Best of Oncology
An ASCO Direct™ Conference

Breast Cancer

PRESENTED BY

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University of Washington

Best of Oncology Conference

Disclosures

Board of Directors, Zymeworks

Thanks to

Drs. Erica Mayer and Antonio Wolff for generously sharing their ASCO discussion slides

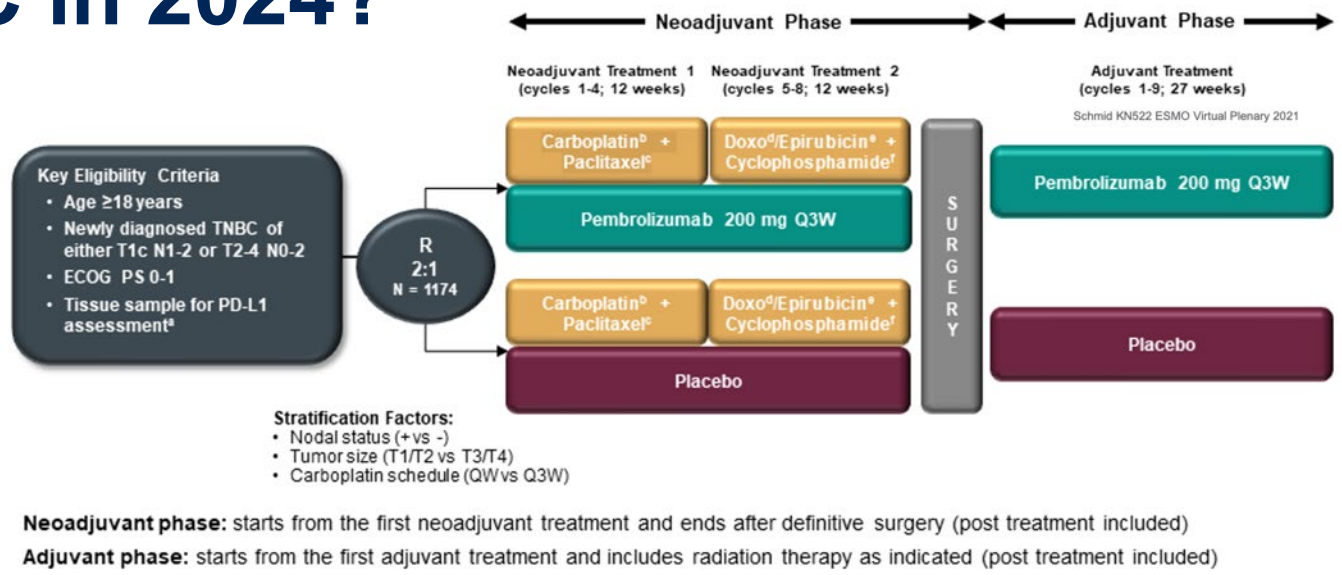
Themes for Early-Stage Breast Cancer—ASCO 2024

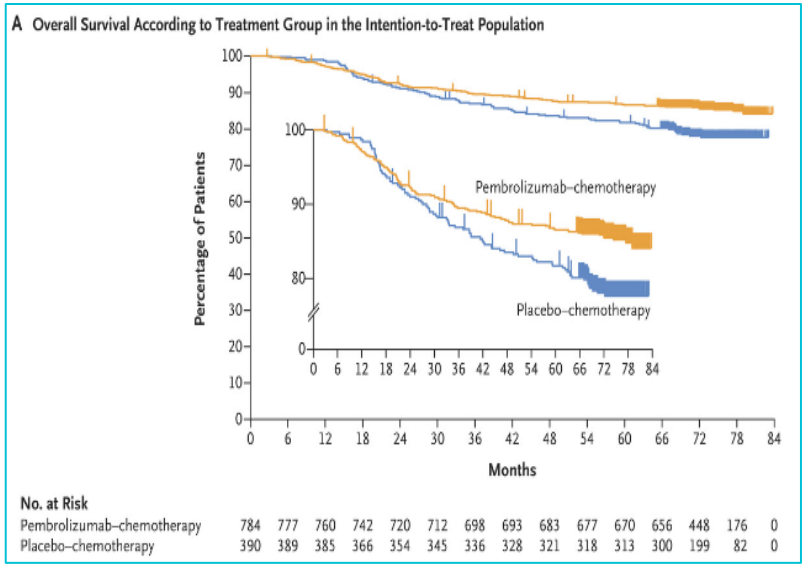
- **TNBC Continued exploration of the role of immunotherapy in perioperative management**
  - ***A-BRAVE** Trial: a phase III randomised trial with Avelumab in early triple negative breast cancer with residual disease after neoadjuvant chemotherapy or at high risk after primary surgery and adjuvant chemotherapy*
  - *Rates of pathologic complete response (pCR) after datopotamab deruxtecan (Dato) plus durvalumab (Durva) in the neoadjuvant setting: Results from the **I-SPY 2.2** trial*

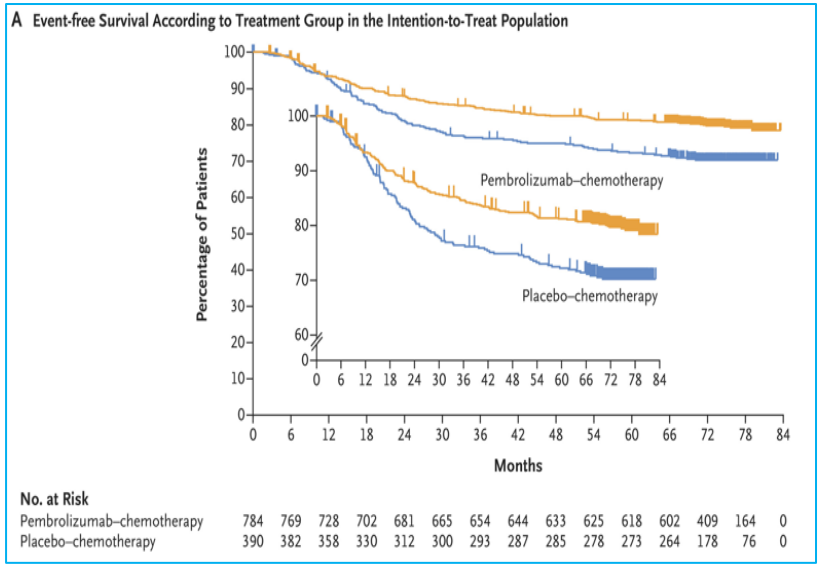
- **ER+/HER2- Role of predictive biomarkers to determine risk/therapy for early breast cancer**
  - *Prognostic utility of ctDNA detection in the **monarchE** trial of adjuvant abemaciclib plus endocrine therapy (ET) in HR+, HER2-, node-positive, high-risk early breast cancer (EBC)*
  - *Serum anti-Mullerian hormone levels refine identification of premenopausal patients with HR+, HER2-, node-positive breast cancer most likely to benefit from adjuvant chemotherapy in SWOG S1007 (**RxPONDER**)*

How Do We Treat Early TNBC in 2024?

- KEYNOTE 522 added the PD-1 inhibitor pembrolizumab to preoperative chemotherapy for early TNBC.
- Significant improvements with median follow-up of 75 mo in:
  - pCR (65%)
  - 5 year EFS--81.2% vs 72.2%
  - 5 year OS --86.6% vs 81.7%
- ***What is the role of adjuvant IO monotherapy?***
- ***Can we replace chemotherapy with ADC + IO?***







Schmid KN522 ESMO Virtual Plenary 2021.

Schmid et al, N Engl J Med, 2024

A-BRAVE Study Design—Adjuvant CPI

A-BRAVE-TRIAL

High Risk TNBC patients who completed locoregional and systemic treatment with curative intent

- TNBC (ER & PgR <10%)
- Prior anthracycline + taxane neo/adjuvant chemo

NO PRIOR IO EXPOSURE

- **Stratum A (Adjuvant): pT2N1, pT3-4 N0-3, pN2-3 anyT**

N=83 (18%)

- **Stratum B (Post-neoadjuvant): residual carcinoma in breast +/- lymph nodes**

N=383 (82%)

Stratum B allowed to receive adjuvant chemotherapy (20%)

R 1:1
N=474

Avelumab
10mg/kg, iv, q 2 weeks for 52 weeks

Observation

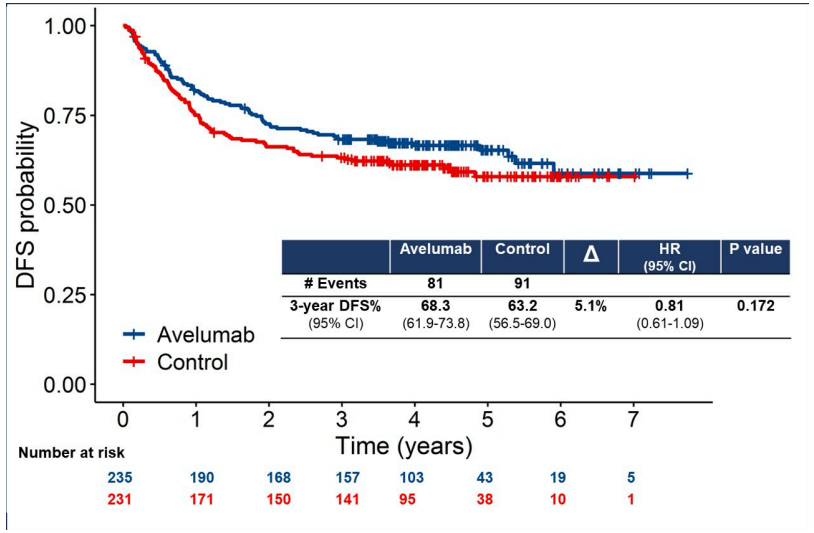
Co-primary endpoints:
- **DFS in all patients**
- **DFS in post-NAC Stratum B**

