Advances in Breast Cancer
Advances in Oncology

Mili Arora, MD

November 11, 2023

Outline

I. Early-stage HR+, HER2 negative breast cancer

- NAC w/immunotherapy for high-risk disease: **KEYNOTE- 756**
- Role of adjuvant CDK 4/6 inhibitors: **NATALEE**

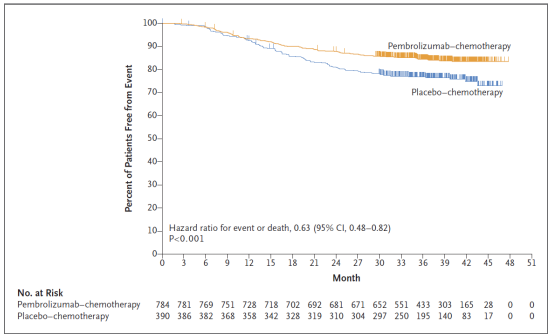
II. Advanced breast cancer

- Upfront rx for HR+/HER2 neg ABC: **SONIA**
- Overcoming endo resistance: **CAPITELLO-291**
- Novel ADC for HR+/HER2 neg ABC: **TROPION-01**

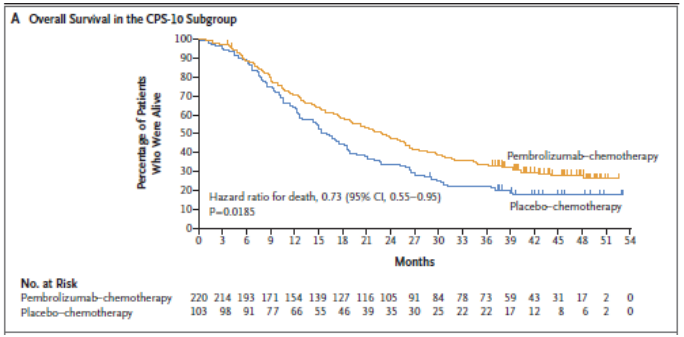
EARLY BREAST CANCER

Immunotherapy in Breast Cancer: FDA Indications

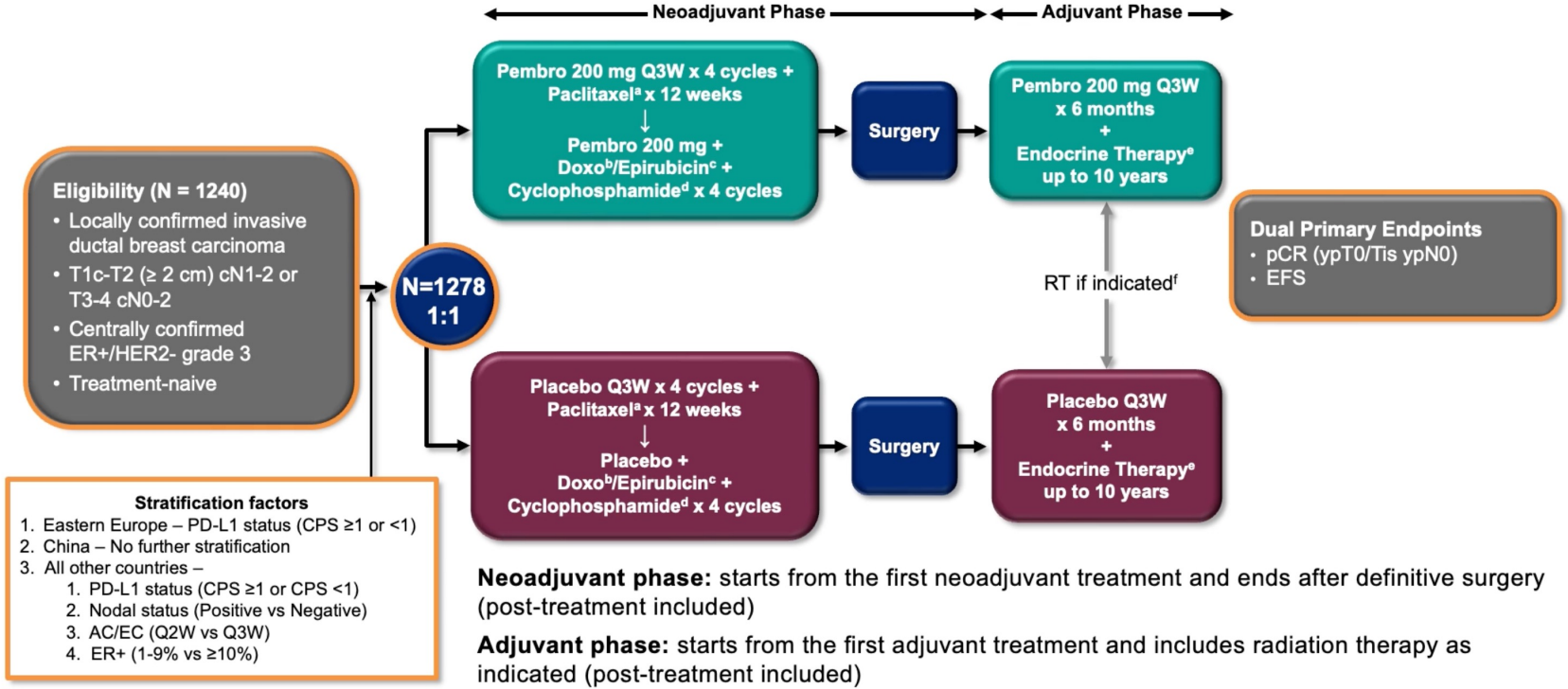
- **TNBC: NAC**
  - KEYNOTE-522: neoadjuvant pembro w/chemo followed post op vs neoadjuvant chemo
  - pCR 64.8% vs 51.2%
  - EFS 84.5% vs 76.8%



- **TNBC: 1st line metastatic**
  - KEYNOTE-355: pembro-chemo vs chemo in pts TNBC
  - CPS 10: PFS 9.7 mos vs 5.6 mos
  - CPS 10: OS 23 mos vs 16.1 mos



KEYNOTE-756: Study Design



Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

[a]Paclitaxel dose was 80 mg/m^2 QW. [b]Doxorubicin dose was 60 mg/m^2 Q3W. [c]Epirubicin dose was 100 mg/m^2 Q3W. [d]Cyclophosphamide dose was 600 mg/m^2 Q3W or Q2W.
[e]Endocrine therapy was administered according to institution guidelines. [f]Radiation therapy (concurrent or sequential) was administered according to institution guidelines.

