L1 = programmed death-ligand 1; AGA = actionable genomic alteration; pembro = pembrolizumab; PFS = progression free survival; OS = overall survival; TROP2 = tumour-associated calcium signal transducer 2.
Collaboration partner: Daiichi Sankyo (Dato-DXd).

AstraZeneca – leading the ADC revolution

1 Target and antibodies

Efficient delivery of antibody drug conjugate payload



2 Warhead

Match disease biology and enable biology-driven combinations to overcome resistance

3 Linkers

Optimise conjugation chemistry and overcome potential off-target toxicity

Establishing AstraZeneca portfolio of differentiated ADCs

Clinical stage trials ongoing in lung, breast, haematology, GYN/GU, and GI

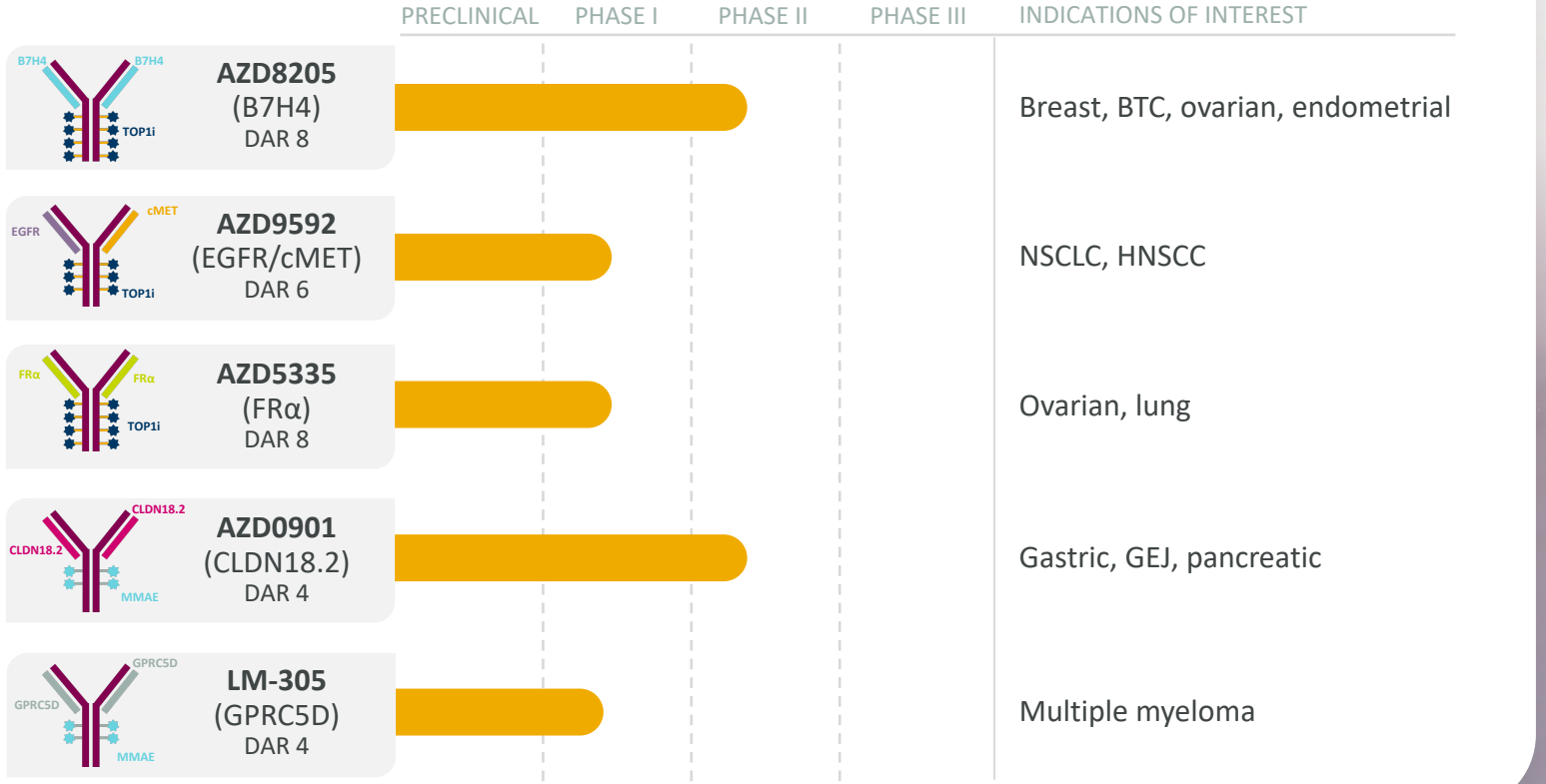


Image is for illustrative purposes only; actual drug positions may vary. ADC = antibody drug conjugate; GYN/GU = gynaecology/genitourinary; GI = gastrointestinal; B7H4 = B7 homolog 4; EGFR= epidermal growth factor receptor: cMET =mesenchymal-epithelial transition factor ; FRα = folate receptor alpha; CLDN18.2 = claudin 18.2; CPRC5D = G-protein coupled receptor C family 5D; TOP1i = topoisomerase 1 inhibitor; DAR = drug antibody ratio; BTC = biliary tract cancer; NSCLC = non-small cell lung cancer; HSNCC = head and neck squamous cell carcinoma; GEJ = gastroesophageal junction.

AstraZeneca – next wave of ADCs and radioconjugates

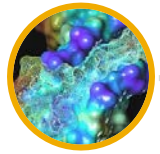
First-in-class targets

Leveraging surface proteomics for target identification

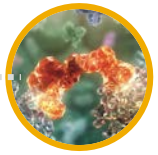
Diversified warheads

Topoisomerase

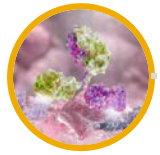
DNA intercalators



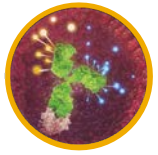
Microtubules



PROTACS

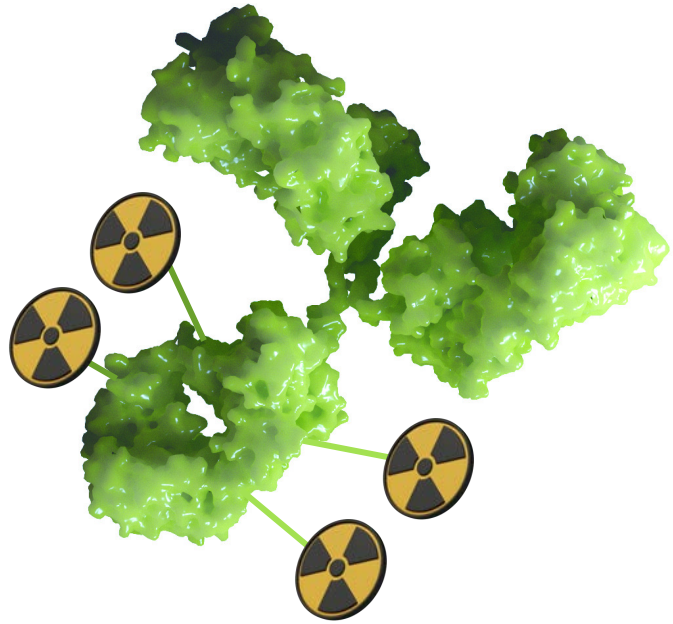


Bispecifics



Dual payloads

Novel radioconjugates



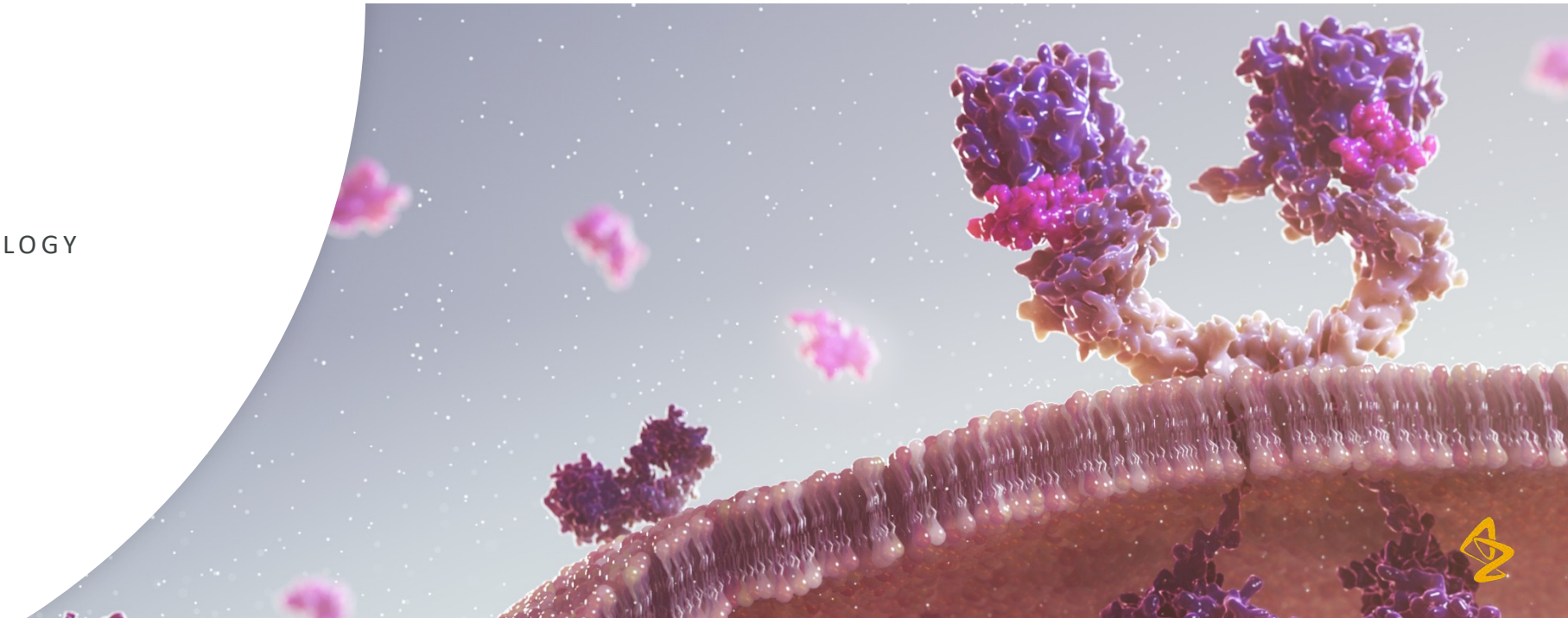
Enabling biology driven combinations and sequencing

ADC = antibody drug conjugates; PROTAC = proteolysis-targeting chimera.