Secondary endpoint:
- **OS**

Adapted from Conte et al, ASCO 2024

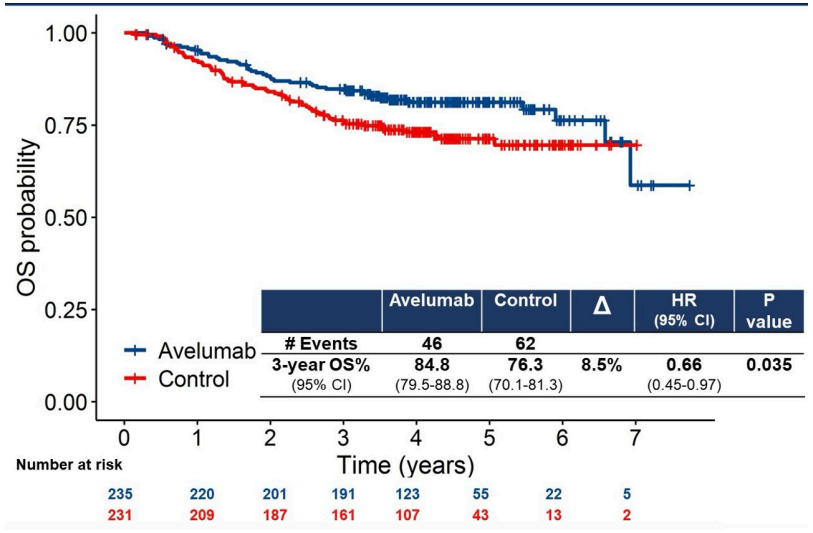
A-BRAVE Trial: Phase III Randomized Trial with Avelumab in Early TNBC with Residual Disease after NAC or High Risk after Primary Surgery +Adjuvant Chemotherapy

DFS: ITT Group



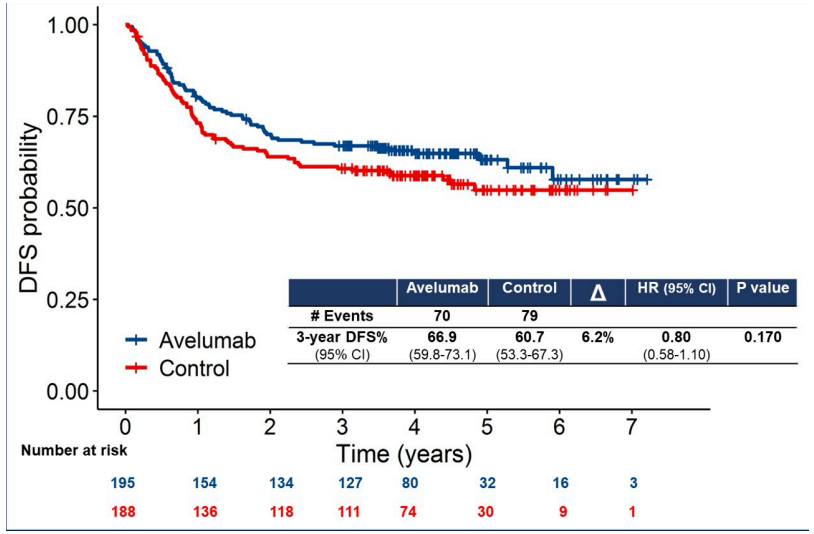
	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	81	91			
3-year DFS% (95% CI)	68.3 (61.9-73.8)	63.2 (56.5-69.0)	5.1%	0.81 (0.61-1.09)	0.172

OS: ITT Group



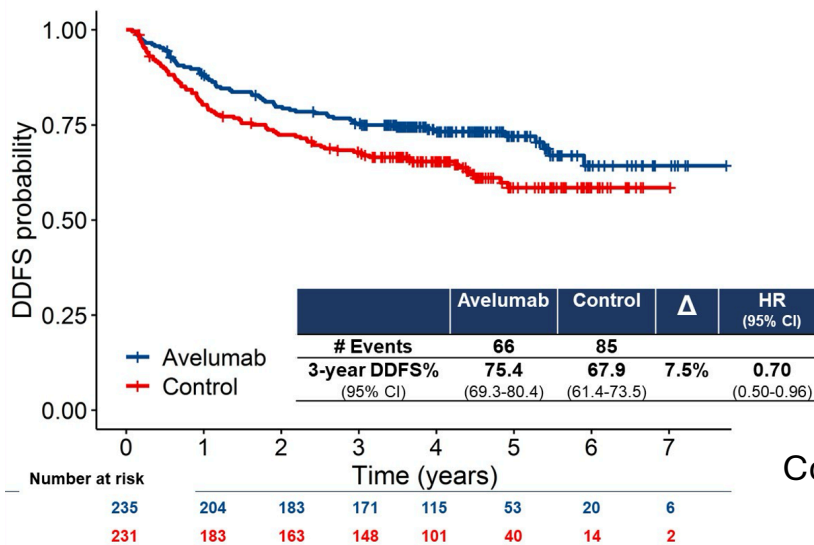
	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	46	62			
3-year OS% (95% CI)	84.8 (79.5-88.8)	76.3 (70.1-81.3)	8.5%	0.66 (0.45-0.97)	0.035

DFS: Stratum B



	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	70	79			
3-year DFS% (95% CI)	66.9 (59.8-73.1)	60.7 (53.3-67.3)	6.2%	0.80 (0.58-1.10)	0.170

DDFS: ITT Group



	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	66	85			
3-year DDFS% (95% CI)	75.4 (69.3-80.4)	67.9 (61.4-73.5)	7.5%	0.70 (0.50-0.96)	0.0277

Conte et al, ASCO 2024

A-BRAVE Trial: Phase III Randomized Trial with Avelumab in Early TNBC with Residual Disease after NAC or High Risk after Primary Surgery + Adjuvant Chemotherapy

Key Findings:

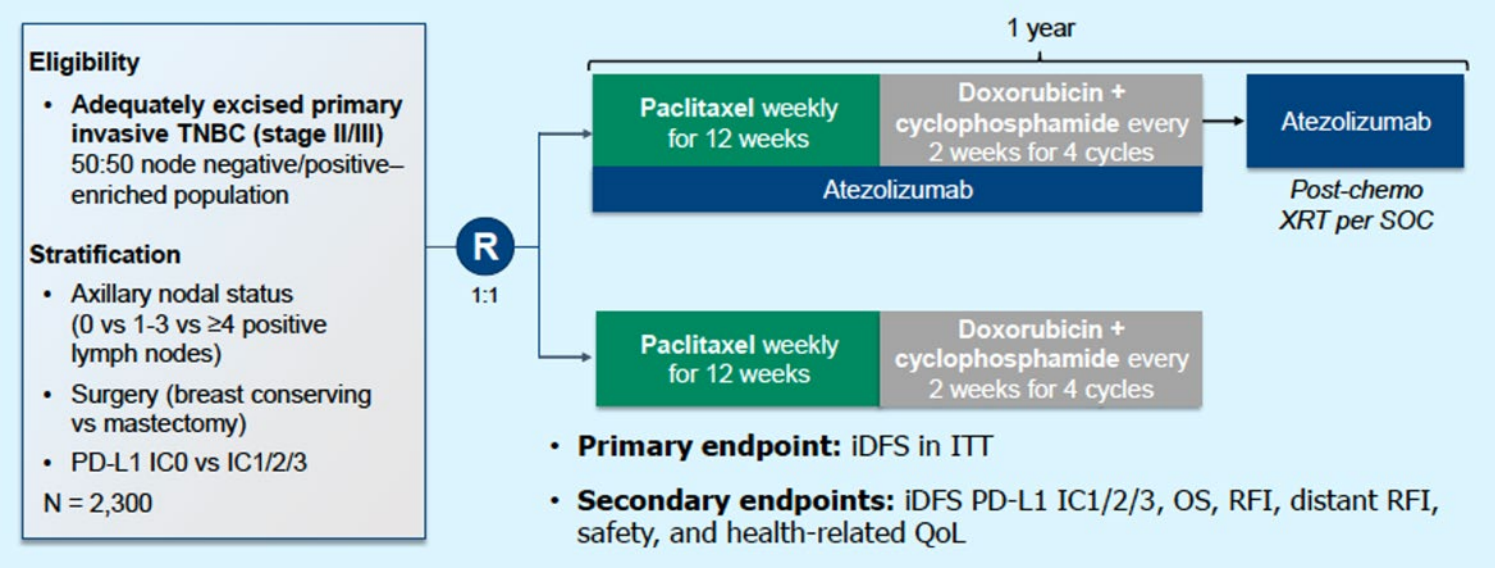
- No statistical difference in 3-year DFS
- Significant improvement in 3-year OS and DDFS
- Well tolerated with expected toxicity profile
- Limitation: KEYNOTE 522 was not SOC at the time this study was designed
- Role of adjuvant IO still unclear