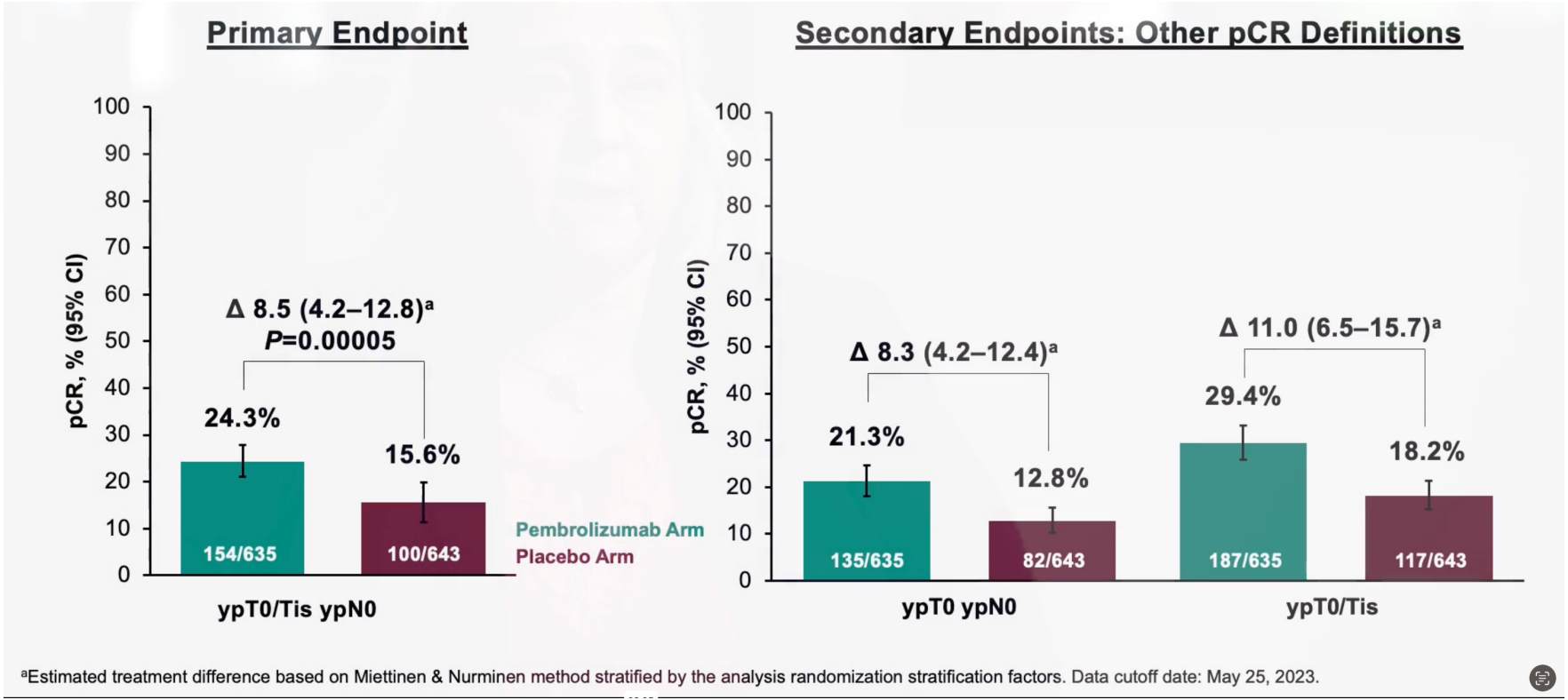
KEYNOTE-756: Baseline Characteristics

Characteristic, n (%)	All Participants[a], N = 1278	
	Pembrolizumab Arm N = 635	Placebo Arm N = 643
Age, median (range), yrs	49 (24-82)	49 (19-78)
ECOG PS 1	65 (10.2)	55 (8.6)
PD-L1[b] CPS ≥1	482 (75.9)	489 (76.0)
Anthracycline schedule		
Q3W	415 (65.4)	425 (66.1)
Q2W	183 (28.8)	187 (29.1)
Not started	37 (5.8)	31 (4.8)
Tumor size		
T1/T2	402 (63.3)	413 (64.2)
T3/T4	233 (36.7)	230 (35.8)
Nodal involvement		
Positive	570 (89.8)	582 (90.5)
Negative	65 (10.2)	61 (9.5)
ER positivity ≥10%	601 (94.6)	600 (93.3)

All GRADE 3

[a]All participants had centrally confirmed grade 3 disease. [b]PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100). Data cutoff date: May 25, 2023.

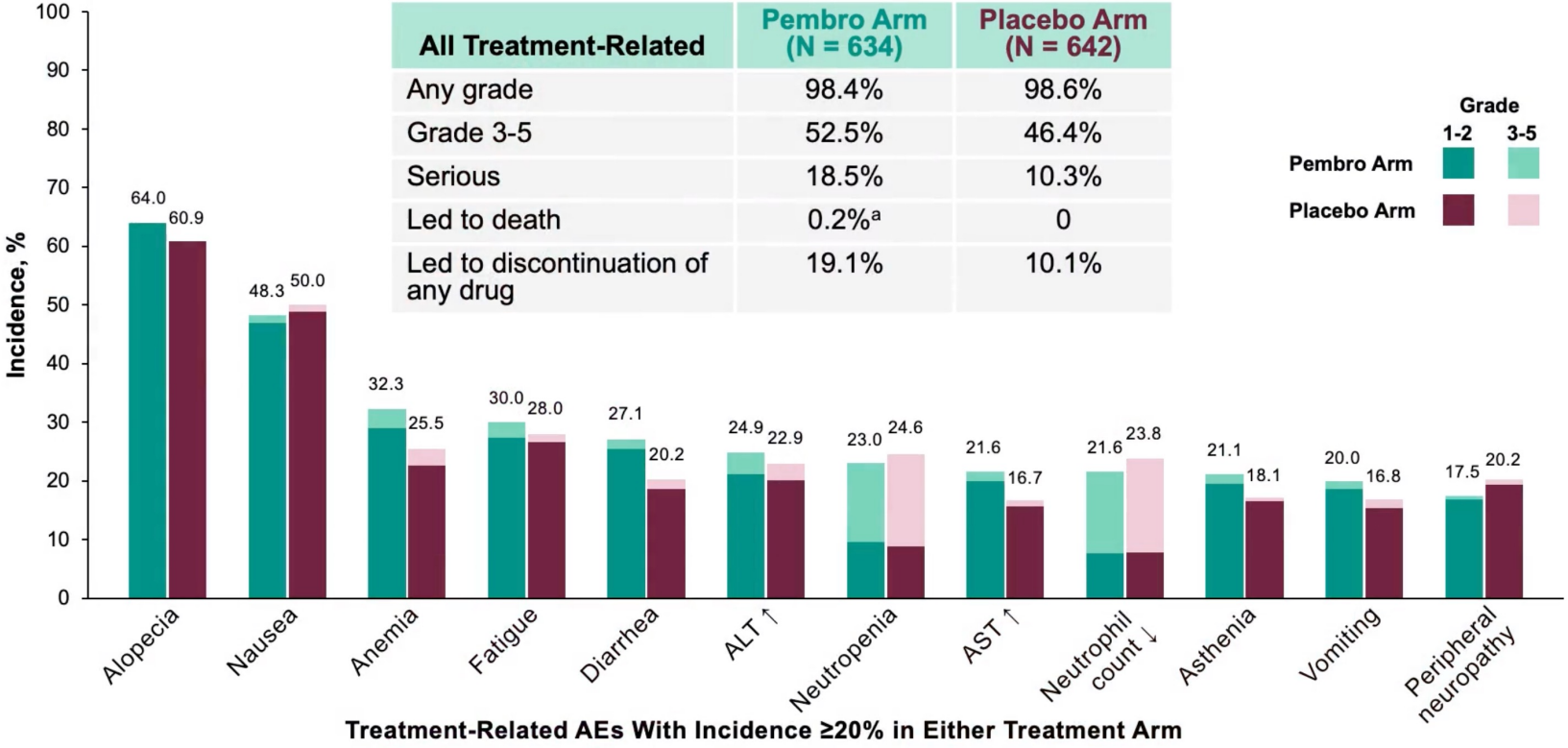
KEYNOTE-756: Pathological Complete Response



[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by the analysis randomization stratification factors. Data cutoff date: May 25, 2023.

KEYNOTE-756: Treatment-Related AEs

All Treatment-Related	Pembro Arm (N = 634)	Placebo Arm (N = 642)
Any grade	98.4%	98.6%
Grade 3-5	52.5%	46.4%
Serious	18.5%	10.3%
Led to death	0.2%[a]	0
Led to discontinuation of any drug	19.1%	10.1%