Advancing our leadership in immuno-oncology

Cristian Massacesi
CHIEF DEVELOPMENT OFFICER, ONCOLOGY
& CHIEF MEDICAL OFFICER

Dave Fredrickson
ONCOLOGY BUSINESS



DUO-E Phase III in advanced endometrial cancer

Sixth most common cancer in women with growing incidence over the coming decades

Newly diagnosed stage III–IV or recurrent endometrial cancer

Known MMR status

Adjuvant chemotherapy allowed if ≥12 months from last treatment to relapse

All histologies except sarcoma

R
1:1:1

Stratified by:

- MMR status
- Disease status
- Geographic region

CTx phase (6 cycles)	Maintenance phase (cycles 7+)
Platinum CTx + ***Imfinzi* placebo**	***Imfinzi* placebo** until progression + ***Lynparza* placebo** until progression
Platinum CTx + ***Imfinzi***	***Imfinzi*** until progression + ***Lynparza* placebo** until progression
Platinum CTx + ***Imfinzi***	***Imfinzi*** until progression + ***Lynparza*** until progression

Only patients with no evidence of PD allowed to continue on maintenance

Endpoints

Primary endpoints

- PFS (investigator) in
  - CTx + *Imfinzi* vs CTx
  - CTx + *Imfinzi* + Lynparza vs CTx

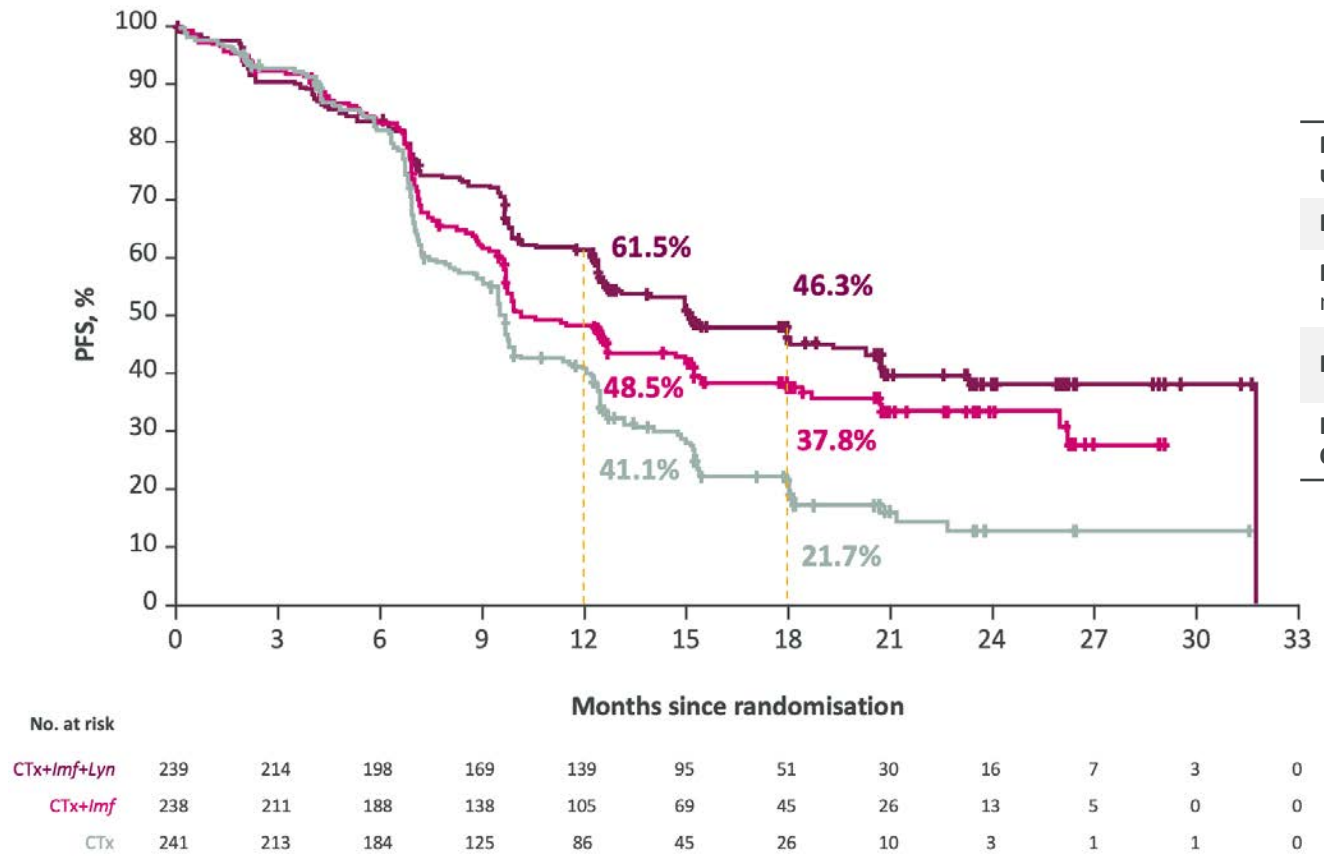
Key secondary endpoints

- OS
- Safety

MMR = mismatch repair; R = randomise; CTx = chemotherapy; PD = progressive disease; PFS = progression-free survival; OS = overall survival.

PFS benefit for both regimens across ITT

Contribution of *Lynparza* demonstrated by longer PFS in the *Imfinzi* + *Lynparza* arm

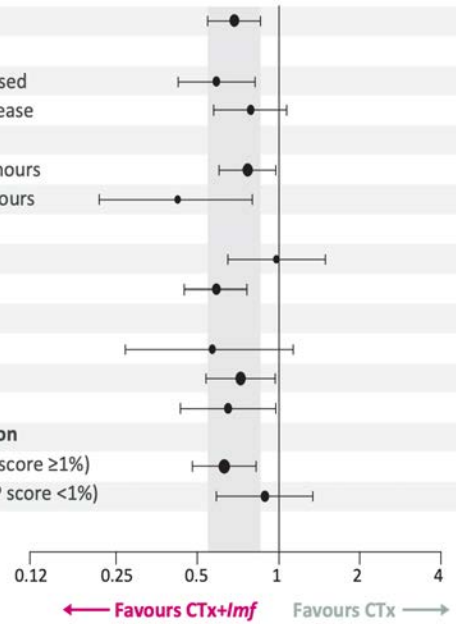


	CTx N=241	CTx + *Imfinzi* N=238	CTx + *Imfinzi* + *Lynparza* N=239
Median (range) follow-up,[1] months	12.6 (0.0–31.6)	15.4 (0.0–29.1)	15.4 (0.0–31.7)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS (95% CI),[1] months	9.6 (9.0–9.9)	10.2 (9.7–14.7)	15.1 (12.6–20.7)
HR (95% CI) vs CTx[2]		**0.71** (0.57–0.89); *P*=0.003	**0.55** (0.43–0.69); *P*<0.0001
HR (95% CI) vs CTx+*Imfinzi*[2]			**0.78** (0.61–0.99)

PFS rates were estimated by the KM method. 1. CI for median PFS is derived based on the Brookmeyer–Crowley method; 2. The primary PFS analysis for each comparison was performed separately. The HR and CI were estimated from a Cox proportional hazards model stratified by MMR and disease status. The CI was calculated using a profile likelihood approach. The P value was calculated using a log-rank test stratified by MMR and disease status.
ITT = intent-to-treat; (m)PFS = (median) progression-free surviva; no. = number; CTx = chemotherapy; *Imf = Imfinzi*; *Lyn = Lynparza*; HR = hazard ratio; CI = confidence interval; KM = Kaplan-Meier; MMR = mismatch repair.

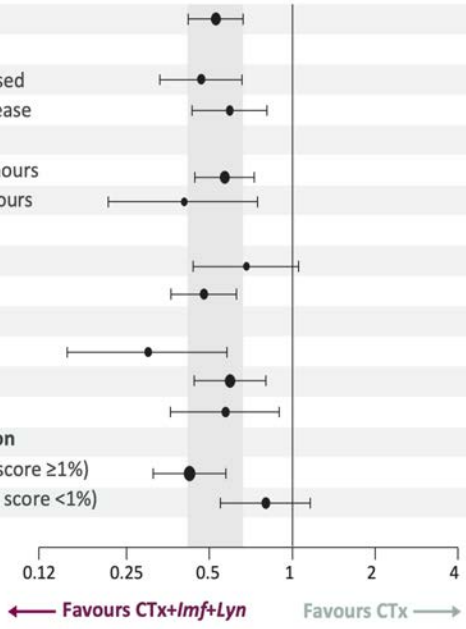
Consistent PFS benefit across key subgroups

CTx + *Imfinzi* → *Imfinzi* vs CTx



	HR (95% CI)	CTx+*Imfinzi* n/N (%)	CTx n/N (%)
All patients	0.68 (0.55–0.86)	139/238 (58.4)	173/241 (71.8)
Disease status			
Newly diagnosed	0.59 (0.42–0.82)	67/113 (59.3)	81/115 (70.4)
Recurrent disease	0.79 (0.58–1.07)	72/125 (57.6)	92/126 (73.0)
MMR status			
Proficient tumours	0.77 (0.60–0.97)	124/192 (64.6)	148/192 (77.1)
Deficient tumours	0.42 (0.22–0.80)	15/46 (32.6)	25/49 (51.0)
Region			
Asia	0.98 (0.65–1.49)	44/68 (64.7)	45/68 (66.2)
RoW	0.59 (0.45–0.76)	95/170 (55.9)	128/173 (74.0)
HRRm status			
HRRm	0.57 (0.27–1.13)	12/26 (46.2)	23/32 (71.9)
Non-HRRm	0.72 (0.54–0.97)	85/138 (61.6)	96/132 (72.7)
Unknown	0.65 (0.43–0.97)	42/74 (56.8)	54/77 (70.1)
PD-L1 expression			
Positive (TAP score ≥1%)	0.63 (0.48–0.83)	97/170 (57.1)	114/163 (69.9)
Negative (TAP score <1%)	0.89 (0.59–1.34)	38/61 (62.3)	57/75 (76.0)
Unknown	NC (NC–NC)	4/7 (57.1)	2/3 (66.7)