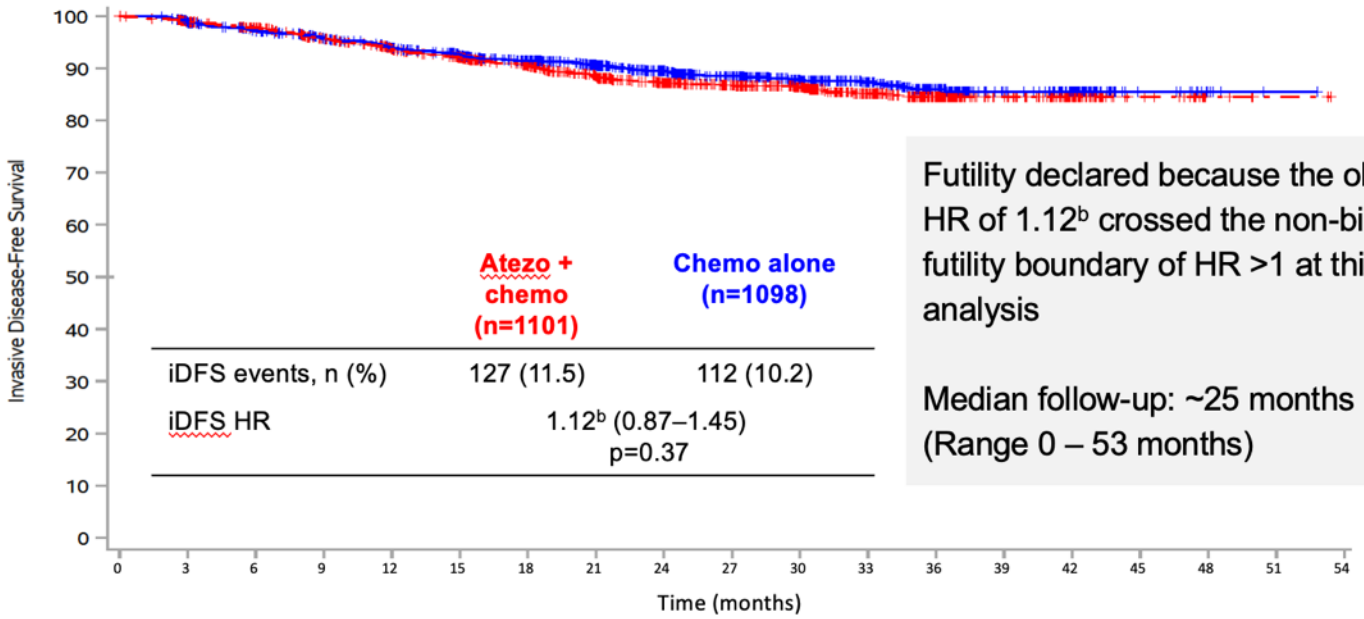
Endpoint and population			Δ 3-yr rate	HR (95% CI)
DFS	ITT	Co-primary	**+ 5.1%**	**0.81** (0.61-1.09)
	Post-neoadj	Co-primary	**+ 6.2%**	**0.80** (0.58-1.10)
OS	ITT	Secondary	**+ 8.5%**	**0.66** (0.45-0.97)
	Post-neoadj	Exploratory	**+ 8.6%**	**0.69** (0.46-1.03)
DDFS	ITT	Exploratory	**+ 7.5%**	**0.70** (0.50-0.96)

Conte et al, ASCO 2024

IMpassion030: Adjuvant Chemotherapy + Atezolizumab

- Concurrent adjuvant AC + T chemotherapy and atezolizumab
- N=2300
- No improvement invasive disease-free survival



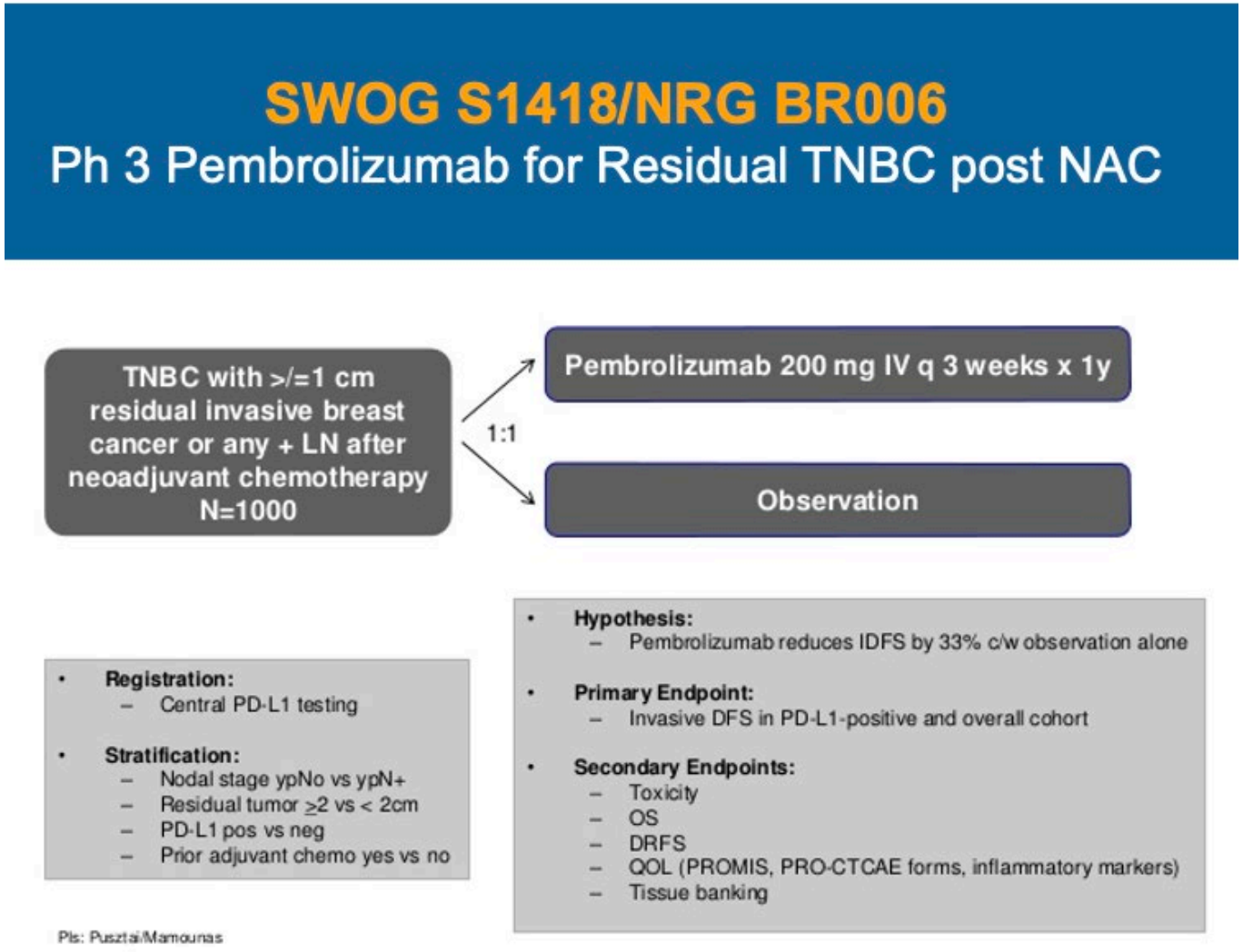


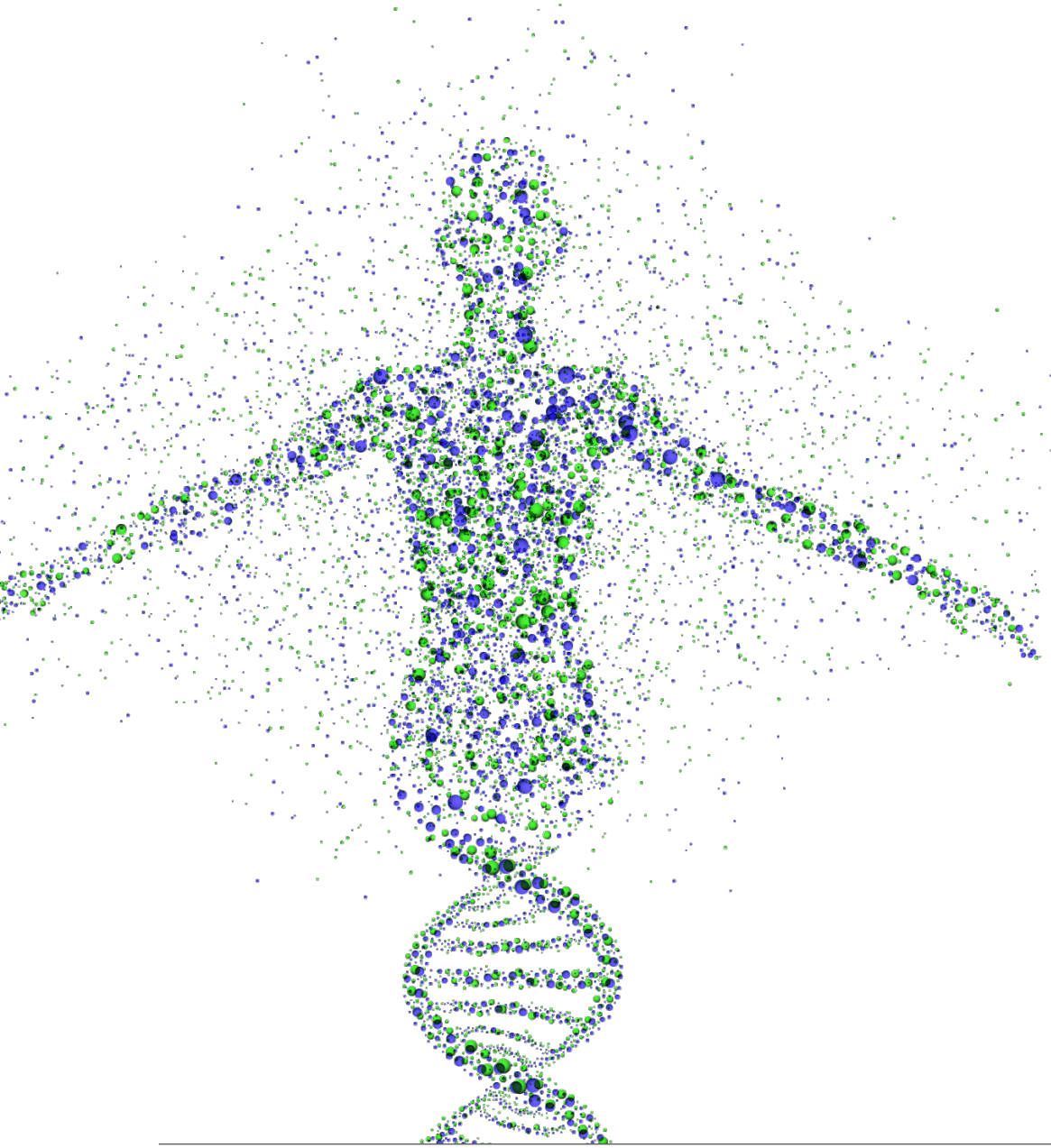
Futility declared because the observed HR of 1.12[b] crossed the non-binding futility boundary of HR >1 at this interim analysis

Median follow-up: ~25 months (Range 0 – 53 months)

Ongoing Exploration of Adjuvant IO Monotherapy

- Await data from SWOG S1418/NRG BR006, a phase 3 trial of pembrolizumab monotherapy for residual TNBC post NAC
- Larger trial than A-BRAVE (n=1000)
- Uses pembrolizumab, the currently available agent





LBA501: Rates of pathologic complete response (pCR) after datopotamab deruxtecan (Dato) plus durvalumab (Durva) in the neoadjuvant setting.