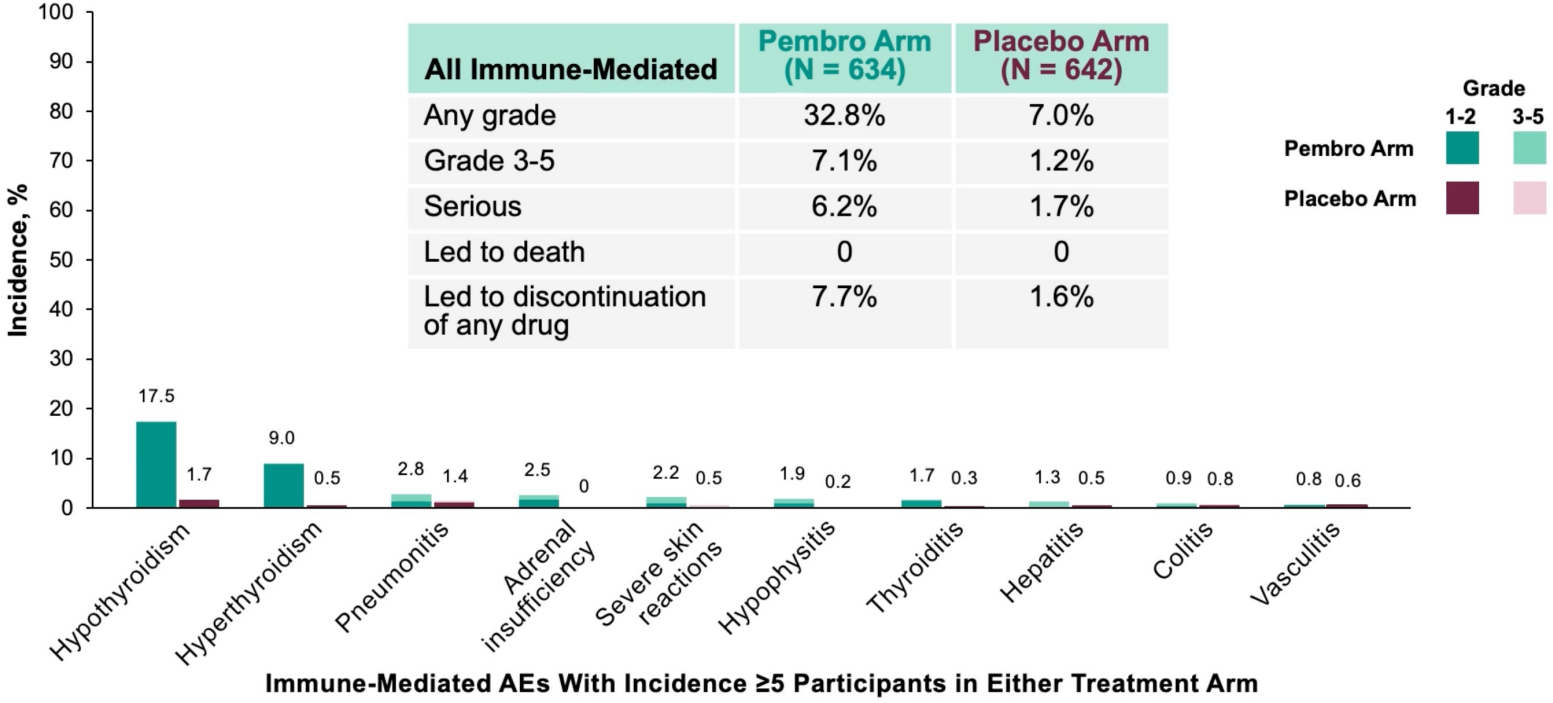


Treatment-Related AEs With Incidence ≥20% in Either Treatment Arm

[a]**1 patient from acute myocardial infarction, considered related to QT.** Data cutoff date: May 25, 2023.

KEYNOTE-756: Immune-Mediated AEs

All Immune-Mediated	Pembro Arm (N = 634)	Placebo Arm (N = 642)
Any grade	32.8%	7.0%
Grade 3-5	7.1%	1.2%
Serious	6.2%	1.7%
Led to death	0	0
Led to discontinuation of any drug	7.7%	1.6%



Immune-Mediated AEs With Incidence ≥5 Participants in Either Treatment Arm

Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed.
Data cutoff date: May 25, 2023.

KEYNOTE-756: Summary

- First positive trial of IO/chemo to improve pCR in high-risk HR+, HER2 neg population
  - 8.5% improvement in pCR regardless of PDL1
- No new safety signals seen
  - Is the benefit worth increase in AEs?
- Cannot change practice, awaiting EFS

Current Data for Adjuvant CDK 4/6 Inhibitors

	PALLAS	PENELOPE-B	monarchE	NATALEE
No of patients	5760	1250	5637	5101
Eligibility	Anatomic stage II/III	Lack of pCR after NAC, CPS EG ≥ 3 or ≥ 2 with ypN+	≥ n2 or n1 w/at least G3 tumor, ≥ 5 cm, Ki-67 ≥ 20%	Included high risk N0 defined as G3 or G2 w/high genomic risk or Ki-67 ≥ 20%
Treatment	Palbociclib 2 years	Palbociclib 1 year	Abemaciclib 2 years	Ribociclib 3 years *400 mg
Discontinuation rate	42%	19.5%	27.7%	21%
IDFS	88.2% (palbociclib) vs 88.5% (endocrine therapy)	73.5% (palbociclib) vs 72.4% (endocrine therapy) at 4 years	92.2% (abemaciclib) vs 88.7% (endocrine therapy)	90.4% (ribociclib) vs 87.1% (endocrine therapy)
DRFS	89.3% vs 90.7%	-	93.8% vs 90.8%	90.8% vs 88.6%

NATALEE: Study Design[1,2]

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥ 20%
      - Oncotype DX Breast Recurrence Score ≥ 26 *or*
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]

R 1:1[c]

Ribociclib
400 mg/day
3 weeks on/1 week off
for 3 y

NSAI
Letrozole or anastrozole[d] for ≥ 5 y
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole[d] for ≥ 5 y
+ goserelin in men and premenopausal women

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

Primary End Point
- iDFS using STEEP criteria

Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.
CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PAM50, prediction analysis of microarray 50; PK, pharmacokinetics; PRO, patient reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol.* 2019;37(15 suppl) [abstract TPS597].

NATALEE: Study Design: unique features

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥ 20%
      - Oncotype DX Breast Recurrence Score ≥ 26 *or*
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]

Ribociclib
400 mg/day
3 weeks on/1 week off
for 3 y

Rationale for broad population of patients
Patients with stage II and III HR+/HER2− EBC, including those with no nodal involvement, are at risk of disease recurrence up to decades after initial diagnosis[3,4]

Rationale for 400 mg RIB
To improve tolerability while maintaining efficacy

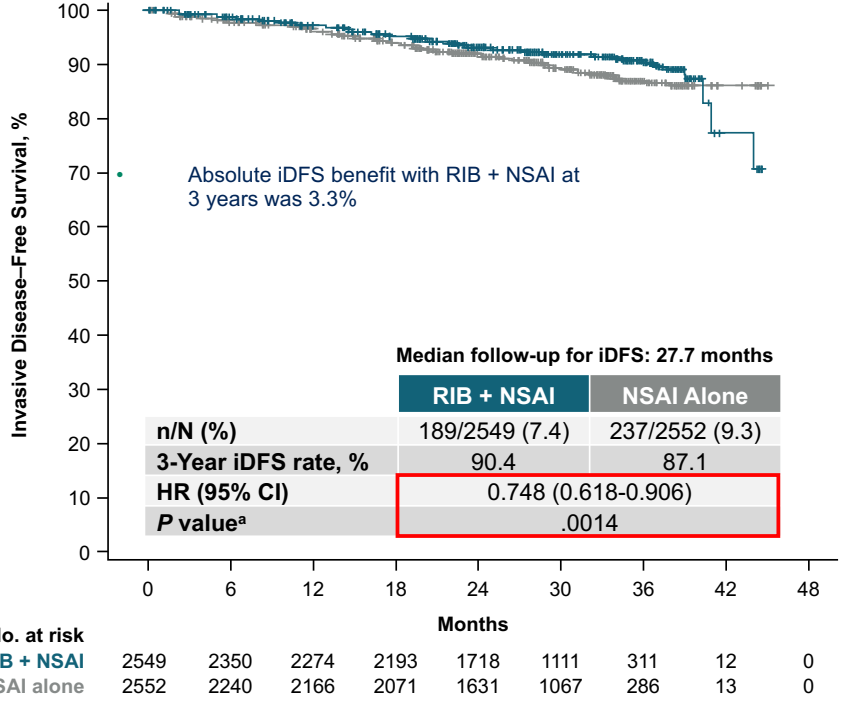
Rationale for 3-year treatment duration
Extended duration of treatment is crucial to prolong cell cycle arrest and drive more tumor cells into irreversible senescence[5-7]

tumor ctDNA/ctRNA samples

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.
CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PAM50, prediction analysis of microarray 50; PK, pharmacokinetics; PRO, patient reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol.* 2019;37(15 suppl) [abstract TPS597].

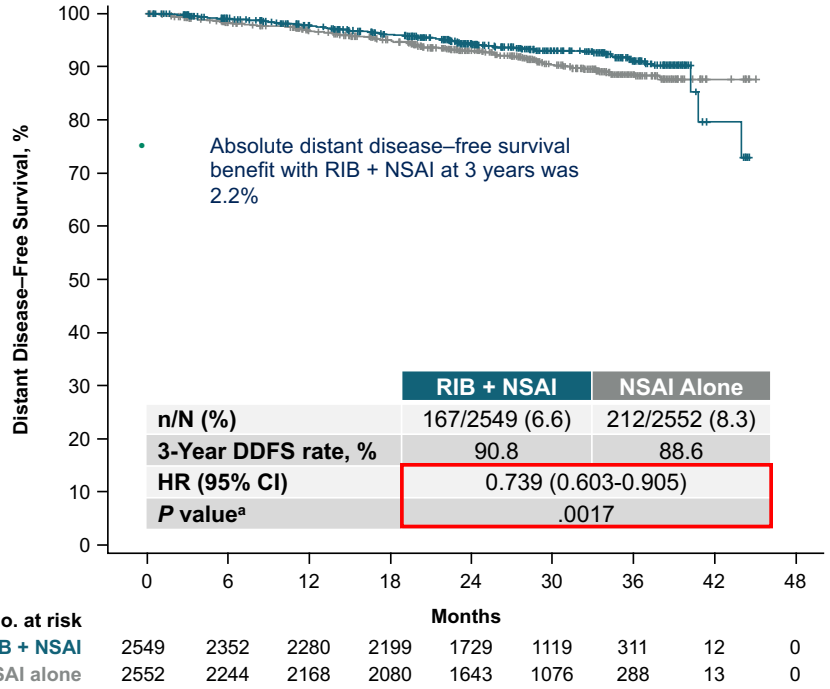
NATALEE: IDFS and DDFS



Median follow-up for iDFS: 27.7 months

	RIB + NSAI	NSAI Alone
n/N (%)	189/2549 (7.4)	237/2552 (9.3)
3-Year iDFS rate, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906)	
P value[a]	.0014	