CTx + *Imfinzi* → *Imfinzi* + *Lynparza* vs CTx

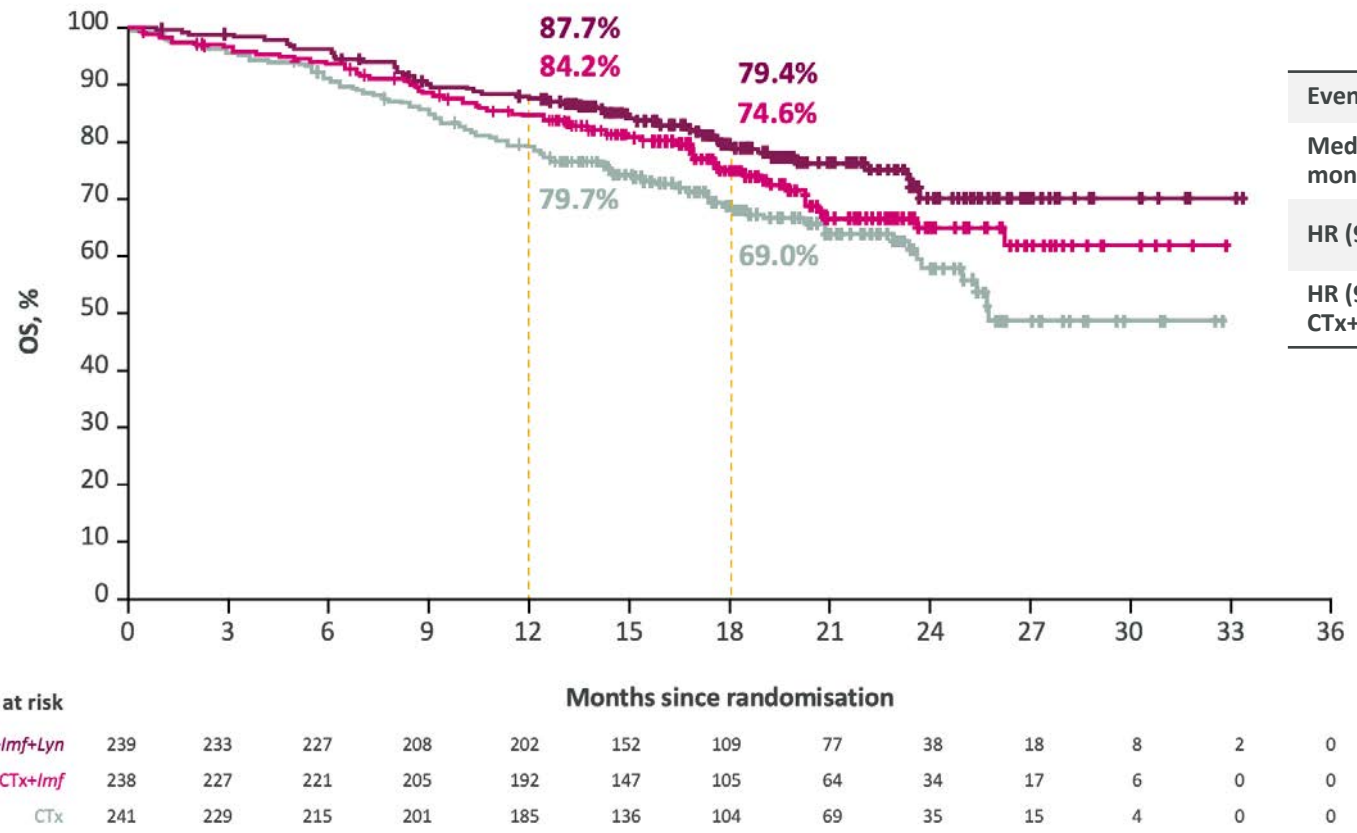


	HR (95% CI)	CTx+*Imf+Lyn* n/N (%)	CTx n/N (%)
All patients	0.53 (0.42–0.67)	126/239 (52.7)	173/241 (71.8)
Disease status			
Newly diagnosed	0.47 (0.33–0.66)	58/114 (50.9)	81/115 (70.4)
Recurrent disease	0.59 (0.43–0.81)	68/125 (54.4)	92/126 (73.0)
MMR status			
Proficient tumours	0.57 (0.44–0.73)	108/191 (56.5)	148/192 (77.1)
Deficient tumours	0.41 (0.21–0.75)	18/48 (37.5)	25/49 (51.0)
Region			
Asia	0.68 (0.44–1.06)	37/67 (55.2)	45/68 (66.2)
RoW	0.48 (0.36–0.63)	89/172 (51.7)	128/173 (74.0)
HRRm status			
HRRm	0.30 (0.15–0.58)	16/39 (41.0)	23/32 (71.9)
Non-HRRm	0.59 (0.44–0.80)	81/141 (57.4)	96/132 (72.7)
Unknown	0.57 (0.36–0.89)	29/59 (49.2)	54/77 (70.1)
PD-L1 expression			
Positive (TAP score ≥1%)	0.42 (0.31–0.57)	68/150 (45.3)	114/163 (69.9)
Negative (TAP score <1%)	0.80 (0.55–1.16)	55/82 (67.1)	57/75 (76.0)
Unknown	NC (NC–NC)	3/7 (42.9)	2/3 (66.7)

All observed HR point estimates favoured the Imfinzi and Imfinzi + Lynparza arms vs. control

Prespecified exploratory subgroup. Stratification factors (disease status [newly diagnosed vs recurrent], MMR status [proficient vs deficient], and geographic region [Asia vs non-Asia]) are per the randomisation code. PD-L1 status in baseline tumour tissue was determined centrally using Ventana PD-L1 SP263 immunohistochemistry assay. HRRm status was assessed in baseline tumour tissue using the Foundation One CDx NGS assay. HRRm status unknown includes patients recruited in China where HRR testing was not performed and patients with samples that were unavailable for testing.
PFS = progression-free survival; CTx = chemotherapy; MMR = mismatch repair; RoW = rest of world; HRRm = homologous recombination repair mutation; PD-L1 = programmed death-ligand 1; TAP = tumour area positivity; HR = hazard ratio; CDx = companion diagnostic; NGS = next generation sequencing.

Early positive OS trend with both regimens



	CTx N=241	CTx + *Imfinzi* N=238	CTx + *Imfinzi* + *Lynparza* N=239
Events, n (%)	82 (34.0)	65 (27.3)	52 (21.8)
Median OS (95% CI),[1] months	25.9 (23.9–NR)	NR (NR–NR)	NR (NR–NR)
HR (95% CI) vs CTx[2]		**0.77** (0.56–1.07); P=0.120	**0.59** (0.42–0.83); P=0.003
HR (95% CI) vs CTx+*Imfinzi*[2]			**0.77** (0.53–1.10)

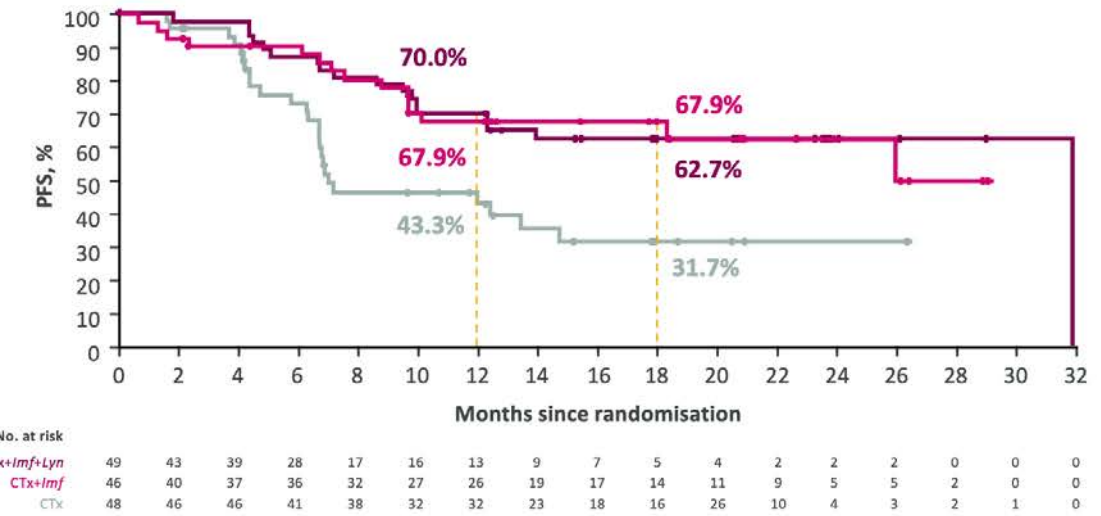
The median (range) duration of follow-up for OS was 18.6 (0.5–32.9), 18.4 (2.1–33.0), and 18.7 (1.1–33.4) months in censored patients for the CTx, CTx+*Imfinzi*, and CTx+*Imfinzi*+*Lynparza* arms, respectively. OS rates were estimated by the KM method. 1. CI for median OS is derived based on the Brookmeyer–Crowley method; 2. The HRs were estimated from an unstratified Cox proportional hazards model. The CI was calculated using a profile likelihood approach. P values were calculated using an unstratified log-rank test. P values failed to reach statistical significance.
OS = overall survival; no. = number; CTx = chemotherapy; *Imf* = *Imfinzi*; *Lyn* = *Lynparza*; CI = confidence interval; NR = not reached; KM = Kaplan Meier; HR = hazard ratio.

Lynparza enhanced benefit in pMMR

Consistent with previous trials, CTx + *Imfinzi* efficacy greatest in dMMR subgroup

dMMR subgroup

20% of population



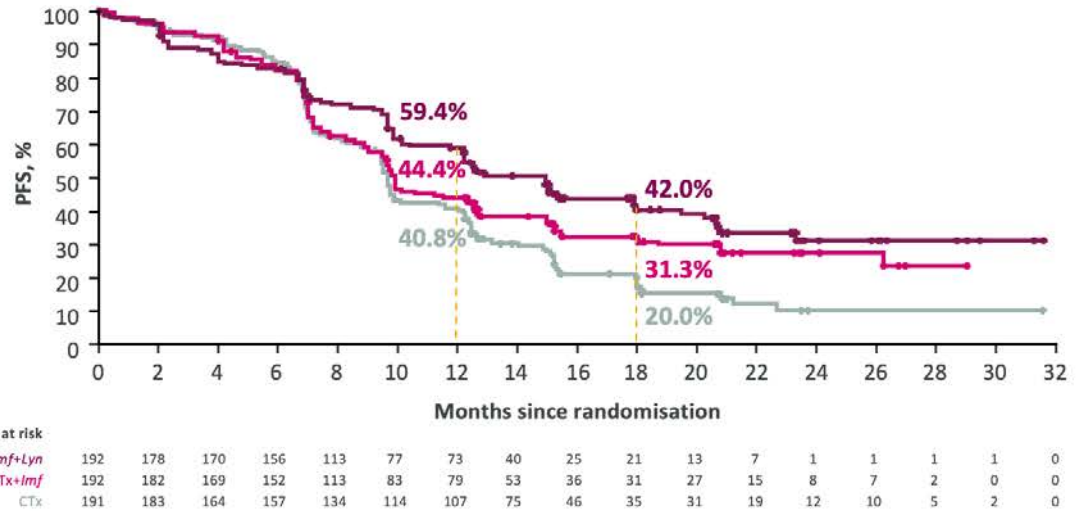
No. at risk

CTx+*Imf*+*Lyn*	49	43	39	28	17	16	13	9	7	5	4	2	2	2	0	0	0
CTx+*Imf*	46	40	37	36	32	27	26	19	17	14	11	9	5	5	2	0	0
CTx	48	46	46	41	38	32	32	23	18	16	26	10	4	3	2	1	0

	CTx N=49	CTx + *Imfinzi* N=46	CTx + *Imfinzi* + *Lynparza* N=48
Events, n (%)	25 (51.0)	15 (32.6)	18 (37.5)
Median PFS (95% CI),[1] months	7.0 (6.7–14.8)	NR (NR–NR)	31.8 (12.4–NR)
HR (95% CI) vs CTx[2]		**0.42** (0.22–0.80)	**0.41** (0.21–0.75)
HR (95% CI) vs CTx+*Imfinzi*[2]			**0.97** (0.49–1.98)

pMMR subgroup

80% of population



No. at risk

CTx+*Imf*+*Lyn*	192	178	170	156	113	77	73	40	25	21	13	7	1	1	1	1	0
CTx+*Imf*	192	182	169	152	113	83	79	53	36	31	27	15	8	7	2	0	0
CTx	191	183	164	157	134	114	107	75	46	35	31	19	12	10	5	2	0

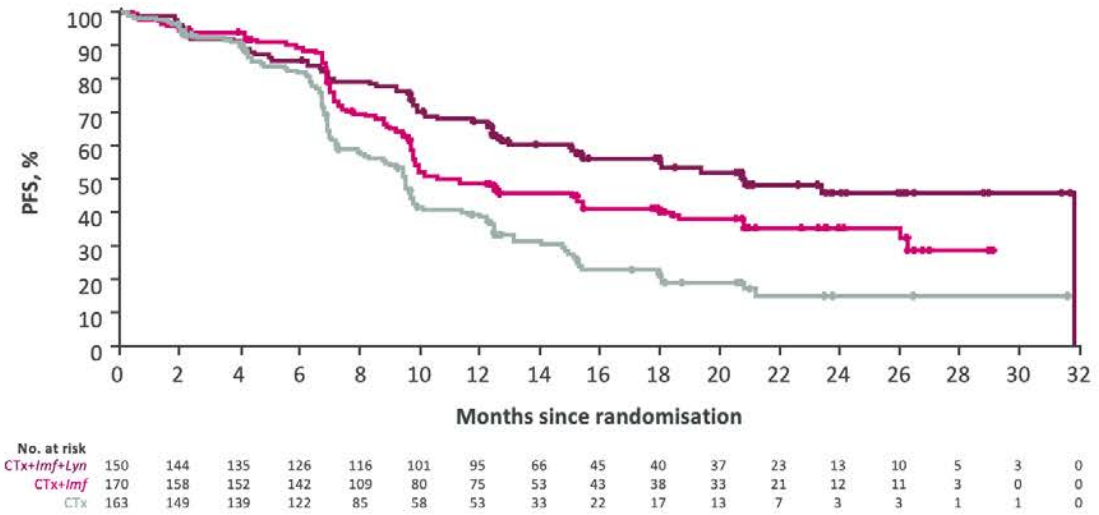
	CTx N=192	CTx + *Imfinzi* N=192	CTx + *Imfinzi* + *Lynparza* N=191
Events, n (%)	148 (77.1)	124 (64.6)	108 (56.5)
Median PFS (95% CI),[1] months	9.7 (9.2–10.1)	9.9 (9.4–12.5)	15.0 (12.4–18.0)
HR (95% CI) vs CTx[2]		**0.77** (0.60–0.97)	**0.57** (0.44–0.73)
HR (95% CI) vs CTx+*Imfinzi*[2]			**0.76** (0.59–0.99)

Exploratory subgroup analysis. MMR status evaluated using the Ventana immunohistochemistry MMR panel. Rates were estimated by the KM method.
1. CI for median PFS was derived based on the Brookmeyer–Crowley method; 2. The HR and CI were estimated from an unstratified Cox proportional hazards model.
p/dMMR = proficient / deficient mismatch repair; CTx = chemotherapy; PFS = progression-free survival; no. = number; *Imf* = *Imfinzi*; *Lyn* = *Lynparza*; CI = confidence interval; HR = hazard ratio; CI = confidence interval; NR = not reached.