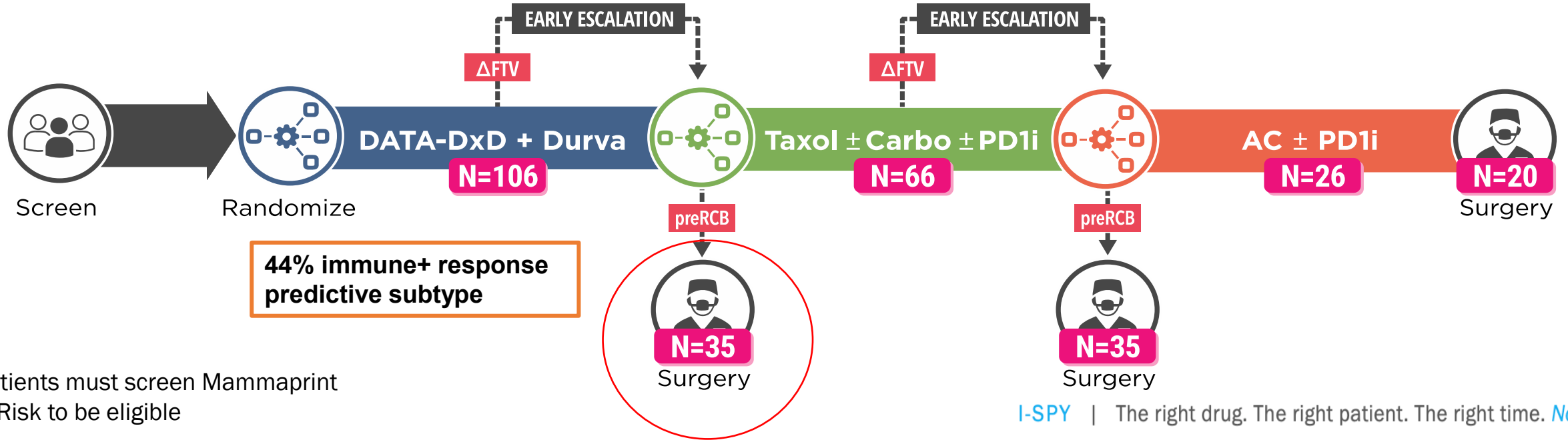
Results from the I-SPY 2.2 trial

Rebecca Shatsky, MD

On behalf of I-SPY2 Investigators

I-SPY 2.2 Dato-Durva Design

- Patients are assessed at the end of each block using MRI and core biopsies for predicted residual cancer burden (preRCB)
- Patients meeting preRCB criteria are offered surgery early
- 106 patients (HER2-) enrolled and received 4 cycles Dato-Durva
- 35 patients (33%) went to surgery after Block A given favorable preRCB



All patients must screen Mammaprint High Risk to be eligible

What Do We Learn from I-SPY2.2 Dato + Durva?

In I-SPY2.2, preoperative Dato+Durva x 4 cycles:

- Allowed 33% of patients to proceed to surgery without NAC exposure
- Met threshold to support further preoperative development
- May have special activity in immune+ subgroup

The addition of IO may increase activity over ADC alone:

Preoperative Trial	Therapy	pCR in TNBC
I-SPY 2.2 Dato	Dato x 4 cycles	35% (14/50)
NEOSTAR	Saci x 4 cycles	30% (15/50)
I-SPY2.2 Dato + Durva	**Dato + Durva x 4 cycles**	**44%***

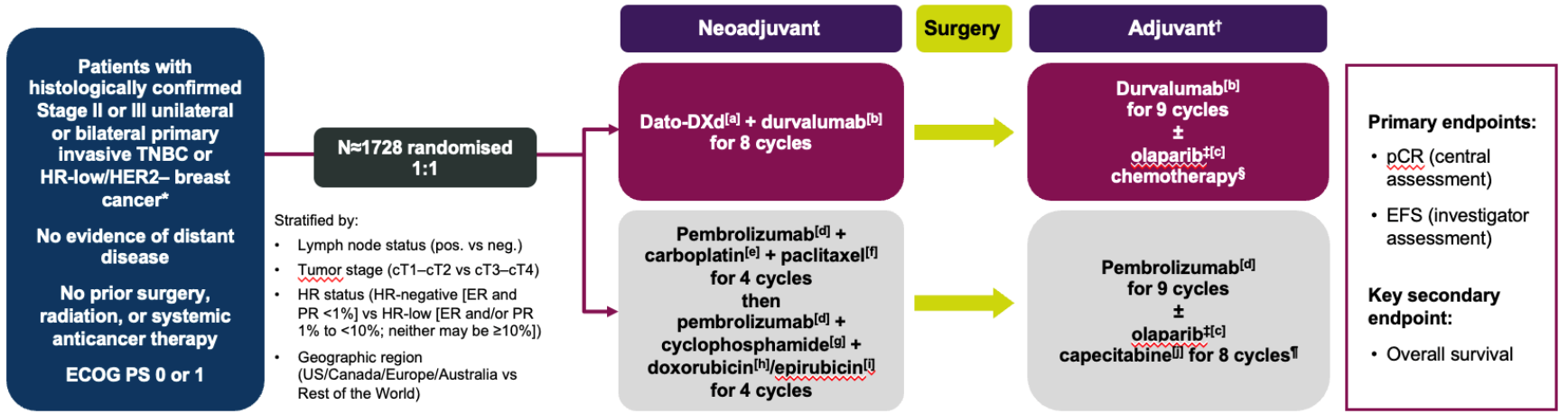
Meisel et al ASCO 2024; Spring at al, Ann Oncol 2023

* Modeled pCR rate

What Do We Learn from I-SPY2.2 Dato + Durva?

- Many remaining questions
- Can 4 cycles of ADC + IO regimen replace anthracyclines?
  - Await further outcomes from I-SPY 2.2 dato + durva for those who complete paclitaxel/carboplatin/pembrolizumab before surgery
- Can ADC + IO replace all preoperative chemotherapy?

TROPION-Breast04: Dato-DXd + durvalumab for Neo/Adjuvant TNBC



PRESENTED BY: Erica L. Mayer MD MPH

2024 ASCO® ANNUAL MEETING

Prognostic utility of ctDNA detection in the monarchE trial of adjuvant abemaciclib plus endocrine therapy (ET) in HR+, HER2-, node-positive, high-risk early breast cancer (EBC)

Sherene Loi[1], Stephen Johnston[2], Carlos L. Arteaga[3], Stephanie L. Graff[4], Sarat Chandarlapaty[5], Matthew P Goetz[6], Christine Desmedt[7], Hironobu Sasano[8], Deli Liu[9],Vanessa Rodrik-Outmezguine[9], Anthony Sireci[9], Cynthia Sandoval[9], Helen Won[9], Lacey M. Litchfield[9], Nicholas Turner[2]

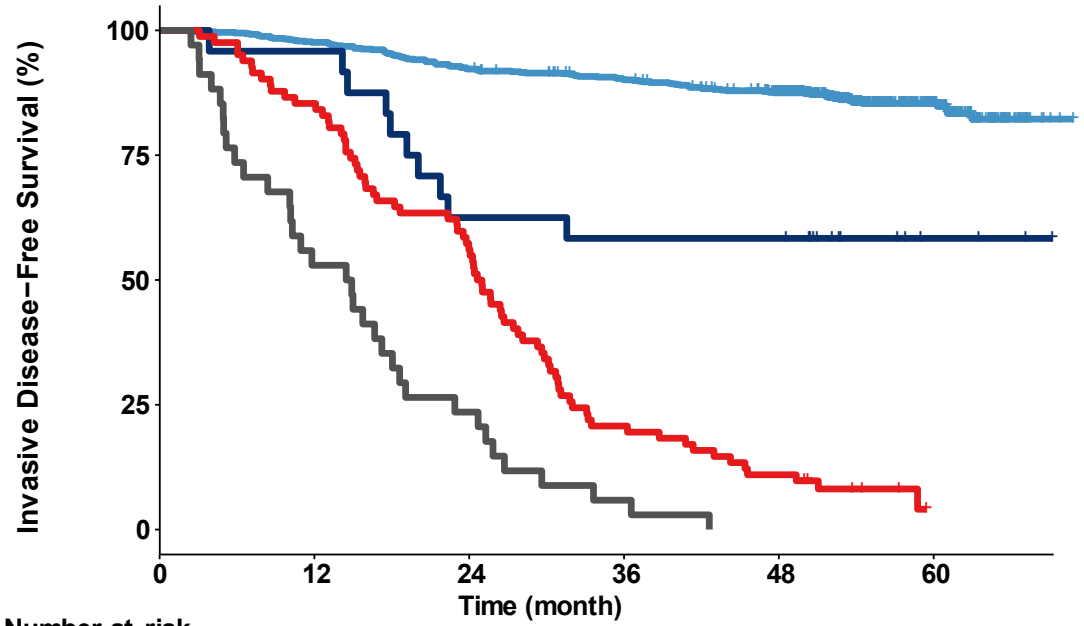
[1]Division of Cancer Research, Peter MacCallum Cancer Center, Melbourne, Australia; [2]Department of Medicine-Breast Unit, Royal Marsden Hospital and Institute of Cancer Research, London, UK; [3]UT Southwestern Simmons Comprehensive Cancer Center, Dallas, Texas, USA; [4]Lifespan Cancer Institute, Legorreta Cancer Center at Brown University, Providence, RI, USA; [5]Human Oncology and Pathogenesis Program, Memorial Sloan Kettering, New York, NY, USA; [6]Department of Oncology, Mayo Clinic, Rochester, New York, USA; [7]Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium; [8]Department of Pathology, Tohoku University Hospital, Sendai, Japan; [9]Eli Lilly and Company, Indianapolis, IN, USA.

monarchE: ctDNA Detection is Uncommon at Baseline

ctDNA cohort (N=910)	ctDNA detection, n (%)
Baseline Negative	**840 (92)**
Persistently negative	749/831 (90)
Became positive	82/831 (10)
Baseline Positive	**70 (8)**
Persistently positive	34/58 (59)
Became negative	24/58 (41)
Positive Anytime	152/840 (17%)