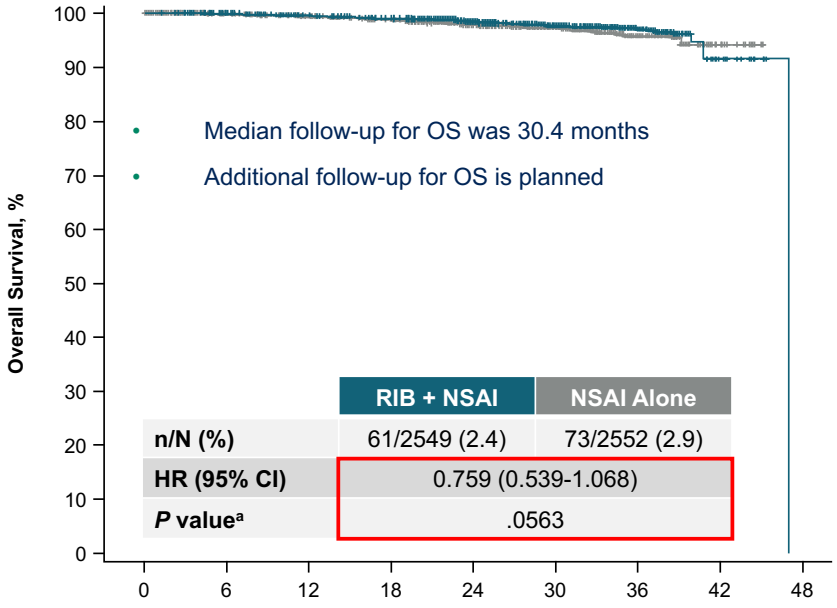
No. at risk									
RIB + NSAI	2549	2350	2274	2193	1718	1111	311	12	0
NSAI alone	2552	2240	2166	2071	1631	1067	286	13	0



	RIB + NSAI	NSAI Alone
n/N (%)	167/2549 (6.6)	212/2552 (8.3)
3-Year DDFS rate, %	90.8	88.6
HR (95% CI)	0.739 (0.603-0.905)	
P value[a]	.0017	

No. at risk									
RIB + NSAI	2549	2352	2280	2199	1729	1119	311	12	0
NSAI alone	2552	2244	2168	2080	1643	1076	288	13	0

NATALEE: OS and AEs



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

- The most frequent all-grade AEs (RIB + NSAI vs NSAI alone) leading to discontinuation were:
  - Liver-related AEs: 8.9% vs 0.1%
  - Arthralgia: 1.3% vs 1.9%
- Most of the AE discontinuations of RIB occurred early in treatment
  - Median time of these discontinuations was 4 months

AE, adverse event; AESI, adverse event of special interest; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] This is a grouped term that combines neutropenia and neutrophil count decreased. [b] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. [c] This is a grouped term. [d] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for interstitial lung disease.

NATALEE: Summary

- Ribociclib improves IDFS, DDFS in high-risk HR+/HER2- early breast cancer
  - High risk is defined more broadly- expanded definition to include any lymph node positive disease, node negative with high risk features
  - Administered at 400 mg for 3 years
  - Approximately 20% of patients completed 3 years at report - short term follow-up
- Ribociclib is not yet FDA approved in early breast cancer
- Who really needs adjuvant CDK 4/6 inhibitors beyond stage II or III patients?
  - ctDNA

Current Data for Adjuvant CDK 4/6 Inhibitors

Abemaciclib

- High risk disease - node positive
- 2 years, continuous dosing
- Same dosing in metastatic trials – 150 mg twice daily
- Adverse effects profile – diarrhea, fatigue, LFT increase
- Longer follow-up data available now including efficacy in subpopulations
- FDA approved in Oct 2021

Ribociclib

- High risk risk disease included any lymph node positive disease, and N0 high risk
- 3 years, intermittent dosing
- 400 mg (dose reduced from metastatic trials)
- Adverse effects profile - less incidence of QTc prolongation and neutropenia due to lower dose
- Shorter follow-up data available
- Not yet FDA approved for this indication

ADVANCED BREAST CANCER

CDK 4/6 Inhibitors for Metastatic Breast Cancer

	PALOMA-2	MONALESSA-2	MONARCH-3
Study Design	Phase III first line	Phase III first line	Phase III first line
Endocrine Partner	Letrozole	Letrozole	Letrozole or anastrozole
CDK 4/6 Inhibitor	Palbociclib	Ribociclib	Abemaciclib
Patients, N	666	668	493
HR	0.58	0.56	0.54
PFS, mos	24.8 vs. 14.5	25.3 vs. 16	28.2 vs. 14.8
ORR, %	55.3 vs. 44.4	52.7 vs. 37.1	59 vs. 44
OS, mos	53.9 vs 51.9	63.9 vs 51.4	67.1 vs 54.5

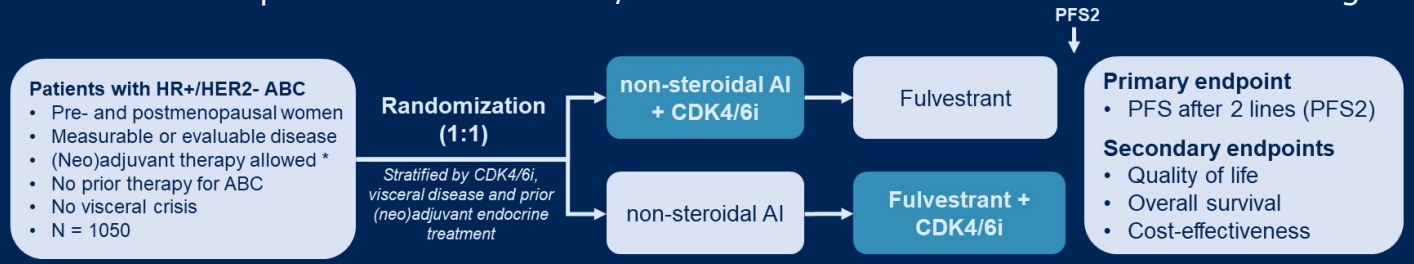
- Combination CDK 4/6i and endocrine therapy:
  - Higher risk of emergence of resistance mutation patterns
  - Increased toxicity and cost

HR = hazard ratio. PFS = progression-free survival. ORR = overall response rate. OS = overall survival

Source: Finn RS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016 Nov 17;375(20):1925-1936. doi: 10.1056/NEJMoa1607303. PMID: 27959613.
Hortobagyi GN, et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. N Engl J Med. 2022 Mar 10;386(10):942-950. doi: 10.1056/NEJMoa2114663. PMID: 35263519.
Goetz MP, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. J Clin Oncol. 2017 Nov 10;35(32):3638-3646. doi: 10.1200/JCO.2017.75.6155. Epub 2017 Oct 2. PMID: 28968163.

SONIA: Study Design

Aim: To compare the use of CDK 4/6 inhibitors in the first vs. second line setting