PD-L1 emerging as potential biomarker across ITT

PD-L1 positive

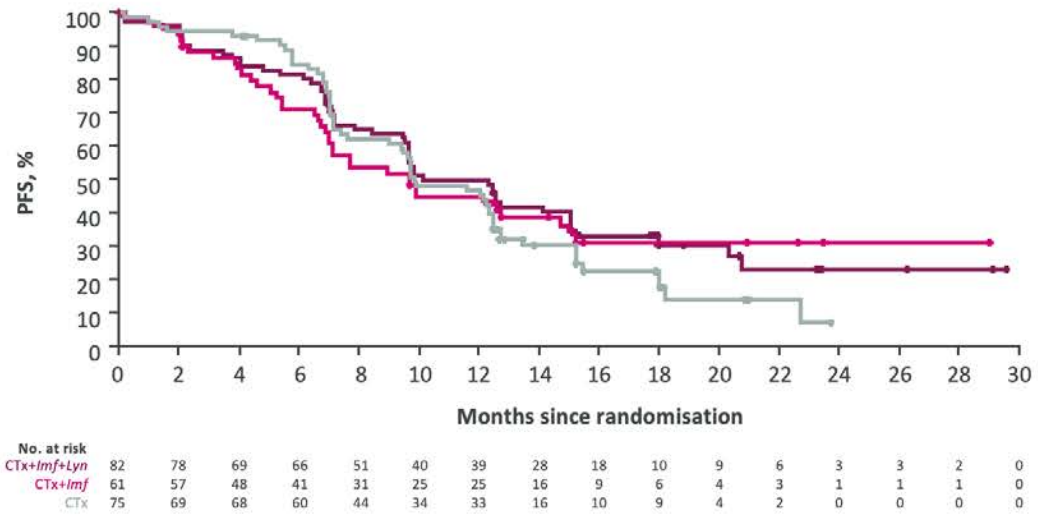
TAP≥1%; 67% of population



	CTx N=163	CTx + *Imfinzi* N=170	CTx + *Imfinzi* + *Lynparza* N=150
Events, n (%)	114 (69.9)	97 (57.1)	68 (45.3)
Median PFS (95% CI),[1] months	9.5	11.3	20.8
HR (95% CI) vs CP[2]		**0.63** (0.48–0.83)	**0.42** (0.31–0.57)
HR (95% CI) vs CTx+*Imfinzi*[2]			**0.67** (0.49–0.91)

PD-L1 negative

TAP<1%; 30% of population



	CTx N=67	CTx + *Imfinzi* N=61	CTx + *Imfinzi* + *Lynparza* N=82
Events, n (%)	57 (76.0)	38 (62.3)	55 (67.1)
Median PFS (95% CI),[1] months	9.9	9.7	10.1
HR (95% CI) vs CP[2]		**0.89** (0.59–1.34)	**0.80** (0.55–1.16)
HR (95% CI) vs CTx+*Imfinzi*[2]			**0.93** (0.61–1.41)

Exploratory subgroup analysis. PD-L1 expression evaluated using Ventana SP263. n=17 had unknown PD-L1 status, as shown within forest plot.

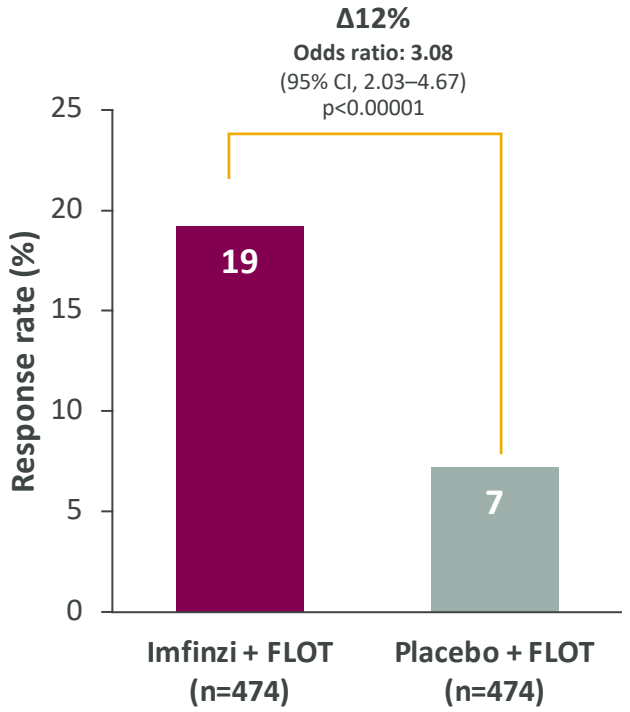
1. CI for median PFS was derived based on the Brookmeyer–Crowley method; 2. The HR and CI were estimated from an unstratified Cox proportional hazards model.

PD-L1 = programmed death-ligand 1; TAP = tumour area positivity; PFS = progression-free survival; no. = number; CTx = chemotherapy; *Imf = Imfinzi*; *Lyn = Lynparza*; CI = confidence interval; HR = hazard ratio.

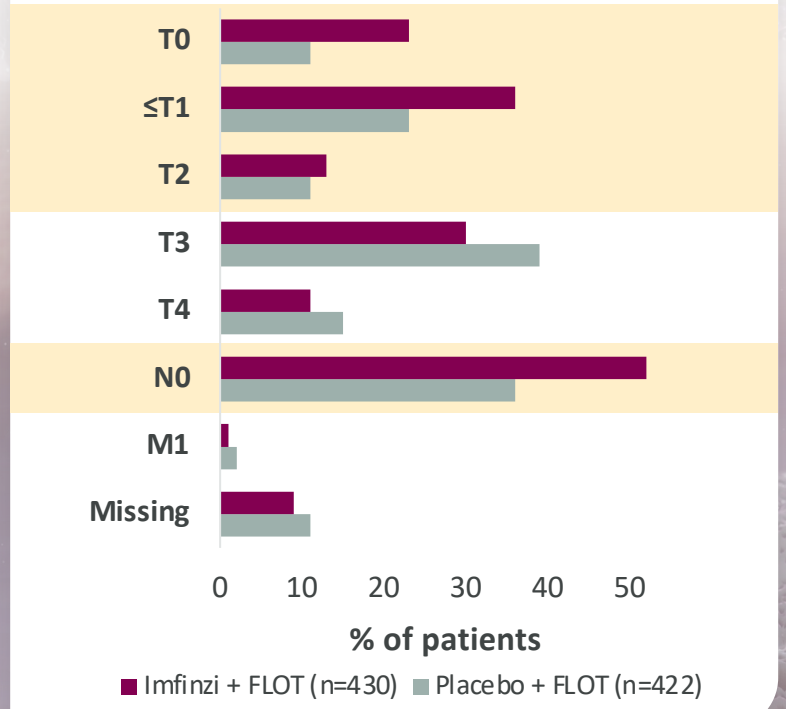
MATTERHORN Phase III trial in resectable GC/GEJC

Early efficacy signal with 12% improvement in key secondary endpoint pCR

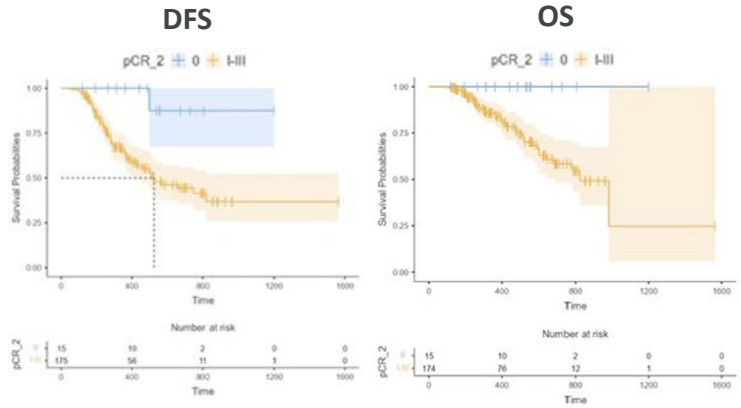
Clinically relevant pCR benefit with *Imfinzi* + FLOT



Improved downstaging with *Imfinzi* + FLOT



RealFLOT trial supports pCR as predictive for survival



Across multicentric observational trial (N=206), **DFS and OS were significantly longer for patients who achieved pCR**

MATTERHORN ongoing for primary endpoint of EFS

*both pCR or near pCR with limited residual cells

Giommoni et al. BMC Cancer_(2021) 21:1086 Results of the observational prospective RealFLOT study, https://doi.org/10.1186/s12885-021-08768-7

GC = gastric cancer; GEJC = gastro-oesophageal junction cancer; pCR = pathologic complete response; CI = confidence interval; FLOT. = 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; EFS = event-free survival

Reinforcing IO leadership

Data at ESMO reinforces *Imfinzi* benefit, sets stage for next-wave IO bispecifics

>70% of global growth driven by new launches:

HIMALAYA (unresectable HCC), **TOPAZ-1** (1L BTC), **POSEIDON** (1L NSCLC)

Imfinzi LCM support further expansion in key tumor areas

NSCLC

- **PACIFIC trials**
- **AVANZAR** 1L NSCLC
- **ADRIATIC** limited-stage SCLC
- **AEGEAN** Neo/adjuvant NSCLC

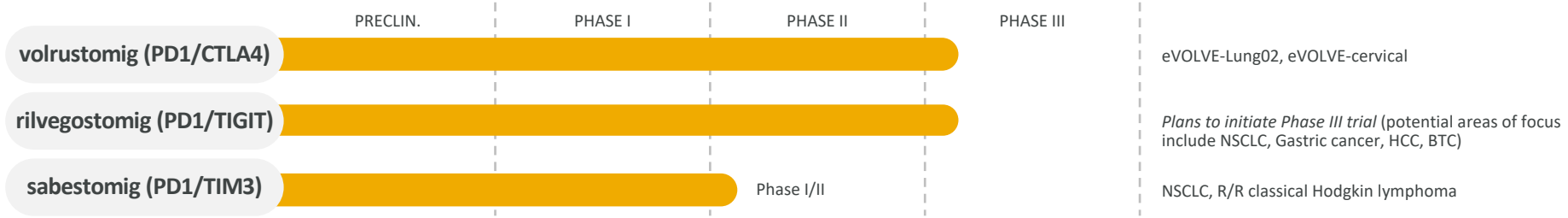
GU

- **DUO-O** ovarian cancer
- **DUO-E** endometrial cancer
- **MATTERHORN** gastric/GEJ cancer

GI

- **POTOMAC** Non-muscle invasive bladder cancer
- **EMERALD-1** locoregional liver cancer
- **EMERALD-2** adjuvant liver cancer