Adapted from Loi et al, ASCO 2024

Baseline ctDNA Detection is Associated with Poor Outcomes and Dynamics of ctDNA Detection on Treatment is Associated with Outcome



Longitudinal Analysis (N=889)**				
	Baseline (–), undetected N=831		Baseline (+), detected N=58	
	Persistently –	Became +	Persistently +	Became – (undetected)
N	749 (90)	82 (10)	34 (60)	24 (40)
IDFS event, n (%)	107 (14)	76 (93)	34 (100)	10 (42)
4-year IDFS rate, % (95% CI)	87.5 (85.1-89.9)	11.0 (5.9-20.3)	NA	58.3 (41.6-81.8)

*The ctDNA subset was enriched by patients with IDFS events within 24 months; therefore, the estimated IDFS rates in each subgroup are not reflective of that in the overall population
**Robust assessment was limited in 194 patients with <3 post-baseline timepoints and there may be differences in IDFS; total events 227

Patients who remained Persistently + or Became + on treatment were more likely to experience an IDFS event compared to those who Became – (undetected) or remained Persistently – on treatment

Suggests ctDNA clearance may be helpful to document potential benefit of new therapies

Ongoing Trials Offering Interventions for ctDNA Positivity

Trial name	NCT#	Phase	Location	Subtype	Target	Intervention
C-TRAK TN (discontinued)	03145961	2	UK	TNBC	Treating molecular relapse	Pembrolizumab
ZEST (discontinued)	04915755	3	Global	TNBC & $gBRCA_{mut}$	Treating molecular relapse	Niraparib
DARE	04567420	2	US	ER+	Treating molecular relapse	Ful. + palbociclib
LEADER	03285412	2	US	ER+	Treating molecular relapse	ET + ribociclib
MiRaDoR	05708235	2	ES	ER+	Treating molecular relapse	Giredestrant +/- abema /inavo
TRAK-ER	04985266	2	UK+FR	ER+	Treating molecular relapse	Ful. + palbociclib
TREAT-ctDNA	05512364	**3**	EU	ER+	Treating molecular relapse	Elacestrant
ASPRIA	04434040	2	US	TNBC	Treating molecular relapse	Atezo. + SG
CUPCAKE	06225505	2	FR	TNBC	Detecting relapse	Imaging with FAPI PET/CT *(TPS1139 ASCO 2024)*
PERSEVERE	04849364	2	US	TNBC	Tailoring adj. treatment	Multiple drugs (umbrella)
KAN-HER2	05388149	2	CA	HER2+	Tailoring adj. treatment	Neratinib (added to T-DM1)
SURVIVE-HERoes	05658172	**3**	GE	HER2+ & $HER2_{low}$	Treating molecular relapse	T-DXd

Slide courtesy of François-Clement Bidard

2024 ASCO® ANNUAL MEETING

SWOG Leading cancer research. Together.

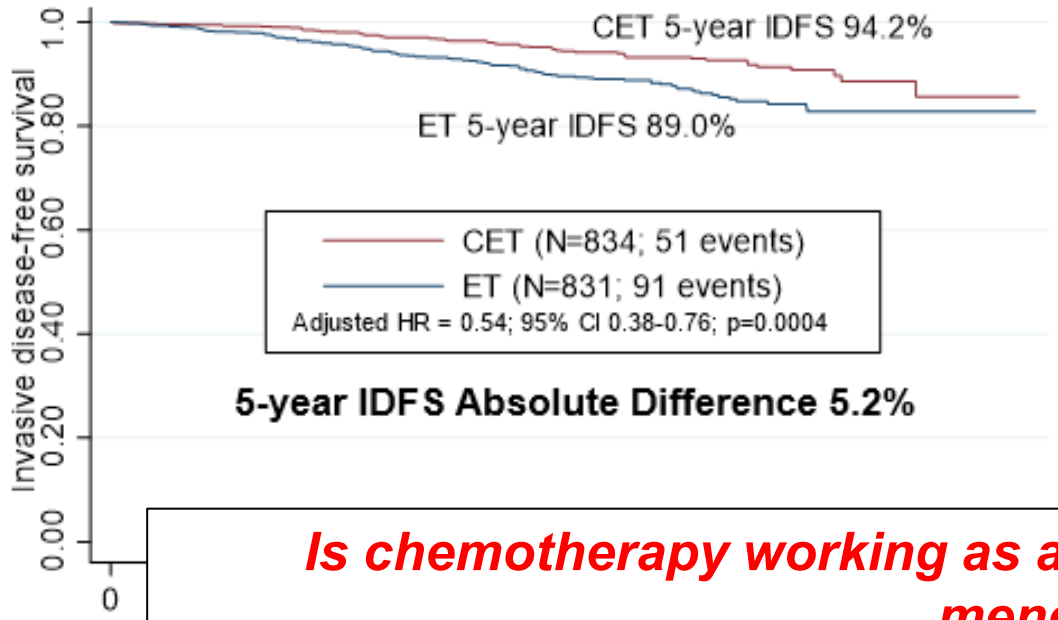
Serum anti-Mullerian hormone levels refine identification of premenopausal patients with HR+, HER2-, node-positive breast cancer most likely to benefit from adjuvant chemotherapy in SWOG S1007 (RxPONDER)

Kevin Kalinsky, William E Barlow, Harsh Pathak, Julie Gralow, Kathy S Albain, Daniel F Hayes, Nancy U Lin, Edith A Perez, Lori J Goldstein, Stephen KL Chia, Priya Rastogi, Anne F Schott, Steven Shak, Debasish Tripathy, Gabriel N Hortobagyi, Funda Meric-Bernstam, Priyanka Sharma, Lajos Pusztai, Alastair Thompson, Andrew K Godwin

PRESENTED BY: Kevin Kalinsky, MD, MS

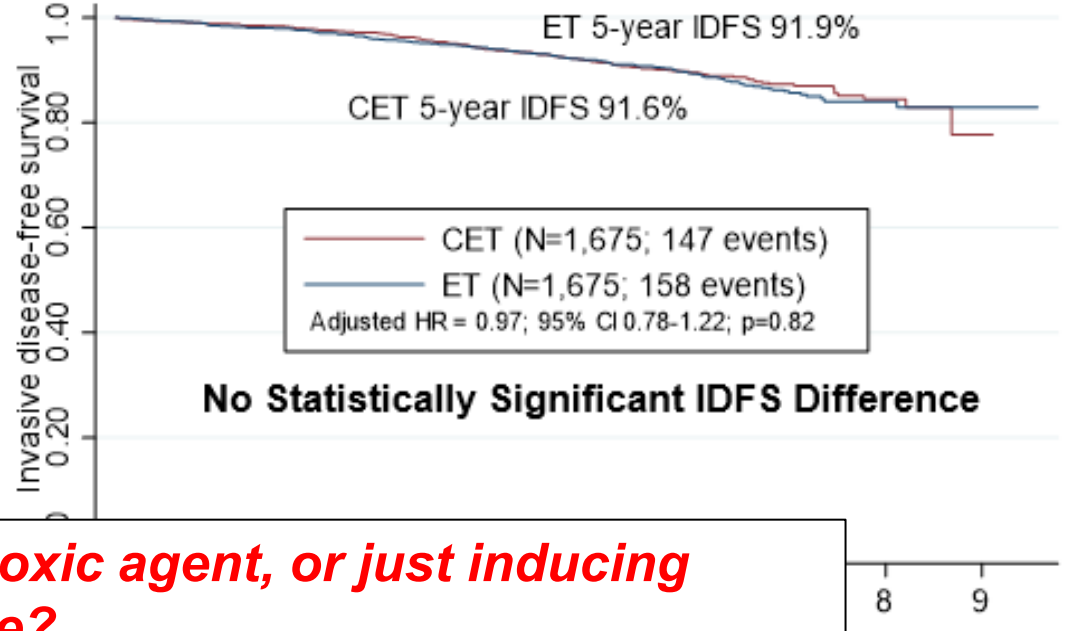
Chemotherapy Benefit Differed by Menopausal Status

"Premenopausal"



5-year IDFS Absolute Difference 5.2%

"Postmenopausal"



No Statistically Significant IDFS Difference

Is chemotherapy working as a cytotoxic agent, or just inducing menopause?

Objective of this analysis:
To determine chemotherapy benefit if < 55 years with low ovarian reserve

BSO

"Premenopausal": LMP < 6 months or age < 50 years with no LMP > 12 months and no BSO

BSO = bilateral salpingo-oophorectomy

Kalinsky et al. NEJM 2021

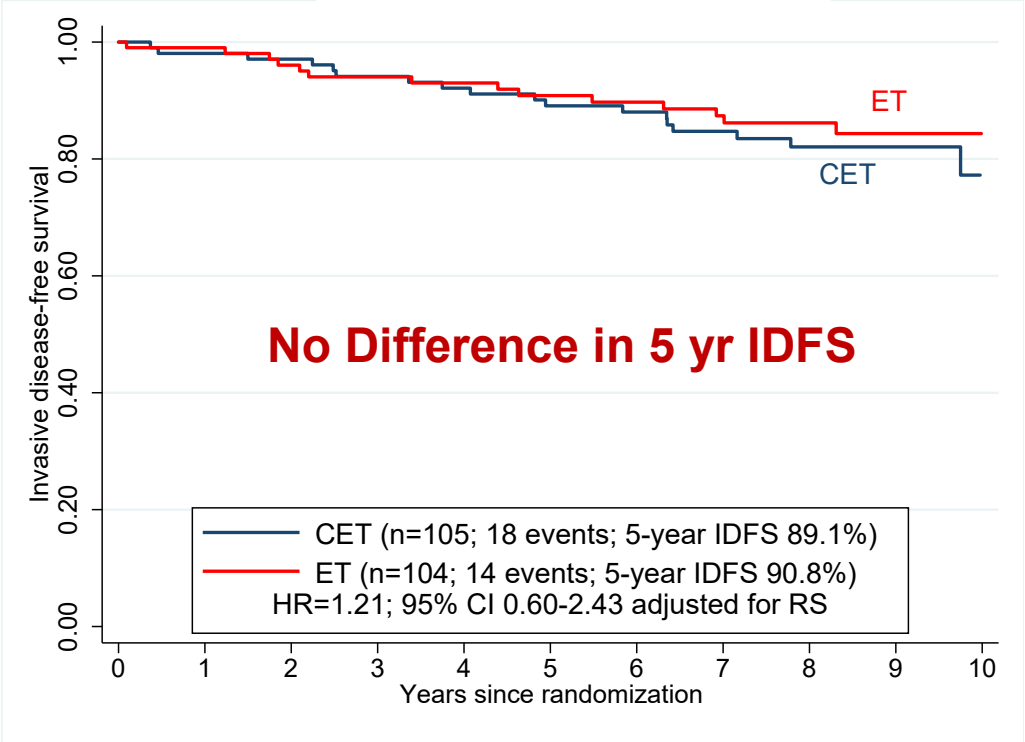
Pre-treatment Serum AMH Predicts Chemotherapy Benefit in "Premenopausal" Women < 55 Years