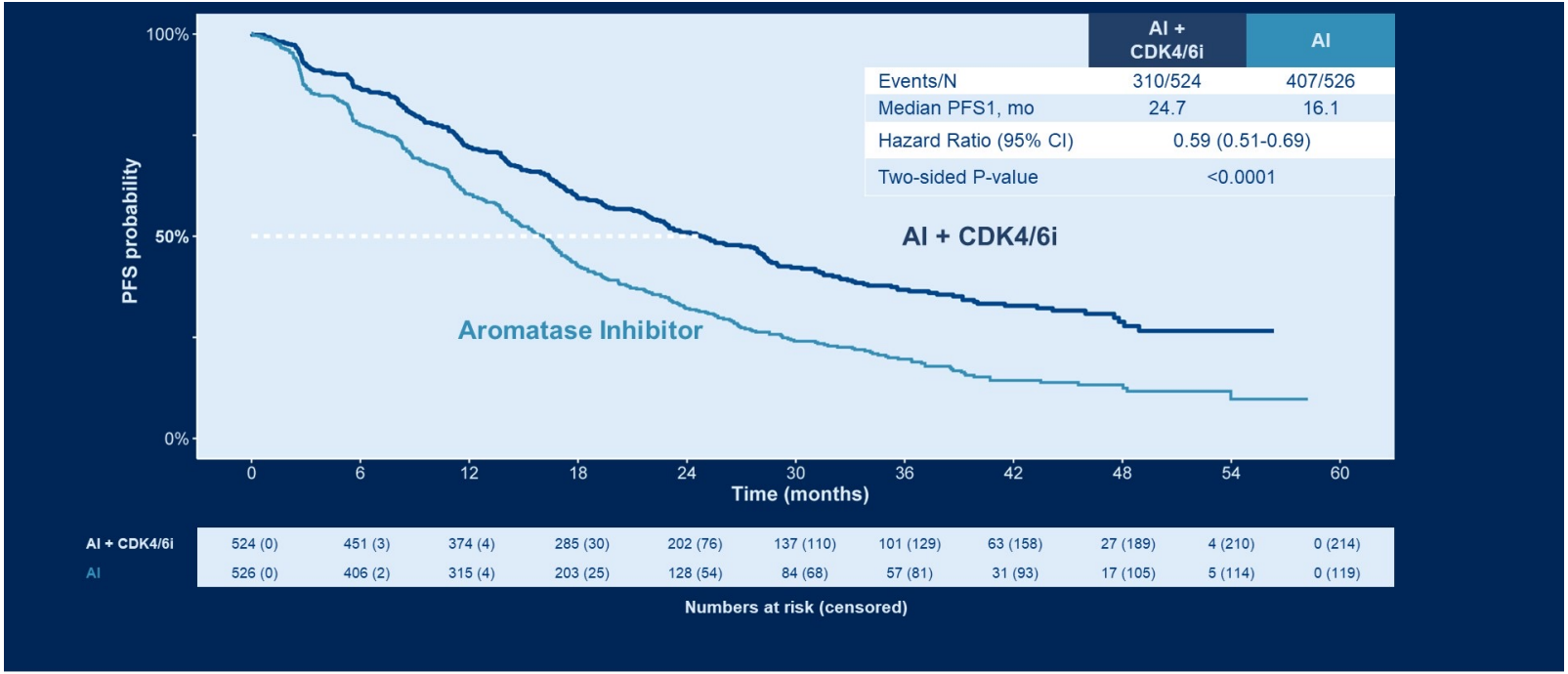
- Tumor assessments every 12 weeks
- PFS locally assessed per RECIST v1.1
- Primary analysis planned after 574 PFS2 events
  - 89% power to detect superiority according to ESMO MCBS (HR lower limit CI ≤0.65 and Δ ≥3 months) with two-sided α=5%[1]

HR+, hormone receptor positive; HER2- , HER2 negative; ABC, advanced breast cancer; AI, aromatase inhibitor; PFS, progression-free survival
* disease-free interval after non-steroidal aromatase inhibitor >12 months. ClinicalTrials.gov (NCT03425838)
1. Cherny NI, et al. Ann Oncol 2017

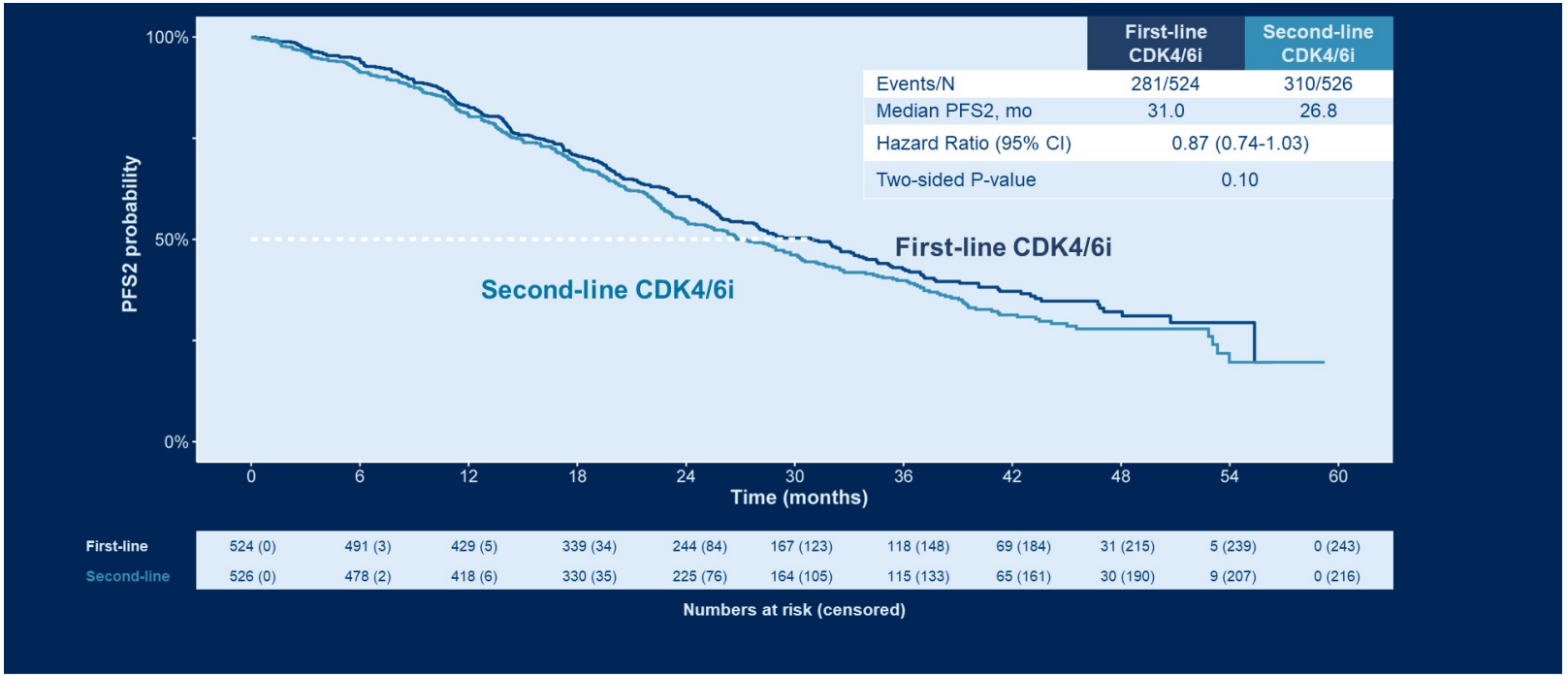
SONIA: Baseline Characteristics

		First-line CDK4/6i N=524	Second-line CDK4/6i N=526
Median age, years (range)		64 (24-88)	63 (25-87)
WHO PS, n (%)	0	257 (49)	257 (49)
	≥1	267 (51)	269 (51)
Menopausal status, n (%)	Pre- / perimenopausal	69 (13)	76 (14)
	Postmenopausal	455 (87)	450 (86)
Disease-free interval, n (%)	Newly diagnosed	182 (35)	182 (35)
	≤24 months	96 (18)	98 (19)
	>24 months	246 (47)	246 (47)
Prior (neo)adjuvant therapy, n (%)	Chemotherapy	212 (40)	210 (40)
	Endocrine therapy	258 (49)	254 (48)
Metastatic site, n (%)	Visceral disease	291 (56)	292 (56)
	Bone-only disease	91 (17)	91 (17)
Measurable disease, n (%)		315 (60)	312 (59)
Type of CDK4/6i, n (%)	Palbociclib	479 (91)	479 (91)
	Ribociclib	42 (8)	44 (8)
	Abemaciclib	3 (1)	3 (1)