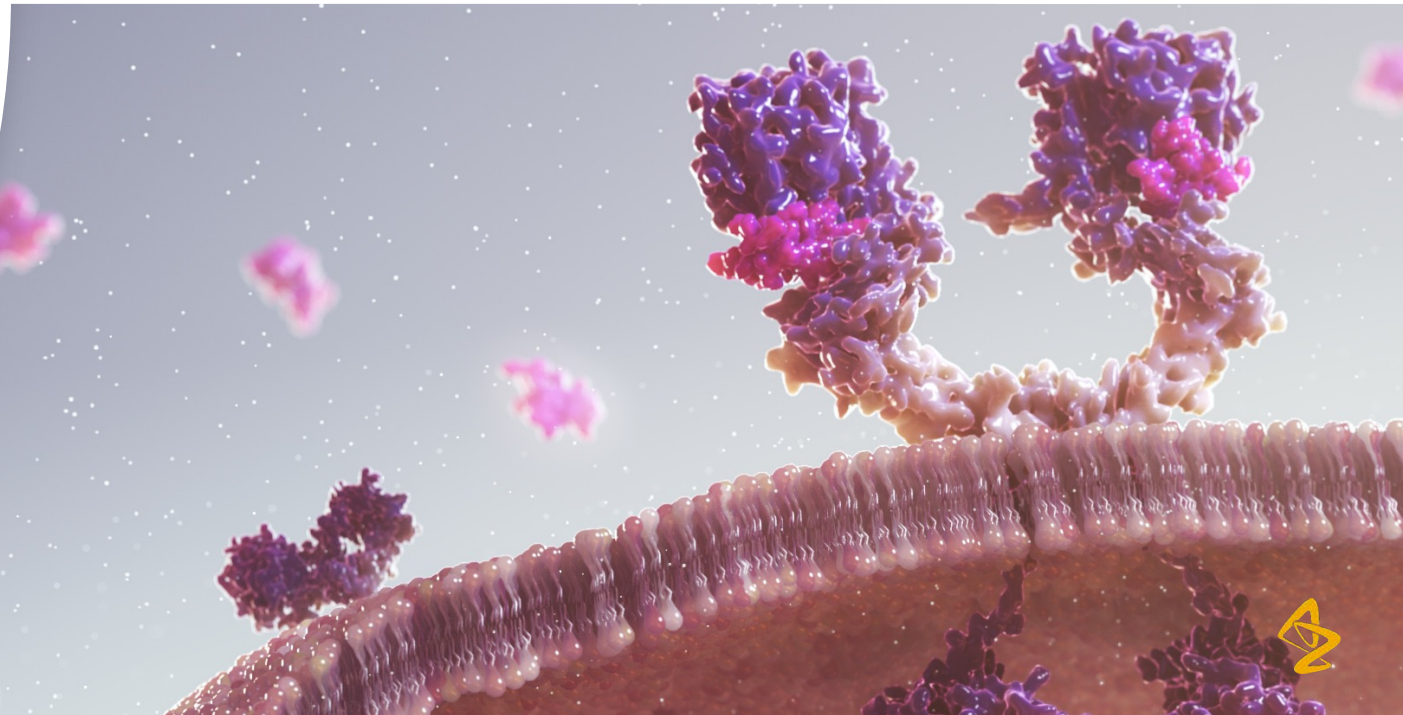
Next-wave bispecifics drive IO growth beyond 2025



IO = immunotherapy; ESMO = European society for medical oncology; HCC = hepatocellcular carcinoma; BTC = biliary tract cancer; NSCLC = non-small cell lung cancer; SCLC = small-cell lung cancer; GEJ = gastroesophageal junction; meso = mesothelial; HNSCC = head and neck squamous cell carcinoma; R/R = relapsed / refractory.
Collaboration partner: Compugen (rilvegostomig).

Establishing *Tagrisso* as backbone TKI in EGFRm NSCLC

Dave Fredrickson
ONCOLOGY BUSINESS



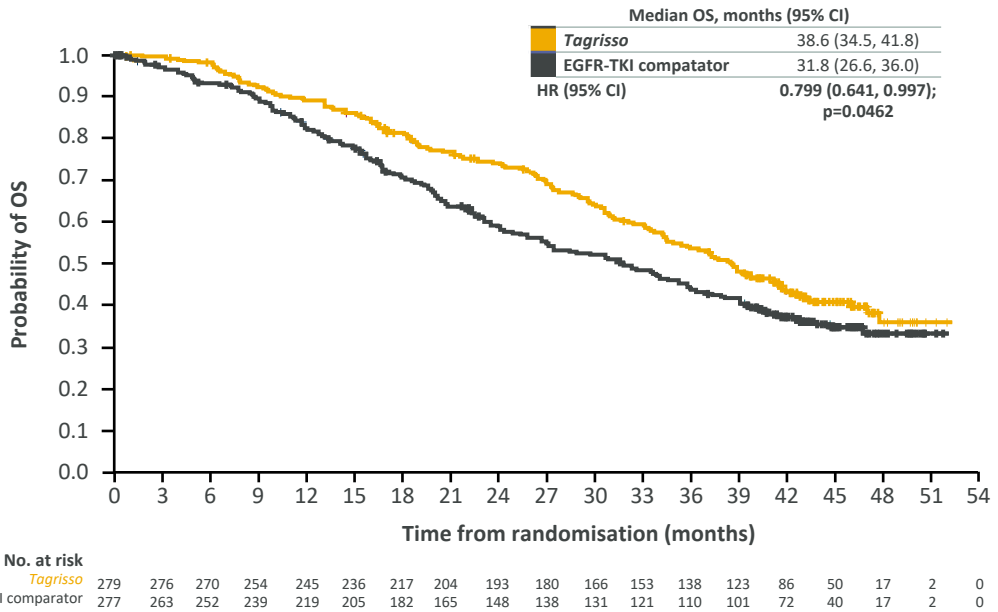
FLAURA2 potential new regimen for 1L EGFRm NSCLC

Builds on established benefit and clinician experience with *Tagrisso* and CTx

Tagrisso monotherapy (FLAURA)[1]

Tagrisso vs. EGFR-TKI comparator

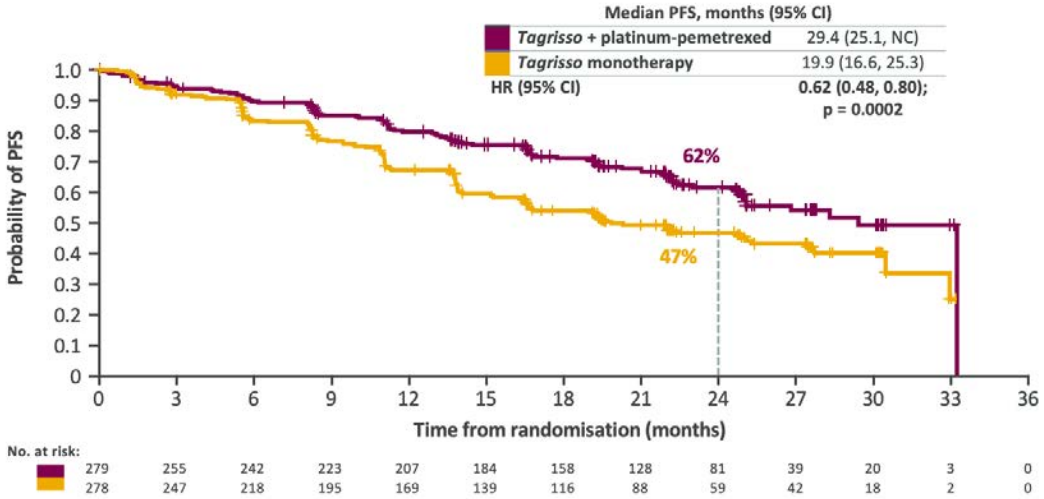
Demonstrated OS improvement of 6.8 months with HR 0.799



Tagrisso + CTx (FLAURA2)[2]

Tagrisso + CTx vs. *Tagrisso* monotherapy

BICR-assessed mPFS improvement of 9.5 months with HR 0.62[3]



- Trend to PFS2 and overall survival benefit for *Tagrisso* + CTx with HR 0.70 and 0.90 at 34% and 27% maturity respectively

1. Ramalingam SS, et al. N Engl J Med. 2020;382(1):41-50; 2. Janne PA et al. Abstract #PL03.13 presented at WCLC 2023. 3. Investigator mPFS primary endpoint and demonstrated mPFS improvement of 8.8 months with HR 0.62; BICR-assessed PFS was key secondary endpoint.

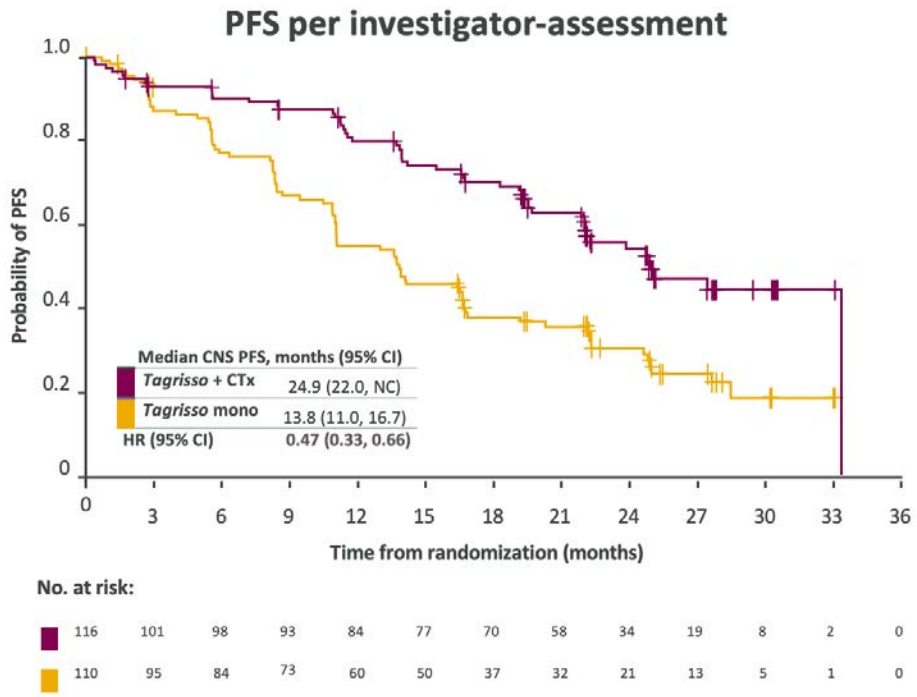
SoC = standard of care; 1L = 1st-line; (m)PFS = (median) progression-free survival; EGFRm = epidermal growth factor receptor mutation; NSCLC = non-small cell lung cancer; CTx = chemotherapy; TKI = tyrosine kinase inhibitor; OS = overall survival; HR = hazard ratio; CI = confidence interval; no. = number; BICR = blinded independent centralised review; mPFS = median progression-free survival; WCLC = World Conference on Lung Cancer.

Tagrisso as SoC backbone in 1L EGFRm NSCLC

CNS data at ESMO reinforces FLAURA and FLAURA2 positioning

Patients with CNS metastases at baseline

CNS ORR 59% (cFAS, N=222) and 48% (cEFR, N=78)



Tagrisso monotherapy remains 1L SoC

- Oral therapy with strong safety, proven tolerability
- Demonstrated OS of 38.6 months

Expect FLAURA2 to be SoC for subset of patients who can benefit from combination approach

- Patients with higher tumour burden, presence of brain metastases or L858R mutations
- Longest PFS benefit with almost 30 months mPFS (BICR), 38% decrease in risk of progression or death (HR, 0.62)

FLAURA2 granted priority review by US FDA

SoC = standard of care; EGFRm = epidermal growth factor receptor mutation; NSCLC = non-small cell lung cancer; CNS = central nervous system; ESMO = European Society of Medical Oncology; ORR = overall response rates; cFAS = CNS full analysis set; cEFR = CNS evaluable-for-response; PFS = progression free survival; HR = hazard ratio; CI = confidence interval; no. = number; 1L = 1st-line; mo = months; SoC = standard of care; Tx = treatment; combo = combination.