Variable (n=1,016)	Cutoff	Chemo IDFS Benefit*: Variable x Treatment (p-value)
Age	≥ 50 years	0.15
AMH	< 10 pg/mL	0.019*
Inhibin B	≤ 12 pg/mL	0.051
Estradiol	≤ 30 pg/ML	0.88
Progesterone	≤ 0.5 ng/mL	0.78
FSH	>20 mIU/mL	0.13
FSH and Estradiol	> 20 and ≤ 30	0.46
LH	> 7 mIU/mL	0.08

*Adjusted for treatment arm, RS, variable and tested the interaction of the variable and treatment for significance ($p<0.05$)
Continuous age, stage, number of nodes, and grade not predictive; AMH and Inhibin B strongly correlated ($r=0.74$)

"Premenopausal" < 55 Years with Low AMH Have NO IDFS Benefit with Chemotherapy (or DRFS Benefit)

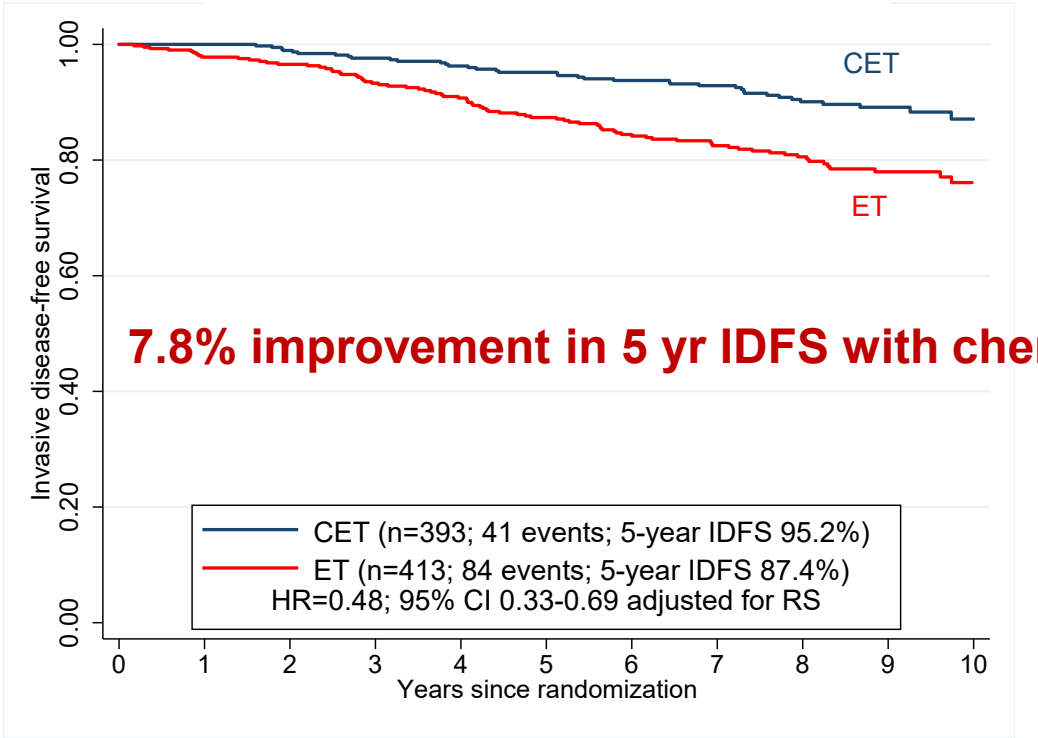
Low AMH (n=209)



No Difference in 5 yr IDFS

Postmenopausal: < 10 pg/mL

Medium/High AMH (n=806)



7.8% improvement in 5 yr IDFS with chemo

Premenopausal: ≥ 10 pg/mL

Significant interaction p=0.019, adjusting for RS

Take Home Messages for Early-Stage Breast Cancer

- **TNBC Continuing exploration of the role of immunotherapy in perioperative management**
  - *A-BRAVE Trial: still need to define role of adjuvant IO*
  - *I-SPY Dato+Durva: ADC and IO combinations are exciting, await phase 3 trials in preoperative setting.*
- **ER+/HER2- Role of predictive biomarkers to determine risk/therapy for early breast cancer**
  - *monarchE: ctDNA positivity rare in adjuvant setting but predicts risk; need to understand best therapeutic strategies to reduce recurrence.*
  - *RxPONDER AMH: continued work to better define populations unlikely to benefit from adjuvant chemotherapy.*

PART 1: Balancing Efficacy & QOL in ER+ MBC

Discussant: Ruth O'Regan, MD, MRCP, FCRP (Rochester)

Abstract #	Presenter	Title	Data Presented	"One Liner"
LBA1001	Kevin Kalinsky, MD (Emory Univ)	postMONARCH: Phase III 2L fulvestrant ± abemaciclib after PD on 1L AI + CDK4/6i (n=368)	Primary outcome: Investigator-assessed PFS	"CDKi-after-CDKi" improves PFS
LBA1002	Yeon Hee Park, MD, PhD (Samsung Med Center)	Young-PEARL: Phase II 2L GnRHa/exemestane + palbociclib vs capecitabine in premenopausal women (n=184)	Extended median f/u 58 mo (from previous original report @ 17 mo)	Improved PFS w/ CDK4/6i, but similar strong OS, especially if control arm gets CDKi later on
1003	Dejan Juric, MD (MGH)	INAVO120: Phase III 1L fulvestrant & palbociclib + inavolisib or placebo in PIK3CA-mutated disease during or within 12 mo of adjuvant Rx (n=325)	Additional analyses (longer follow-up) and PROs	Usual toxicities (mucositis, hyperglycemia) manageable; longer time w/ less pain

postMONARCH as 2L ER+ MBC

Investigator-Assessed PFS

Eligibility

HR+, HER2- ABC

Men & Pre/post menopausal women

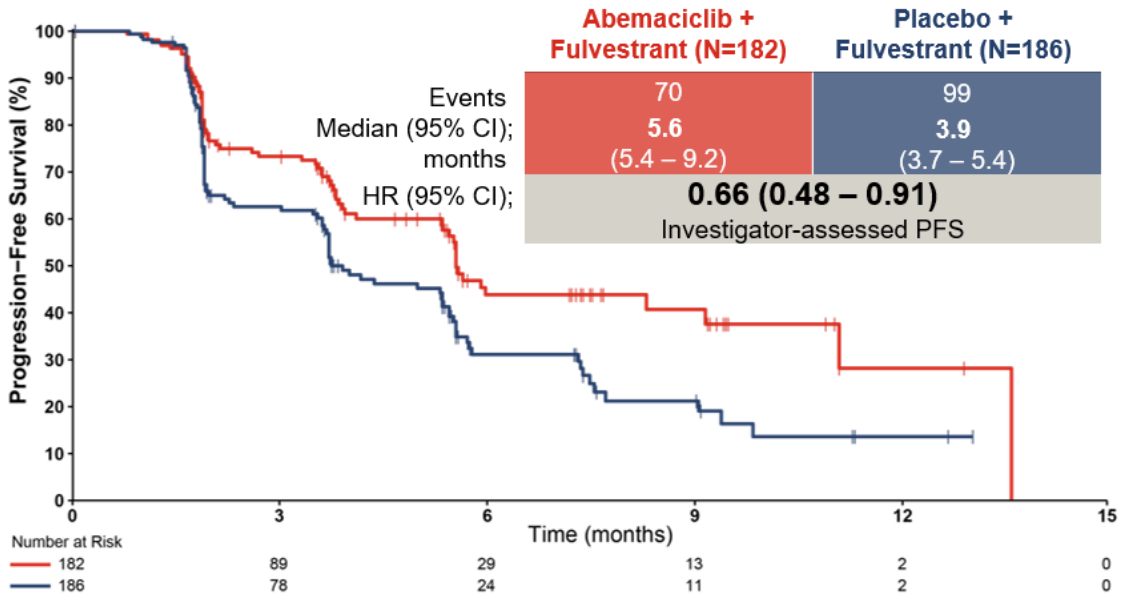
Prior Therapy:
- **ABC**: Disease progression on CDK4/6i + AI as initial therapy
- **Adjuvant**: Disease recurrence on/after CDK4/6i + ET
- No other therapy for ABC