SONIA: Progression-free Survival in First Line

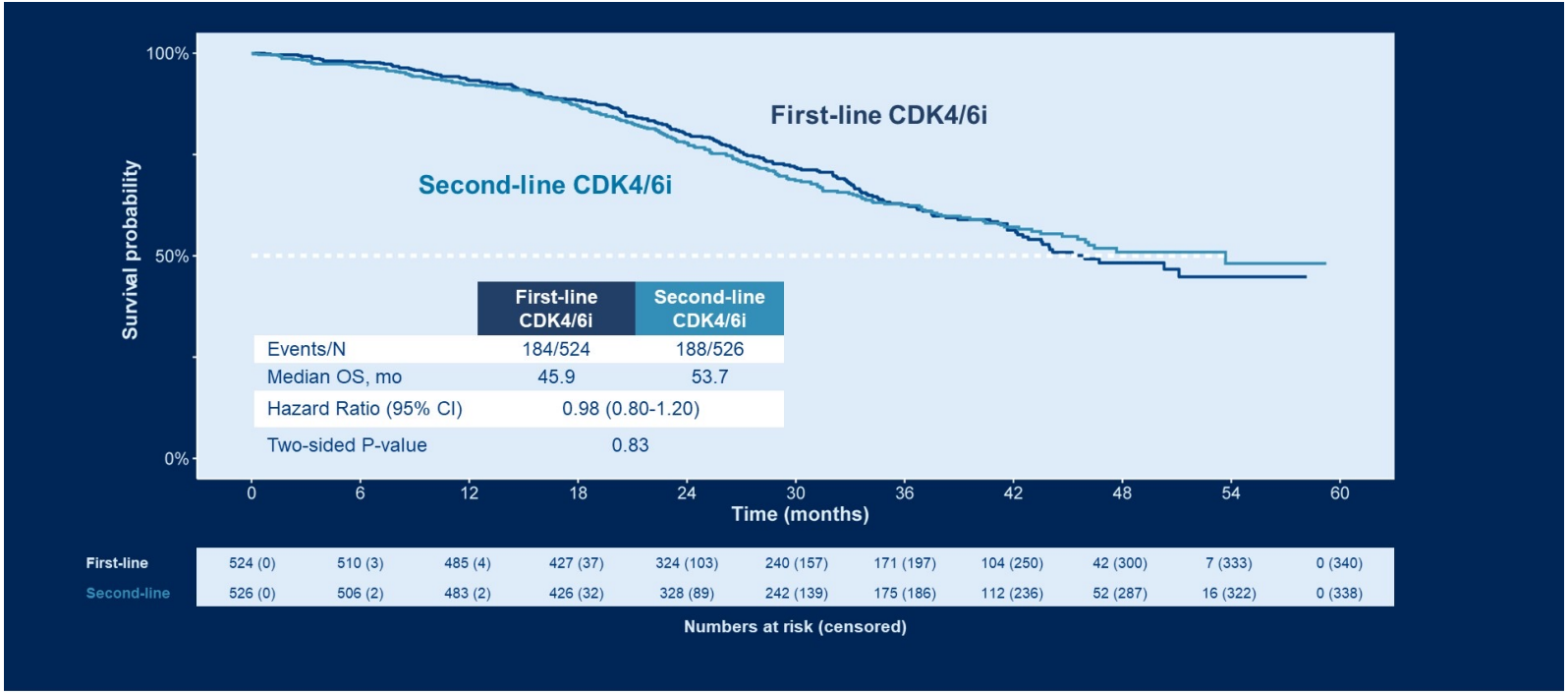


SONIA: Primary Endpoint – PFS2



	First-line CDK4/6i	Second-line CDK4/6i
Events/N	281/524	310/526
Median PFS2, mo	31.0	26.8
Hazard Ratio (95% CI)	0.87 (0.74-1.03)	
Two-sided P-value	0.10	

SONIA: Overall Survival



	First-line CDK4/6i	Second-line CDK4/6i
Events/N	184/524	188/526
Median OS, mo	45.9	53.7
Hazard Ratio (95% CI)	0.98 (0.80-1.20)	
Two-sided P-value	0.83	

Numbers at risk (censored)

First-line	524 (0)	510 (3)	485 (4)	427 (37)	324 (103)	240 (157)	171 (197)	104 (250)	42 (300)	7 (333)	0 (340)
Second-line	526 (0)	506 (2)	483 (2)	426 (32)	328 (89)	242 (139)	175 (186)	112 (236)	52 (287)	16 (322)	0 (338)

PRESENTED BY: Prof. Gabe S. Sonke, MD, PhD

SONIA: Summary

CDK4/6 inhibition in first-line compared to second-line

- Does not improve Progression-Free Survival
- Does not improve Overall Survival
- Does not improve Quality of Life
- Extends time on CDK4/6i by 16.5 months
- Increases incidence of grade 3-4 toxicity by 42%
- Increases drug expenditure by $200,000 per patient[1]

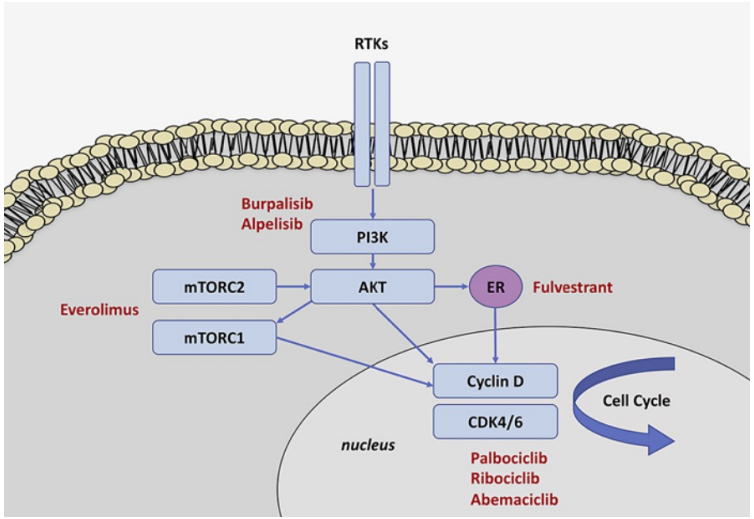
1. CMS drug prices: CMS.gov, Centers for Medicare & Medicaid Services

SONIA: Conclusions

- Do all patients need a CDK 4/6i in the first line setting?
  - How do we determine which subset of pts could be appropriate to not receive 1st line CDK 4/6i?
    - ctDNA?
- Does the CDK 4/6i matter?
  - 90% pts rec'd Palbociclib; OS data, adjuvant data for ribo and abema
- SONIA challenges the need for CDK 4/6i upfront for all pts

Overcoming Endocrine Resistance: what do we do post progression on CDK 4/6i?

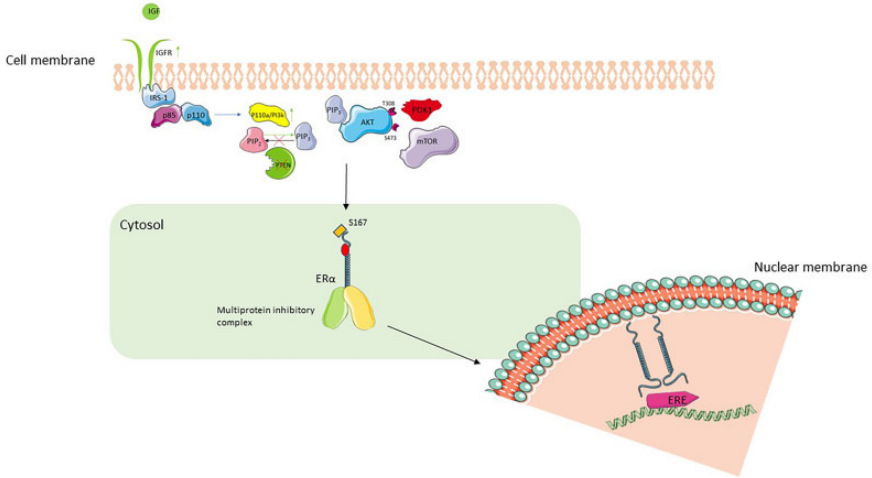
- Shorter PFS, heterogeneity
- Primary endocrine resistance:
  - relapse within 2 years of adjuvant endocrine treatment for EBC
  - disease progression during the first 6 months of first-line endocrine therapy for ABC
- Secondary endocrine resistance:
  - relapse that occurs after at least 2 years of endocrine therapy and during or within the first year of completing adjuvant endocrine therapy for EBC
  - disease progression after more than 6 months of endocrine therapy for ABC
- NGS: *ESR1, PIK3CA, AKT, PTEN*
- Comorbidities
- Patient goals, toxicity



Source: Hartkopf A, D, Grischke E, -M, Brucker S, Y: Endocrine-Resistant Breast Cancer: Mechanisms and Treatment. Breast Care 2020;15:347-354. doi: 10.1159/000508675

Targeting PI3K/AKT/pTEN Pathway

- Signaling in this pathway regulates growth, metabolism, and survival
- Overactivation occurs in 50% of HR+ ABC via activation mutations in PI3K and AKT pathways or inactivating mutations in pTEN pathway
- Alterations can be acquired from prior rx
- AKT pathway signaling can occur in the absence of genetic alterations
- Alpelisib and everolimus FDA approved
  - Prior to availability of CDK 4/6i



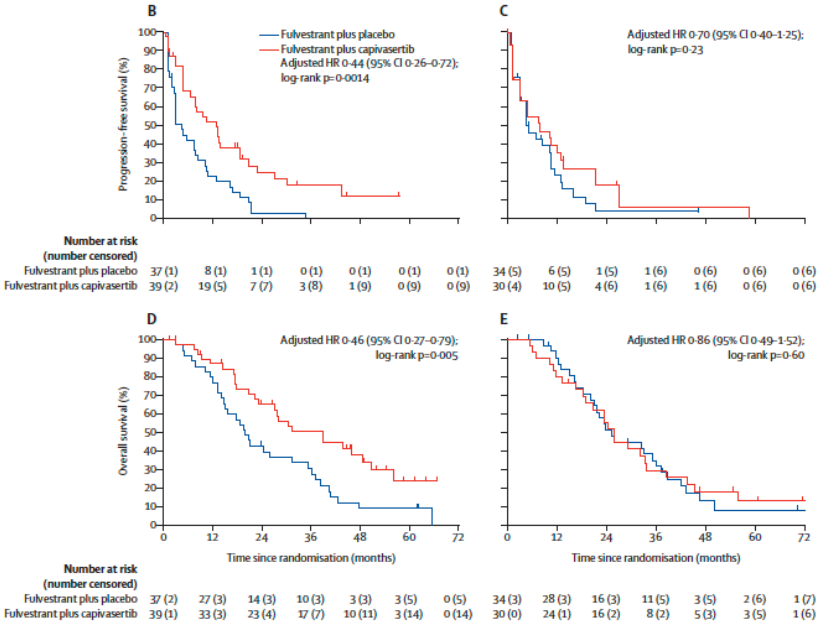
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9400772/

Capivasertib

- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)
- FAKTION trial
  - Ph II trial of capi w/fulvestrant in AI

    resistant (no prior CDK 4/6i) HR+/HER2 neg ABC
  - PFS and OS benefit, more pronounced in

    AKT pathway altered tumors



Source: Howell SJ, Casbard A, Carucci M, Ingarfield K, Butler R, Morgan S, Meissner M, Bale C, Bezecny P, Moon S, Twelves C, Venkitaraman R, Waters S, de Bruin EC, Schiavon G, Foxley A, Jones RH. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive, HER2-negative breast cancer (FAKTION): overall survival, updated progression-free survival, and expanded biomarker analysis from a randomised, phase 2 trial. Lancet Oncol. 2022 Jul;23(7):851-864. doi: 10.1016/S1470-2045(22)00284-4. Epub 2022 Jun 4. PMID: 35671774; PMCID: PMC9630162.