Q&A Session

Participating speakers and panelists

KEY EXTERNAL EXPERT
Dr Aaron Lisberg,
Thoracic Medical Oncologist, UCLA

Pascal Soriot,
Chief Executive Officer

Susan Galbraith,
Executive Vice President, Oncology R&D

Sunil Verma,
Global Head of Oncology, Medical

KEY EXTERNAL EXPERT
Dr Aditya Bardia,
Breast Medical Oncologist, MGH

Dave Fredrickson,
Executive Vice President, Oncology Business

Cristian Massacesi,
Chief Medical Officer & Oncology Chief Development Officer

SPECIALIST AREA LEADERSHIP

Niko Andre,
Global Franchise Head, Immuno-oncology

Matt Hellman,
VP, Head of Clinical Group, Early Oncology

Leora Horn,
Head of Clinical Development, Late Development Oncology, Global Clinical Strategy Head, Lung Cancer

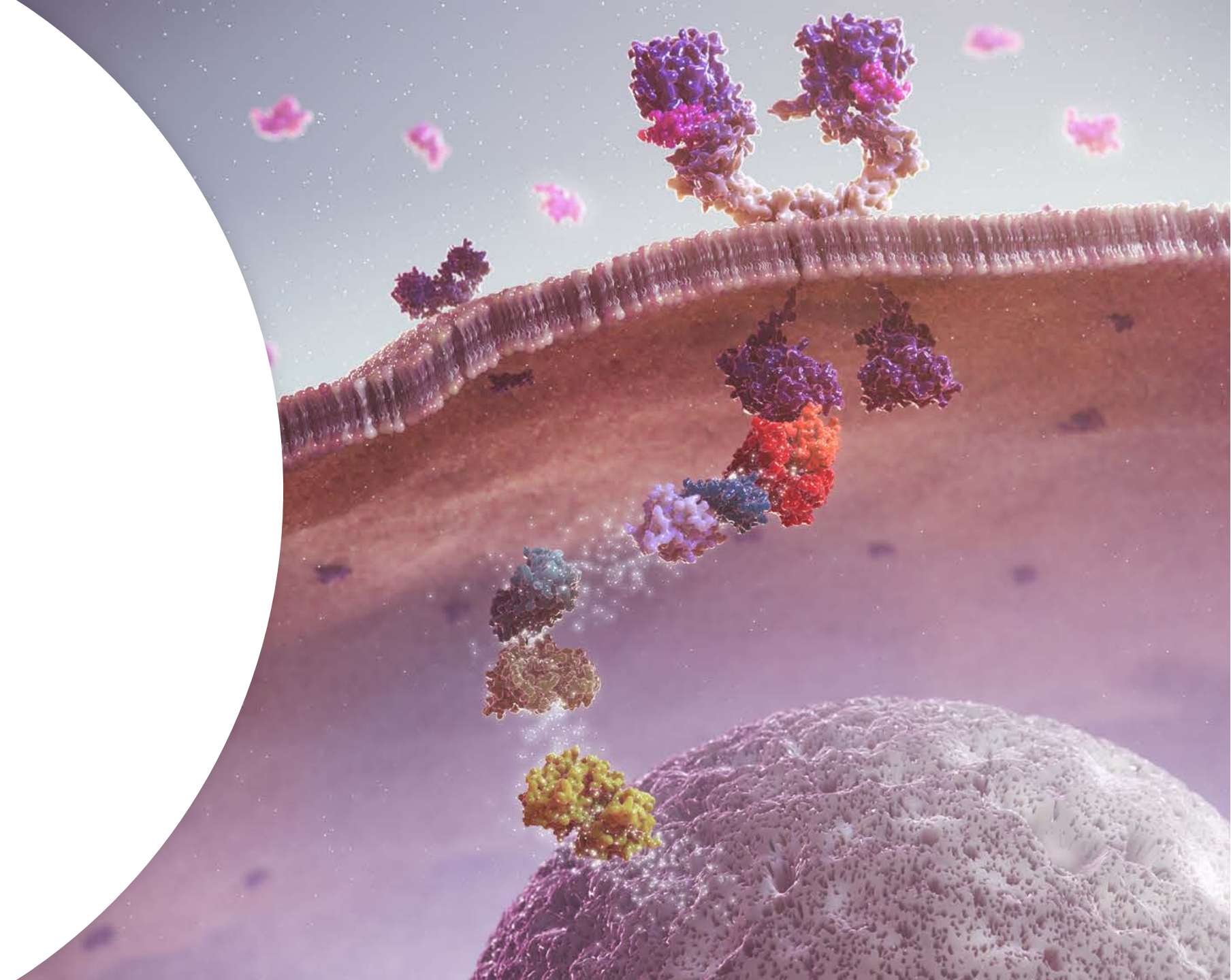
Puja Sapra,
SVP, Biologics Engineering & Targeted Delivery

Vikram Chand,
VP, Global Franchise Head, Dato-DXd

Simon Hollingsworth,
Global Franchise Head, IO Bispecifics

Ingrid Mayer,
Global Clinical Strategy Head, Breast Cancer

Appendix



TROPION-Breast04 Phase III in early TNBC

Neoadjuvant Dato-DXd + *Imfinzi* followed by adjuvant *Imfinzi* ± CTx vs SoC

- Stage II-III unilateral or bilateral primary invasive breast cancer
- TNBC or HR-low HER2-negative
- No evidence of distant disease
- No prior surgery, radiation, or systemic anticancer therapy

R
1:1

Neoadjuvant (24 weeks)

- **Dato-DXd + *Imfinzi***
- **pembrolizumab + carboplatin + paclitaxel → pembrolizumab + AC/EC**

Surgery

Adjuvant (9 cycles)

- ***Imfinzi* ± CTx**
- **pembrolizumab ± CTx**

Endpoints

Primary endpoints

- pCR and EFS

Key secondary endpoints

- OS
- DDFS
- Safety and tolerability
- PROs

Stratified by:

- Lymph node status (positive vs negative)
- Tumour stage (cT1 to cT2 versus cT3 to cT4)
- HR status (HR-negative vs HR-low)
- Geographic region (US/Canada/Europe/Australia vs RoW

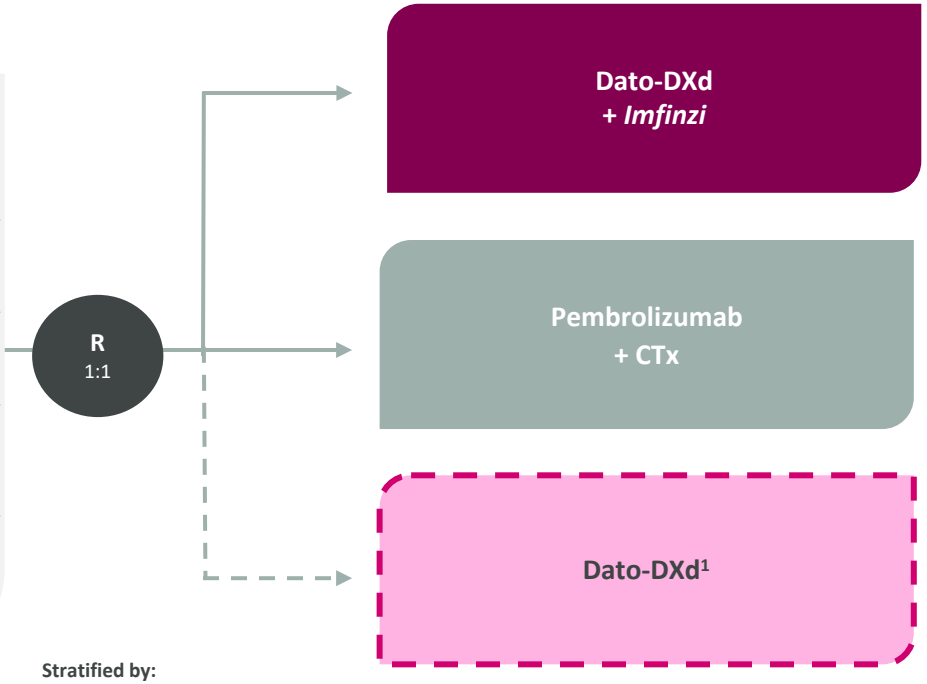
*TROPION-Breast04 has not begun enrollment as of 23 October 2023. TNBC = triple negative breast cancer; Dato-DXd = datopotamab deruxtecan; CTx = chemotherapy; SoC = standard of care; HR = hormone recetor; HER2 = human epidermal growth factor receptor 2; R = randomise; RoW = rest of world; AC/EC = doxorubicin and cyclophosphamide/ epirubicin and cyclophosphamide; pCR = pathologic complete response; EFS = event-free survival; OS = overall survival; DDFS = distant disease-free survival; PROs = patient reported outcomes.

Collaboration partner: Daiichi Sankyo (Dato-DXd).

TROPION-Breast05 Phase III in 1L PD-L1+ mTNBC

Dato-DXd + *Imfinzi* vs pembrolizumab + CTx

- Metastatic or locally advanced inoperable TNBC
- PD-L1+ (CPS ≥ 10 IHC 22C3)
- No prior treatment for advanced disease
- DFI ≥ 6 m since treatment in curative setting
- Prior PD-1/PD-L1 treatment for early stage TNBC allowed



Stratified by:

- DFI (*de novo* or prior DFI 6-12m vs prior DFI >12 m)
- Geographic region (US/Canada/Europe vs Dato-DXd monotherapy arm enrolling countries vs RoW)
- Prior PD-1/PD-L1 treatment for early stage TNBC (yes vs no)

Endpoints

Primary endpoints

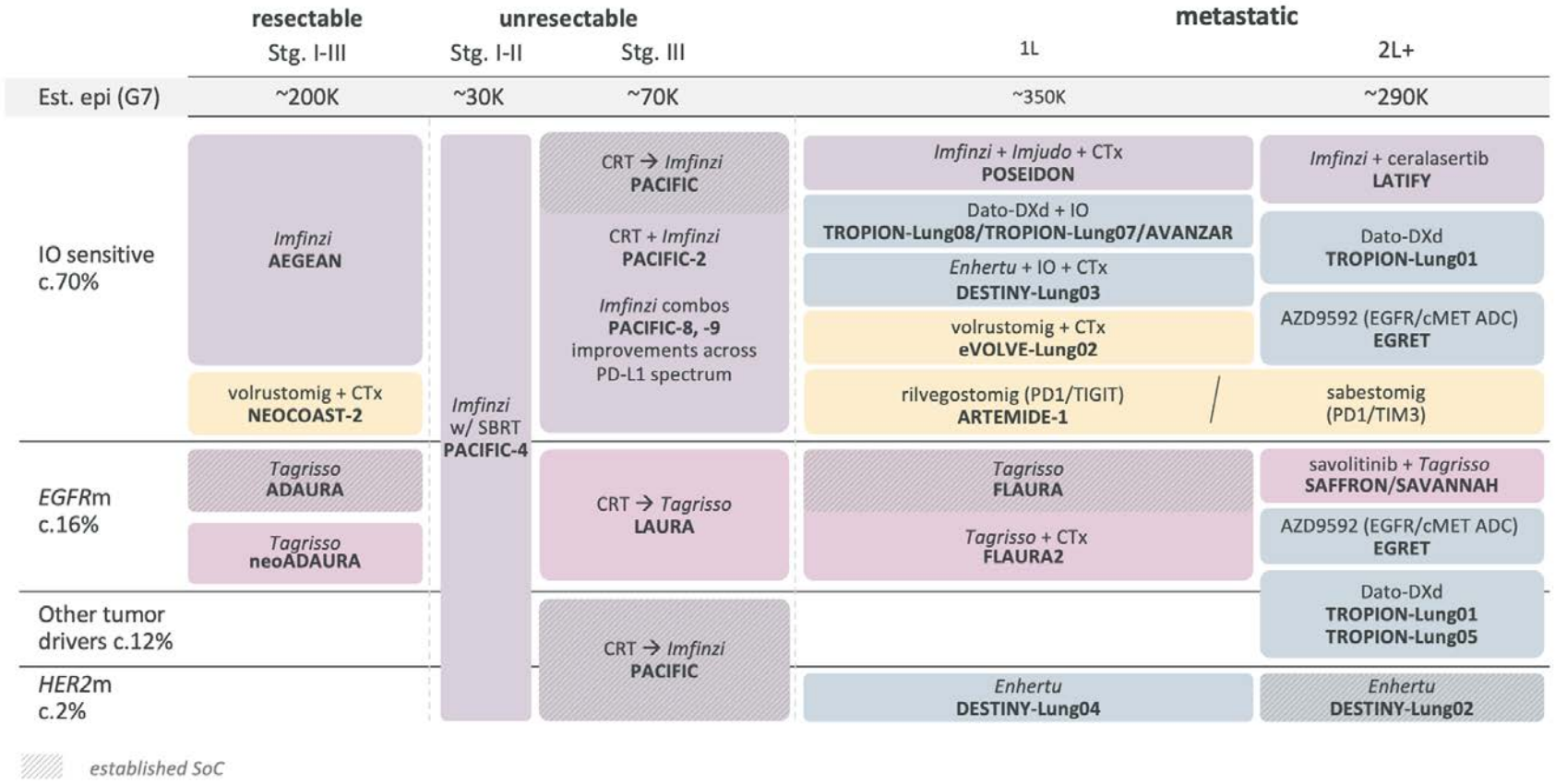
- PFS (BICR)