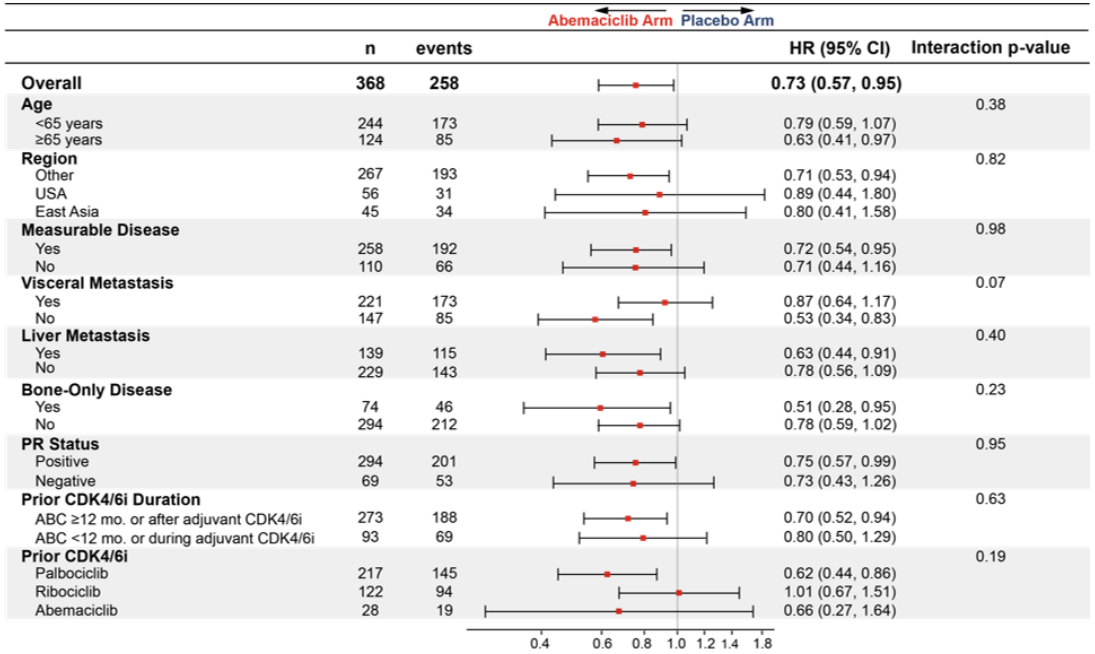
Randomization 1:1

- Abemaciclib + Fulvestrant
- Placebo + Fulvestrant

N = 368

		Abemaciclib + Fulvestrant N=182 (%)	Placebo + Fulvestant N=186 (%)
Measurable Disease		72	68
Visceral metastasis		62	59
Site of Metastasis	Liver	37	38
	Bone-Only	18	23
Prior CDK4/6i Setting	ABC	100	98
	Adjuvant	0	2
Prior CDK4/6i	Palbociclib	59	59
	Ribociclib	34	33
	Abemaciclib	8	8
Prior CDK4/6i Duration	≥12 months*	71	77
	<12 months^	29	22





Phase II GnRHa/Exemestane + Palbociclib vs Capecitabine (Young-PEARL) LBA002: Yeon Hee Park, MD, PhD et al

- Premenopausal women
- HR+/HER2- mBC
- Tamoxifen pretreated
- Prior 1 line of cytotoxic chemotherapy for mBC was allowed

R 1:1

N=184

D1-21 Palbociclib 125mg QD for 3wks
D1-28 Exemestane 25mg QD for 4wks
D1 Leuprolide 3.75mg SC q4weeks

D1-14 Capecitabine 1250mg/m² bid for 2weeks q3weeks

Stratification factors:
- Prior cytotoxic chemotherapy for MBC
- Presence of visceral metastases

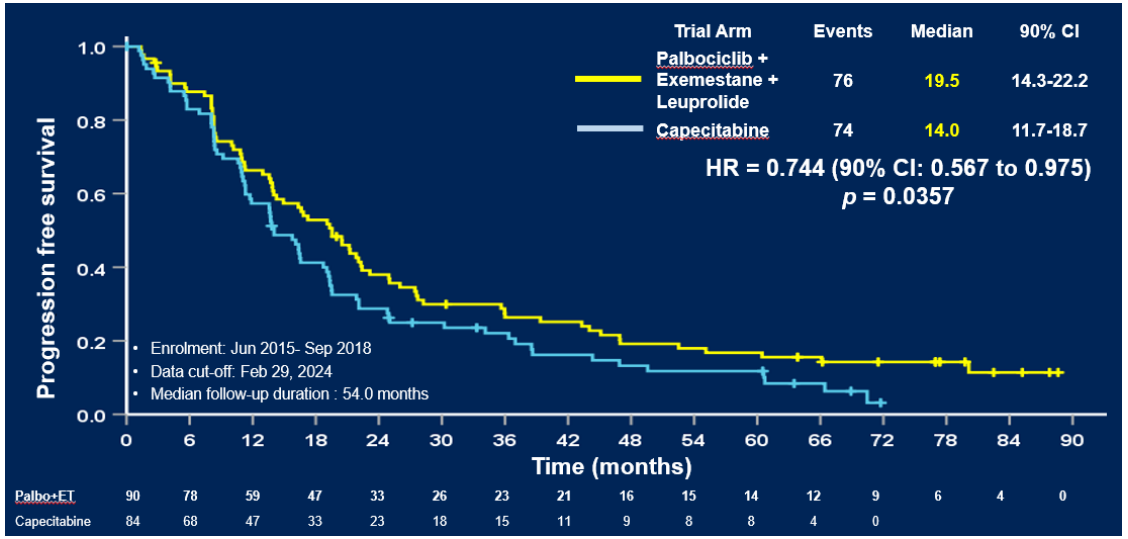
Endpoints
- **Primary :**Investigator-assessed Progression-Free Survival (PFS)

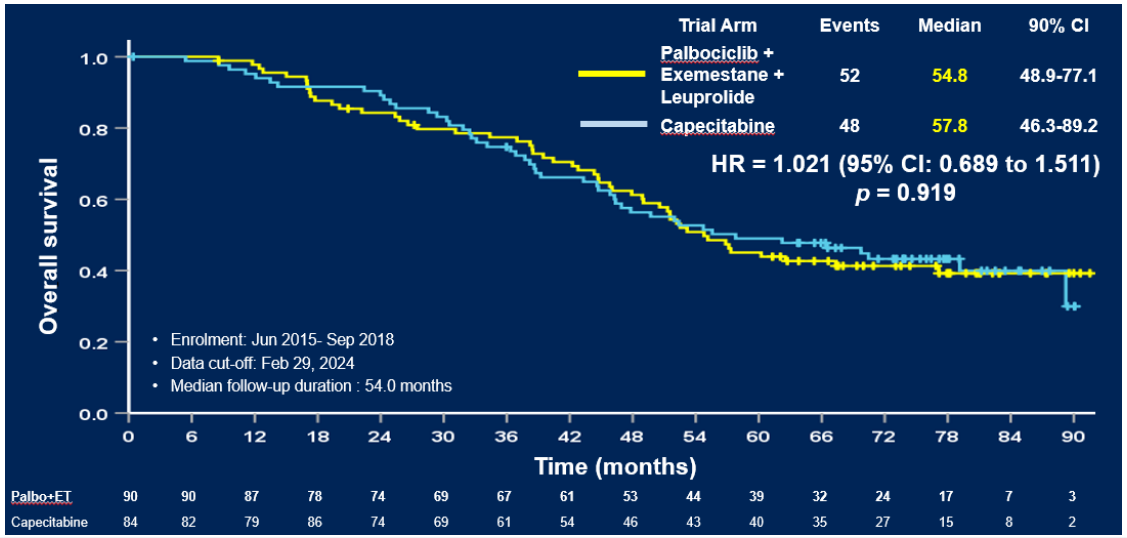
First Subsequent Treatment after Progression

	Palbociclib + ET arm N=71		Capecitabine arm N=71	
Endocrine Treatment	20	28.2%	57	80.3%
CDK4/6 inhibitor + ET	4[a]	5.6%	19[b]	26.8%
Tamoxifen or AI	6	8.5%	35	49.3%
Fulvestrant	8	11.3%	2	2.8%
Alpelisib + ET	2	2.8%	1	1.4%
Chemotherapy	45	63.4%	13	18.3%
Capecitabine	28	39.4%	0	0.0%
Taxane	11	15.5%	6	8.5%
Anthracycline	3	4.2%	2	2.8%
others	3	4.2%	5	7.0%
Clinical trial	6	8.5%	1	1.4%

a, all 4 patients received palbociclib; b, 14 palbociclib, 3 abemaciclib, 2 ribociclib

- 15.5% (11/71) of Palbociclib + ET arm and 49.3% (35/71) of Capecitabine arm received CDK4/6 inhibitor treatment during follow up period, after disease progression.





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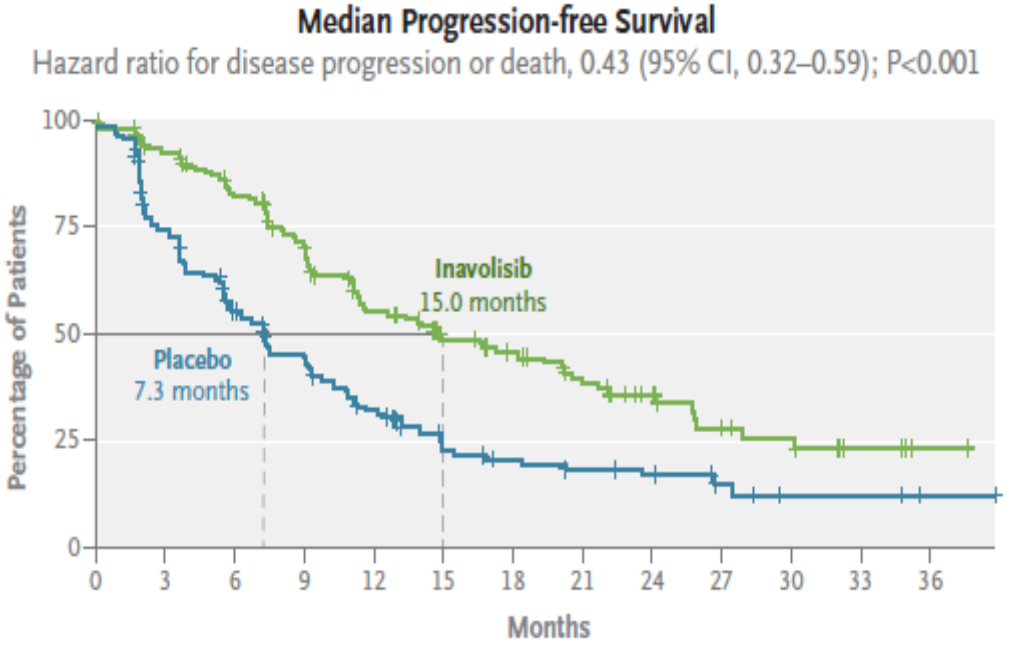
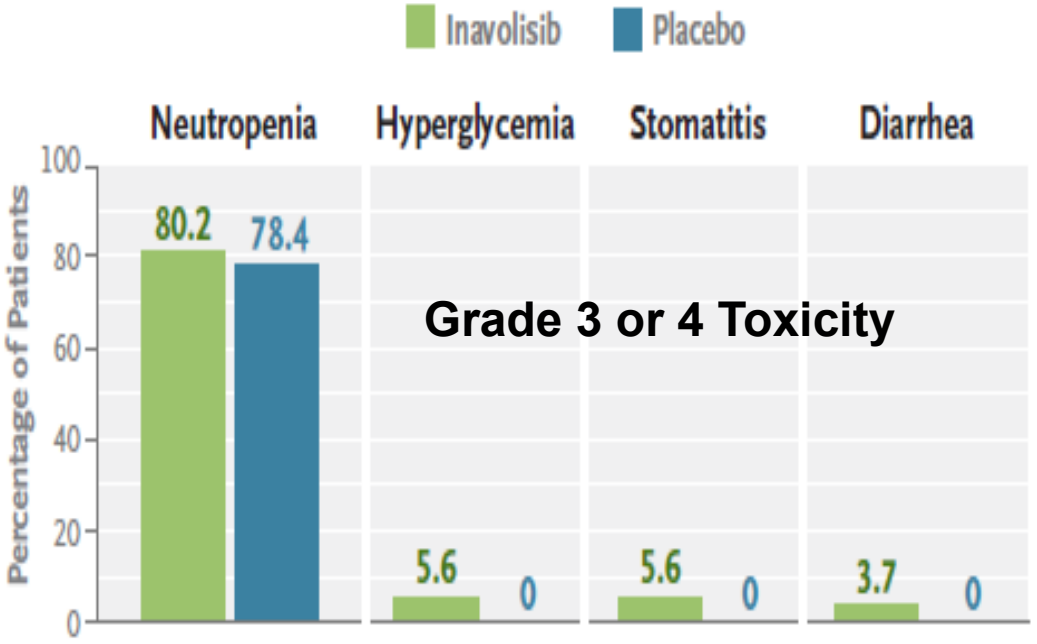
INAVO120: Phase III 1L Fulvestrant & Palbociclib + Inavolisib or Placebo in PIK3CA-mutated Disease (N=325)