CAPItello-291: Study Design

Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

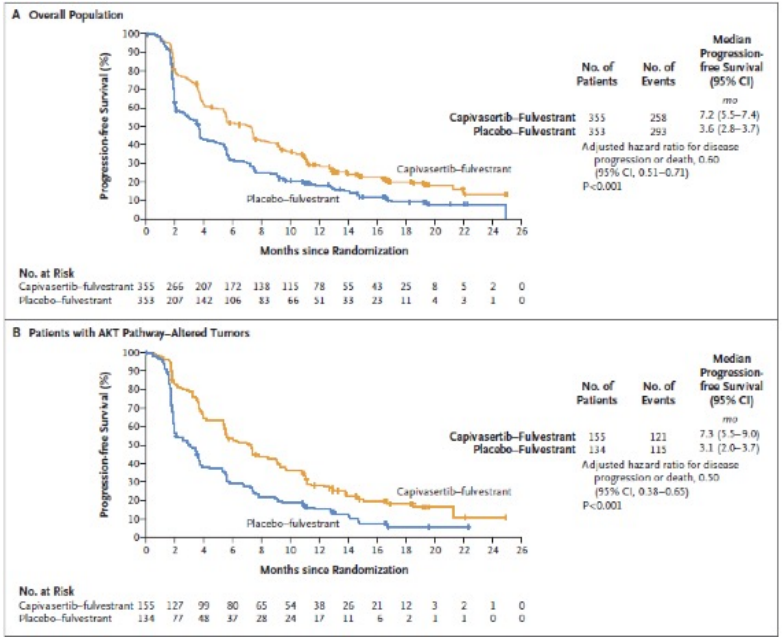
*HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia v s Region 3: Asia.*
ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.
Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatm ent˚

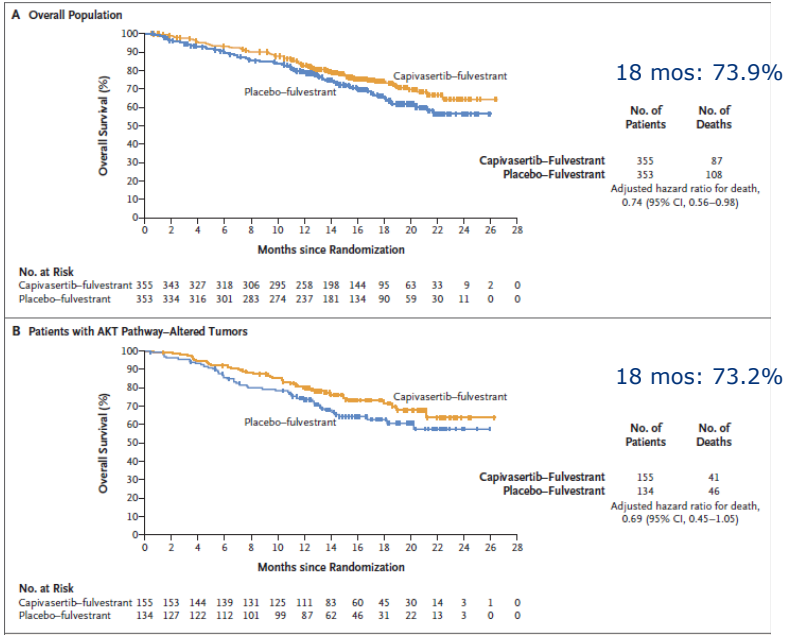
CAPItello-291: Characteristics

Site of metastases — no. (%)				
Bone only	51 (14.4)	52 (14.7)	25 (16.1)	16 (11.9)
Liver	156 (43.9)	150 (42.5)	70 (45.2)	53 (39.6)
Viscera	237 (66.8)	241 (68.3)	103 (66.5)	98 (73.1)
[illegible] — no. (%)§				
0	37 (10.4)	52 (14.7)	12 (7.7)	20 (14.9)
1	235 (66.2)	208 (58.9)	107 (69.0)	79 (59.0)
2	73 (20.6)	77 (21.8)	31 (20.0)	29 (21.6)
3	10 (2.8)	16 (4.5)	5 (3.2)	6 (4.5)
Hormone-receptor status — no. (%)¶				
ER-positive, PR-positive	255 (71.8)	246 (69.7)	116 (74.8)	101 (75.4)
ER-positive, PR-negative	94 (26.5)	103 (29.2)	35 (22.6)	31 (23.1)
ER-positive, with unknown PR status	5 (1.4)	4 (1.1)	4 (2.6)	2 (1.5)
[illegible] — no. (%)‖				
Primary resistance	127 (35.8)	135 (38.2)	60 (38.7)	55 (41.0)
Secondary resistance	228 (64.2)	218 (61.8)	95 (61.3)	79 (59.0)
No. of previous endocrine therapies for advanced breast cancer — no. (%)				
0	39 (11.0)	54 (15.3)	13 (8.4)	20 (14.9)
1	287 (80.8)	252 (71.4)	131 (84.5)	96 (71.6)
2	29 (8.2)	47 (13.3)	11 (7.1)	18 (13.4)
Previous CDK4/6 inhibitor — no. (%)				
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
As therapy for advanced breast cancer	245 (69.0)	244 (69.1)	113 (72.9)	91 (67.9)
[illegible] (%)				
As neoadjuvant or adjuvant therapy	180 (50.7)	170 (48.2)	79 (51.0)	67 (50.0)
As therapy for advanced breast cancer	65 (18.3)	64 (18.1)	30 (19.4)	23 (17.2)

Alteration; n (%)		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
Non-altered		**200 (56.3)**	**219 (62.0)**
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
No sample available		10 (2.8)	4 (1.1)
Preanalytical failure		39 (11.0)	34 (9.6)
Post analytical failure		9 (2.5)	10 (2.8)

CAPItello-291: PFS and OS





18 mos: 73.9% vs 65%

18 mos: 73.2% vs 62.9%

CAPItello-291: Safety

Table 2. Most Frequent Adverse Events in the Overall Population (Safety Population).*

Event	Capivasertib–Fulvestrant (N=355)					Placebo–Fulvestrant (N=350)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)									
Any adverse event	343 (96.6)	52 (14.6)	139 (39.2)	139 (39.2)	9 (2.5)	288 (82.3)	115 (32.9)	118 (33.7)	44 (12.6)	10 (2.9)
Diarrhea	257 (72.4)	164 (46.2)	60 (16.9)	33 (9.3)	0	70 (20.0)	60 (17.1)	9 (2.6)	1 (0.3)	0
Rash†	135 (38.0)	57 (16.1)	35 (9.9)	43 (12.1)	0	25 (7.1)	19 (5.4)	5 (1.4)	1 (0.3)	0
Nausea	123 (34.6)	85 (23.9)	35 (9.9)	3 (0.8)	0	54 (15.4)	42 (12.0)	10 (2.9)	2 (0.6)	0
Fatigue	74 (20.8)	49 (13.8)	23 (6.5)	2 (0.6)	0	45 (12.9)	35 (10.0)	8 (2.3)	2 (0.6)	0
Vomiting	73 (20.6)	54 (15.2)	13 (3.7)	6 (1.7)	0	17 (4.9)	10 (2.9)	5 (1.4)	2 (0.6)	0
Headache	60 (16.9)	47 (13.2)	12 (3.4)	1 (0.3)	0	43 (12.3)	33 (9.4)	8 (2.3)	2 (0.6)	0
Decreased appetite	59 (16.6)	37 (10.4)	21 (5.9)	1 (0.3)	0	22 (6.3)	11 (3.1)	9 (2.6)	2 (0.6)	0
Hyperglycemia	58 (16.3)	24 (6.8)	26 (7.3)	7 (2.0)	1 (0.3)	13 (3.7)	8 (2.3)	4 (1.1)	1 (0.3)	0
Stomatitis	52 (14.6)	24 (6.8)	21 (5.9)	7 (2.0)	0	17 (4.9)	15 (4.3)	2 (0.6)	0	0
Asthenia	47 (13.2)	29 (8.2)	14 (3.9)	4 (1.1)	0	36 (10.3)	31 (8.9)	3 (0.9)	2 (0.6)	0
Pruritus	44 (12.4)	32 (9.0)	10 (2.8)	2 (0.6)	0	23 (6.6)	19 (5.4)	4 (1.1)	0	0
Anemia	37 (10.4)	15 (4.2)	15 (4.2)	7 (2.0)	0	17 (4.9)	4 (1.1)	9 (2.6)	4 (1.1)	0
Urinary tract infection	36 (10.1)	8 (2.3)	23 (6.5)	5 (1.4)	0	23 (6.6)	2 (0.6)	21 (6.0)	0	0