Key secondary endpoints

- OS
- PFS (inv)
- ORR
- Safety and tolerability
- PROs

TROPION-Breast05 has not begun enrollment as of 23 October 2023. 1. Dato-DXd monotherapy arm only in select countries with 1:1:1 randomisation strategy, otherwise 1:1 in arms A:B. 1L = 1st-line; PD-(L)1 = programmed death-(ligand) 1; TNBC = triple negative breast cancer; Dato-DXd = datopotamab deruxtecan; CTx = chemotherapy; CPS = combined positive score; IHC = immunohistochemistry; DFI = disease-free interval; R = randomise; RoW = rest of world; PFS = progression-free survival; BICR = blinded independent centralised review; OS = overall survival; inv = investigator-assessed; ORR = objective response rate; PROs = patient-reported outcomes.
Collaboration partner: Daiichi Sankyo (Dato-DXd).

AstraZeneca in NSCLC

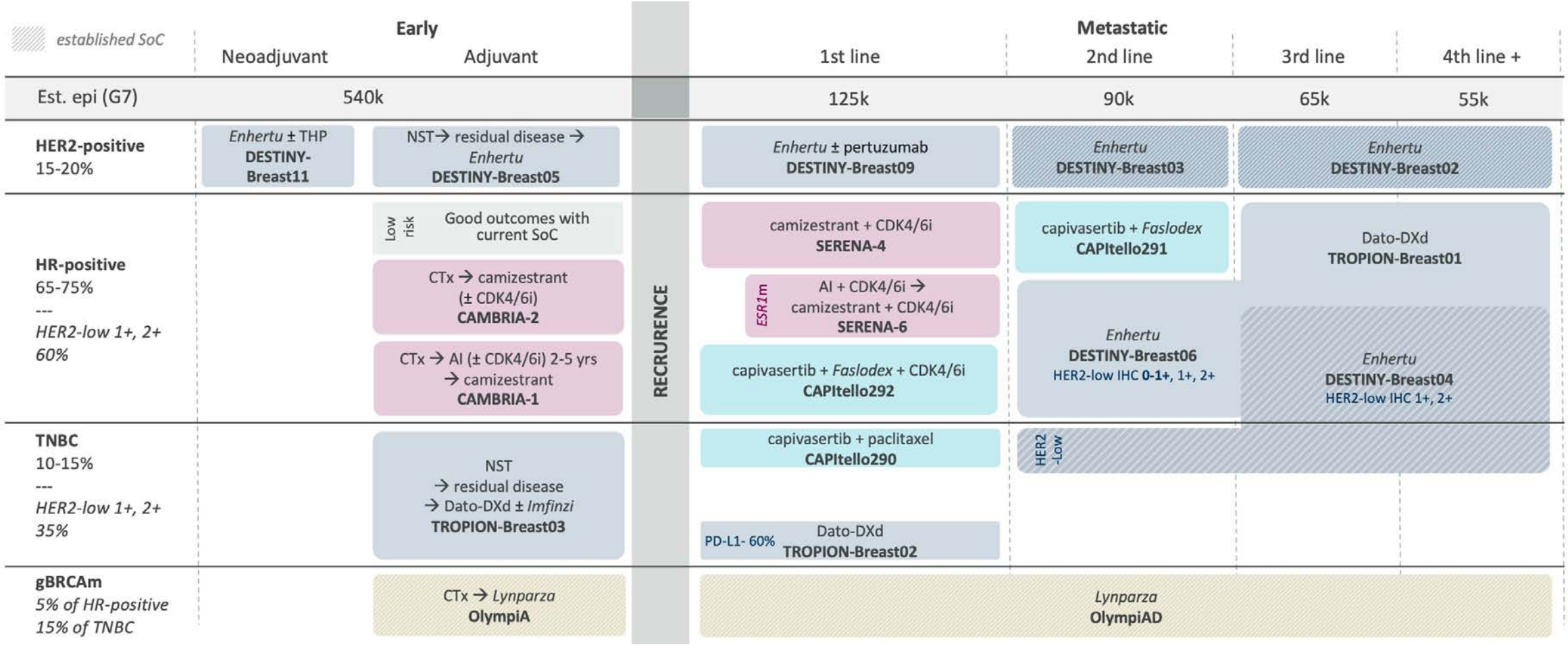


- Establishing *Tagrisso* as backbone TKI in *EGFR*m
- *Imfinzi* leading IO in unresectable
- Advancing best-in-class ADCs to replace systemic chemotherapy
- Delivering next-wave bispecifics to improve on PD1/PD-L1
- Developing novel combinations, including IO + ADCs
- Investing behind new technologies and platforms, including cell therapy and testing/screening

Ambition for >50% of all treated lung cancer patients to be eligible for an AstraZeneca medicine by the year 2030

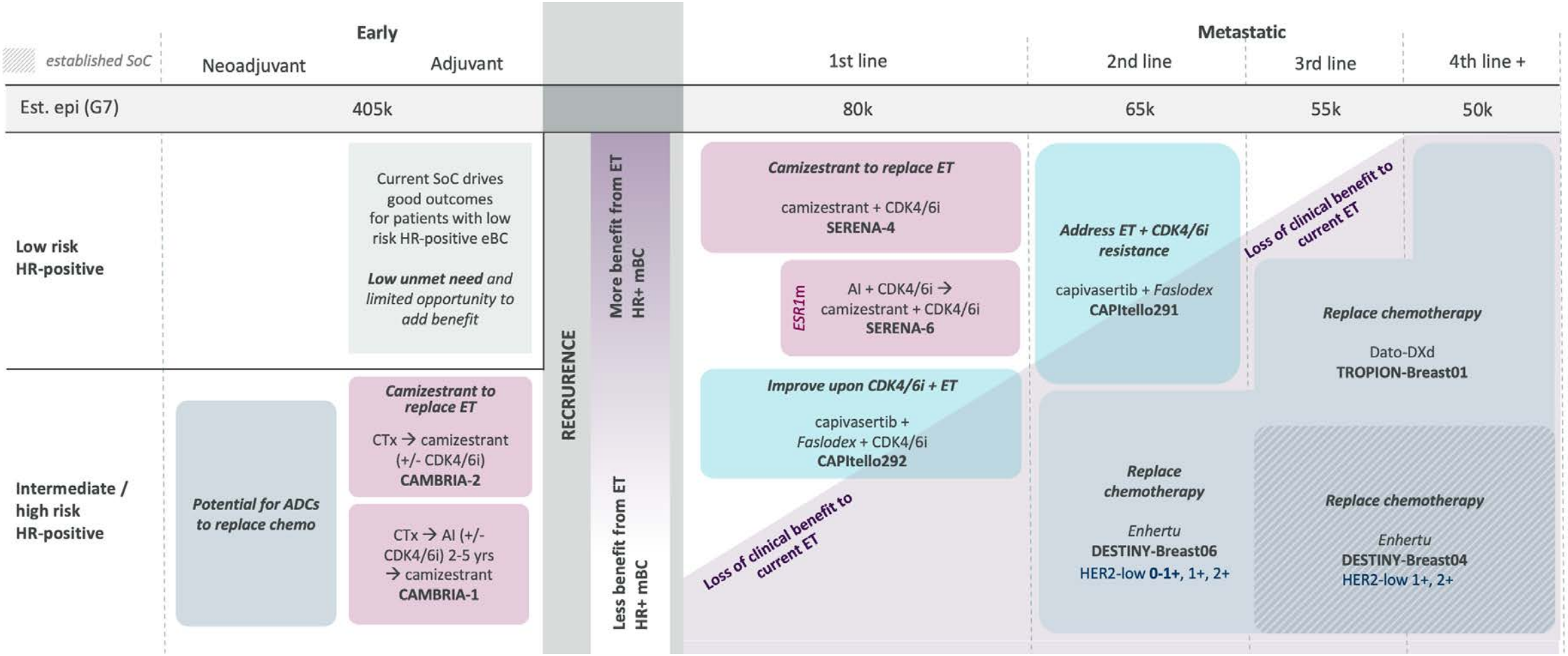
Est epi (G7) = estimated epidemiology across G7 (US, EU5, JP); Stg. = stage; CTx = chemotherapy; SBRT = stereotactic body radiation therapy; CRT = chemoradiotherapy; pembro = pembrolizumab; IO = immunotherapy; ADC = antibody-drug conjugate; PD1 = programmed cell death protein 1; EGFR = epidermal growth factor receptor; c-MET = mesenchymal-epithelial transition factor; TIGIT = T-cell immunoreceptor with immunoglobulin and ITIM domains; CTLA4 = cytotoxic T-lymphocyte associated protein 4; TIM3 = T-cell immunoglobulin and mucin domain-containing protein 3; SoC = standard of care; TKI = tyrosine kinase inhibitor.
Collaboration partners: Daiichi Sankyo (*Enhertu*, Dato-DXd), Compugen (rilvegostomig).

AstraZeneca in Breast Cancer



All numbers are approximate. Illustrative settings and populations, not to scale.
1/2/3/4L = 1st/2nd/3rd/ 4th-line; est epi (G7) = estimated epidemiology across G7 (US, EU5, JP for drug treated patients. HER2 = human epidermal growth factor receptor 2; THP = docetaxel, trastuzumab, and pertuzumab; NST = neoadjuvant systemic treatment; HR = hormone receptor; SoC = standard of care; CTx = chemotherapy; AI = aromatase inhibitor; CDK4/6i = cyclin-dependent kinase 4 and 6 inhibitor; yrs = years; ESR1m = oestrogen receptor 1 gene mutation; Dato-DXd = datopotamab deruxtecan; TNBC = triple negative breast cancer; PD-L1 = programmed cell death ligand 1; gBRCAm = germline BRCA-mutated.
Collaboration partners: Daiichi Sankyo (*Enhertu*, Dato-DXd), Merck & Co., Inc. (*Lynparza*).

AstraZeneca in HR-positive Breast Cancer

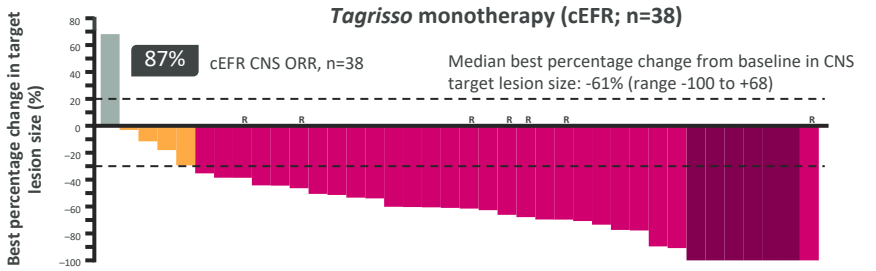


All numbers are approximate. Illustrative settings and populations, not to scale.
HR = hormone receptor; est epi (G7) = estimated epidemiology across G7 (US, EU5, JP for drug treated patients; SoC = standard of care; ADC = antibody drug conjugate; ET = endocrine therapy; CTx = chemotherapy; AI = aromatase inhibitor; CDK4/6i = cyclin-dependent kinase 4 and 6 inhibitor; yrs = years; ESR1m = oestrogen receptor 1 gene mutation; ER = oestrogen receptor; Dato-DXd = datopotamab deruxtecan.
Collaboration partners: Daiichi Sankyo (*Enhertu*, Dato-DXd).

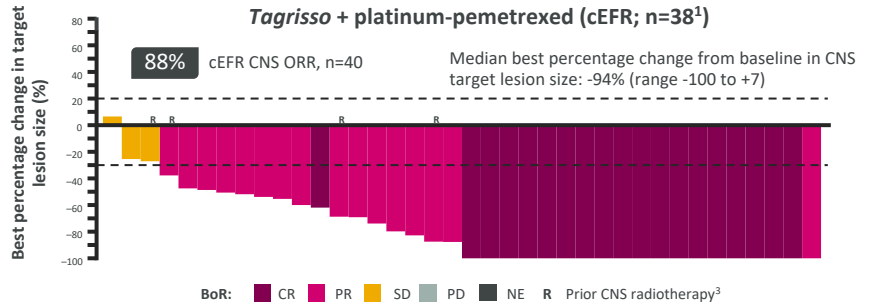
Complete and durable CNS responses in FLAURA2

Deep, sustained CNS response observed for patient in FLAURA2

Tagrisso has clinically established activity in brain

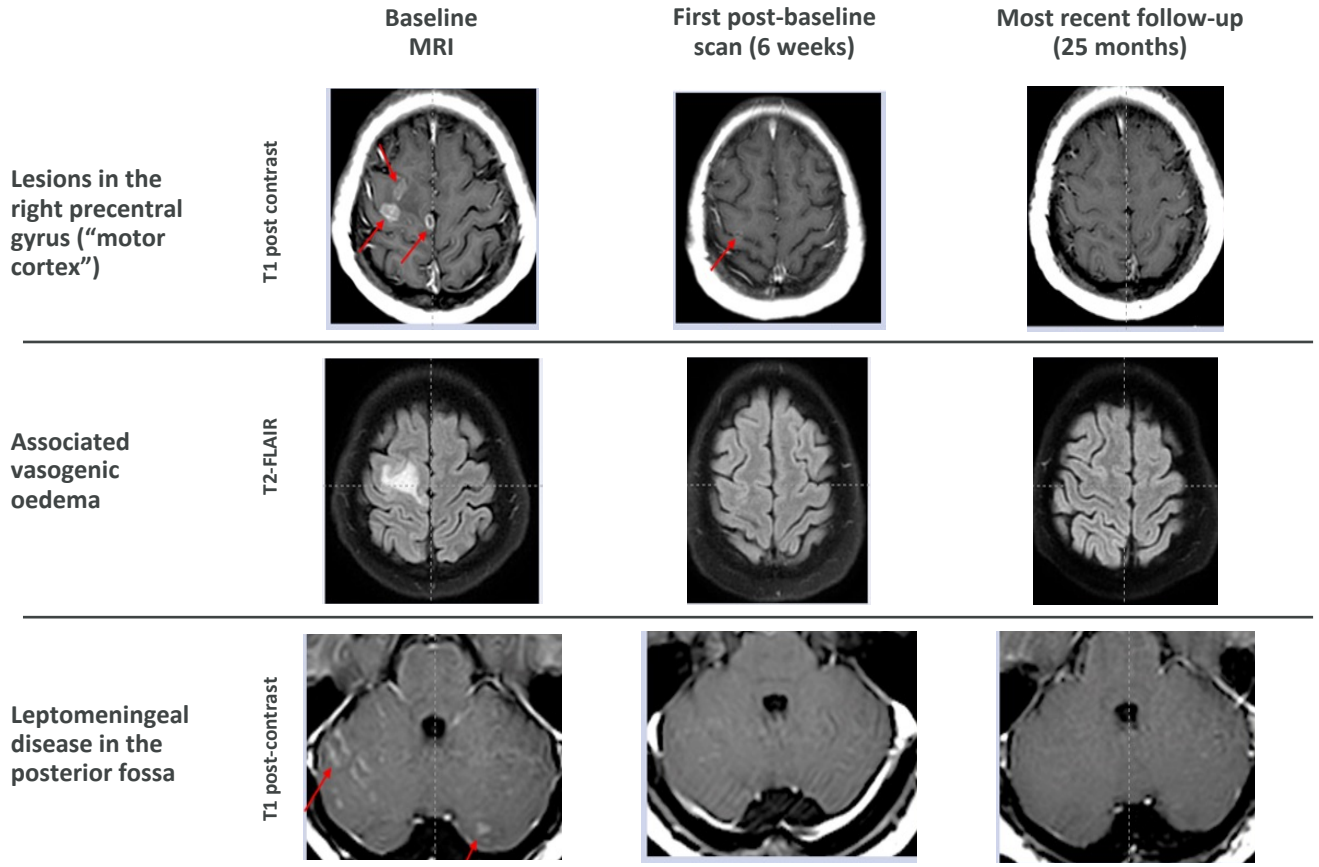


With the addition of CTx 50% patients with CNS metastases[2] had complete responses



In FLAURA2 all patients had brain imaging at baseline and on progression. In patients known brain metastases, imaging was 6, 12 and every 12 weeks

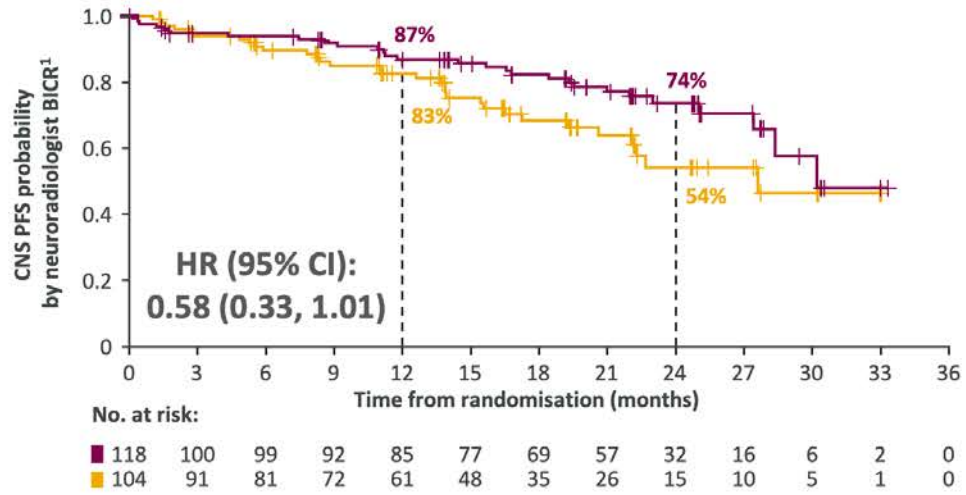
Patient with CNS leptomeningeal disease has an ongoing deep and durable sustained response with *Tagrisso* + CTx



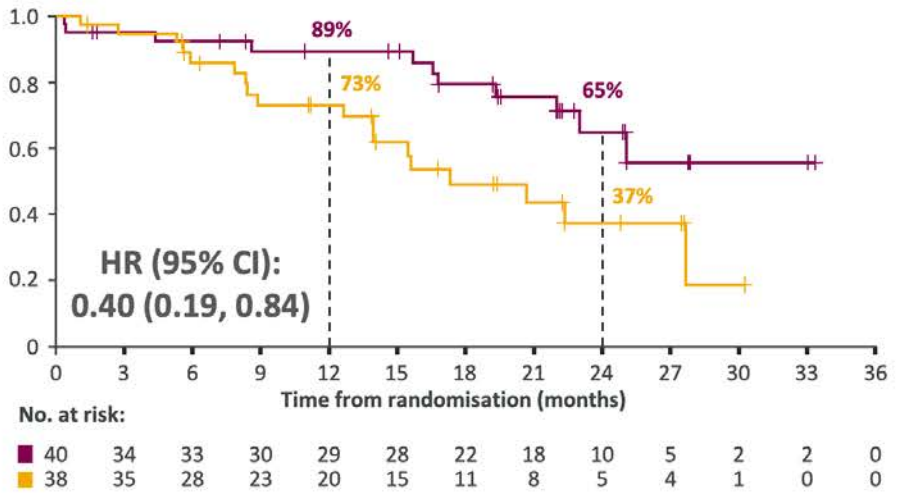
Patient scans with permission from FLAURA2 investigator. 1. Two pts had ≥1 measurable CNS lesion at baseline by CNS BICR but died before the follow-up CNS BICR scan; 2. With measurable disease at baseline; 3. In the cEFR, 4/40 pts (10%) in the *Tagrisso* + platinum-pemetrexed arm and 7/38 pts (18%) in the *Tagrisso* arm had received prior CNS radiotherapy; stable neurological status for ≥2 weeks after completion of definitive treatment and steroids was required before study entry, if received. CNS = central nervous system; cEFR = CNS evaluable-for-response set; cFAS = CNS full analysis set; ORR = objective response rate; CTx = chemotherapy; BoR = best overall response; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; MRI = magnetic resonance imaging.

Improved CNS PFS by CNS BICR with *Tagrisso* + CTx

cFAS - Measurable and non-measurable BM



cEFR - Measurable BM



	cFAS (n=222) Measurable + non-measurable BM		cEFR (n=78) Measurable BM	
n (%)[2]	*Tagrisso* + CTx (n=118)	*Tagrisso* mono (n=104)	*Tagrisso* + CTx (n=40)	*Tagrisso* mono (n=38)
Any CNS RECIST progression[3]	11 (9)	20 (19)	5 (13)	13 (34)
Progression in CNS target lesions	2 (2)	7 (7)	2 (5)	7 (18)
Progression in non-target CNS lesions	0	4 (4)	0	3 (8)
Progression due to new CNS lesions	9 (8)	12 (12)	3 (8)	6 (16)
Death without CNS progression	17 (14)	11 (11)	6 (15)	5 (13)

1. Median follow-up for CNS PFS in the cFAS was 20.1 months (range 0-33.3) in the *Tagrisso* + platinum-pemetrexed arm and 13.9 months (0-33.1) in the *Tagrisso* monotherapy arm. CNS PFS data maturity was 27% (59/222 events across both arms); 2. Only includes CNS progression events that occurred within two consecutive scheduled visits (plus visit window) of the last CNS assessment or randomisation; 3. Target lesions, non-target lesions, and new lesions were not necessarily mutually exclusive. CNS = central nervous system; PFS = progression-free survival; BICR = blinded independent centralised review; CTx = chemotherapy; cFAS = CNS full analysis set; BM = brain metastases; cEFR = CNS evaluable-for-responsel; HR = hazard ratio; CI = confidence interval; no. = number; RECIST, Response Evaluation Criteria in Solid Tumours.

Data cut-off: 03 April 2023.