SAE:
-16.1% vs 8%

Discontinuation rate:
-9.3% vs 0.6%

Dose interruption:
-34.9% vs 10.3%

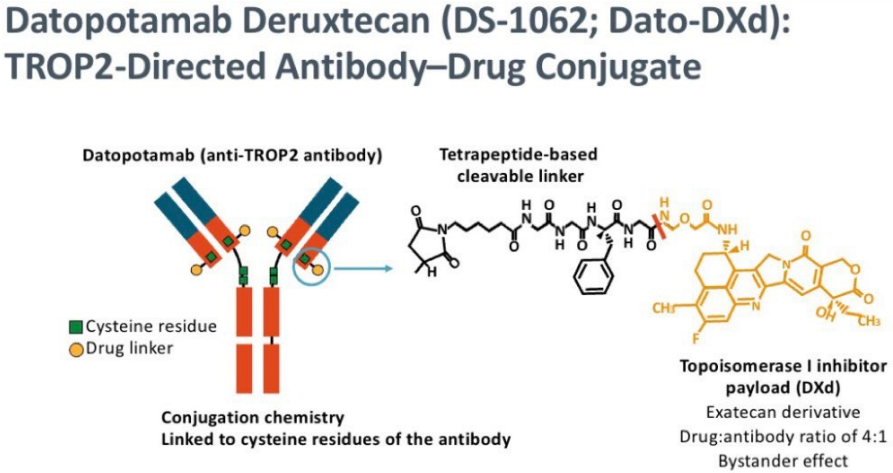
Dose reduction:
-19.7% vs 1.7%

CAPItello-291: Summary

- Capivasertib with Fulvestrant improves PFS in the overall and AKT altered population
  - Activity in non-AKT pathway-altered tumors
  - Activity post progression on CDK 4/6i
- Safety: diarrhea and rash most common
  - Hyperglycemia mainly grade 1 and 2
- Capivasertib ongoing investigation, as well other *PIK3CA* inhibitors

Datopotamab Deruxtecan (Dato-Dxd)

- TROP2 directed antibody drug conjugate (ADC)
  - humanized anti-TROP2 IgG1 monoclonal antibody bound to topoisomerase I inhibitor payload via tetrapeptide-based cleavable, DAR 4:1
  - Sacituzumab govitecan has efficacy but notable toxicity: diarrhea, thrombocytopenia, and neutropenia
  - TROPION-PanTumor01: activity and safety previously reported in patients with pretreated HR+/HER2- ABC



TROPION Breast01: Study Design

Randomised, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

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

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Key secondary:** ORR, PFS (investigator assessed) and safety

Randomisation stratified by:

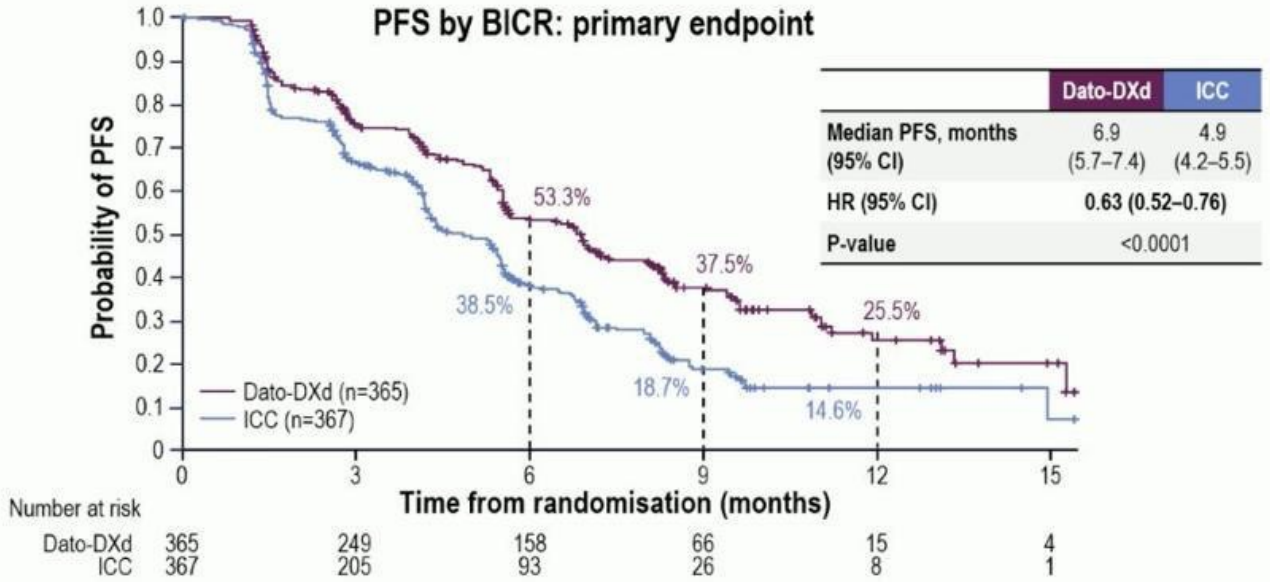
- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)

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

Detailed description of the statistical methods published previously.[1] *Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. †ICC was administered as follows: eribulin mesylate, 1.4 mg/m^2 IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m^2 orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice); vinorelbine, 25 mg/m^2 IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m^2 IV on Days 1 and 8, Q3W. BICR, blinded independent central review; CDK4/6, cyclin-dependent kinase 4/6; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; IV, intravenous; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world.

1. Bardia A, et al. *Future Oncol* 2023; doi: 10.2217/fon-2023-0188.

TROPION Breast01: Progression Free Survival



	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)

CI, confidence interval; HR, hazard ratio

MADRID 2023 ESMO congress

Aditya Bardia

TROPION Breast01: Overall Safety Summary

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

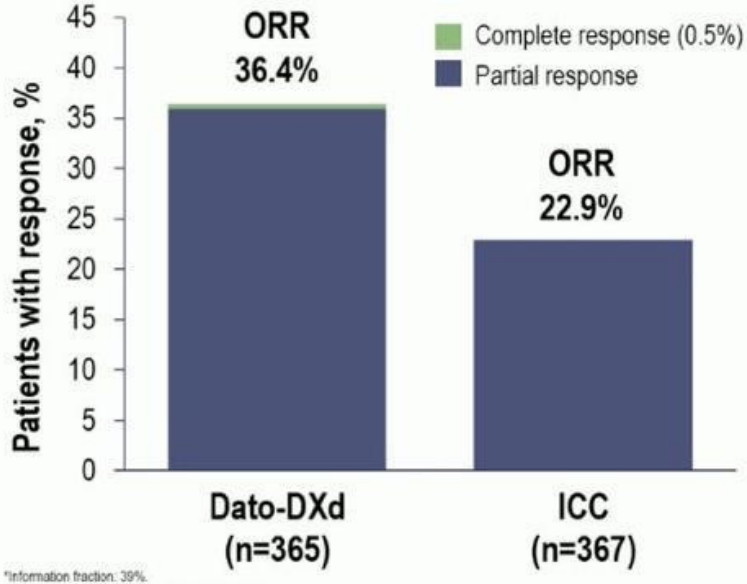
TRAEs, treatment-related adverse events

MADRID 2023 ESMO congress

Aditya Bardia

TROPION Breast01: Response and Interim OS

Response Rate



*Information fraction: 39%.
ORR, confirmed objective response rate by BICR

OS: Dual Primary Endpoint

- OS data not mature:*
  - 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

MADRID 2023 ESMO congress

Aditya Bardia

TROPION-Breast01 Summary

- Dato-Dxd significantly improved PFS compared to physician choice chemotherapy
  - Trend for OS benefit
  - Improved ORR
- Fewer grade ≥ 3 AE w/dato-dxd vs chemo
- Dato-Dxd ongoing investigation