- Hormone receptor-positive/HER-2 negative LABC or stage IV
- Positive for PIK3CA mutations
- Disease recurrence or progression on or within 12 months of adjuvant endocrine therapy (predates adjuvant CDK4/6i)



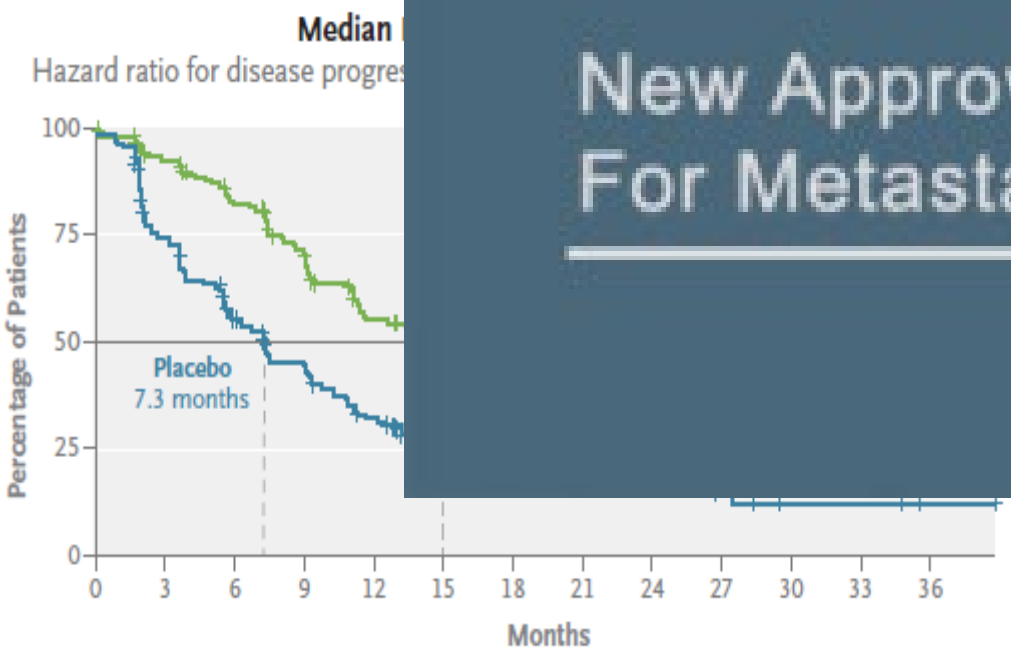


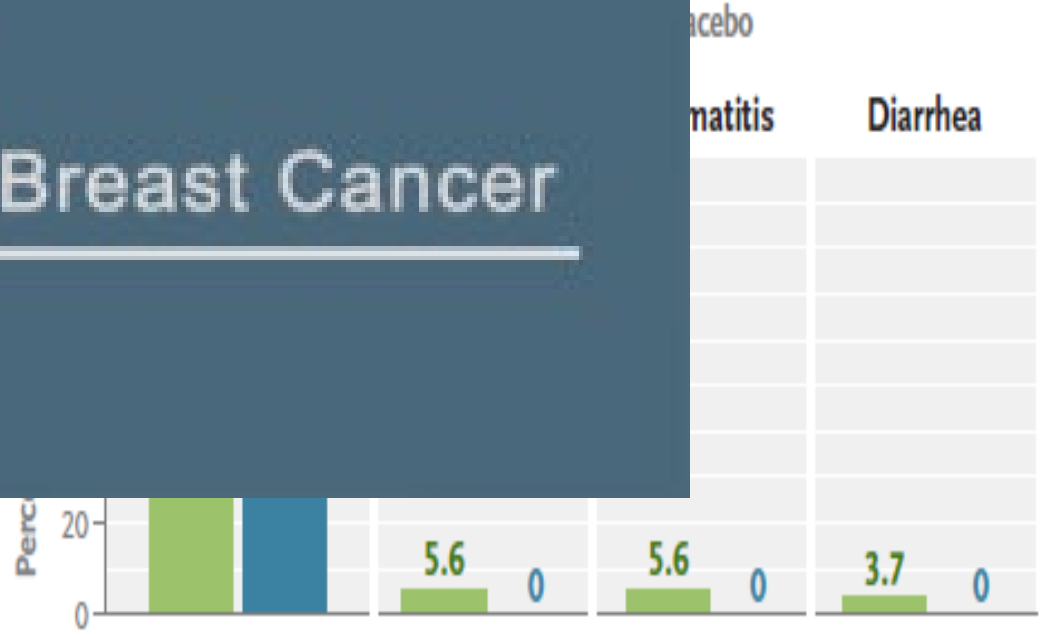
Dura et al, ASCO 2024 and Turner et al, N Engl J Med, 2024

INAVO120: Phase III 1L Fulvestrant & Palbociclib + Inavolisib or Placebo in PIK3CA-mutated Disease (N=325)

- Hormone receptor-
- Positive for PIK3CA
- Disease recurrence
- y (predates adjuvant CDK4/6i)

New Approval
For Metastatic Breast Cancer





Dura et al, ASCO 2024 and Turner et al, N Engl J Med, 2024

PART 2: The Ongoing ADC Revolution in Breast Cancer

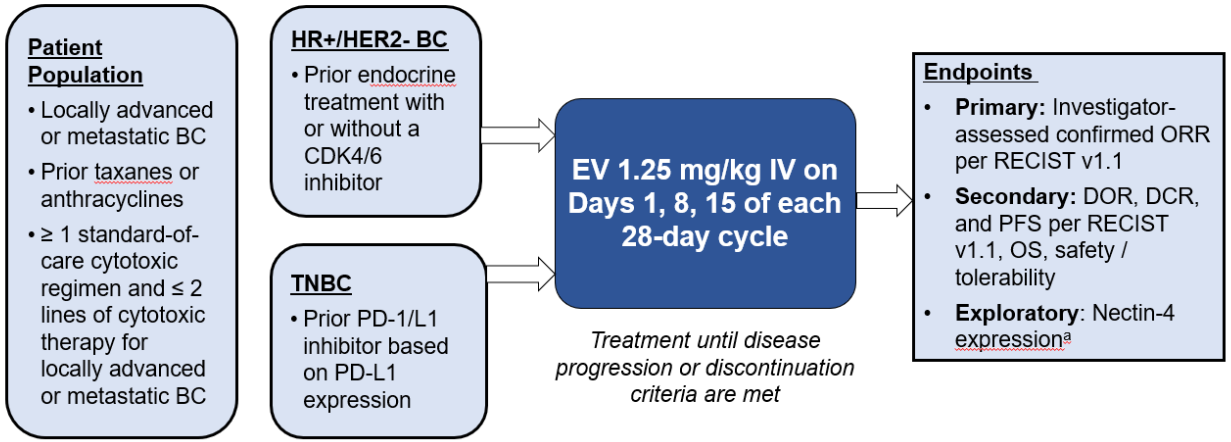
Discussant: Shanu Modi, MD (MSKCC)

Abstract #	Presenter	Title	Data Presented	"One Liner"
LBA1004	Ana Christina Garrido-Castro, MD (DFCI)	SACI-IO HR+: Phase II trial sacituzumab govitecan ± pembrolizumab as 1L/2L (n=110)	Efficacy of the ADC (PFS ITT pop, then subsets)	ICI did not improve overall PFS (but numerical improvement if PD-L1+)
1005	Antonio Giordano, MD, PhD (DFCI)	EV-202: Enfortumab vedotin in TNBC & ER+ MBC cohorts (n=87)	ORR with ADC to cell adhesion molecule (CAM) Nectin-4	Response observed, but below statistical threshold
1006	Sonia Pernas, MD, PhD (Institut Català d'Oncologia)	TROPION-Breast01: Phase III datopotamab deruxtecan (Dato-DXd) vs chemotherapy as 1L/2L (n=732)	PROs (ESMO '23: PFS 6.9 vs 4.9 mo, HR 0.64)	Improved TTD in GHS/QOL 9.0 vs 4.8 mo, HR 0.76

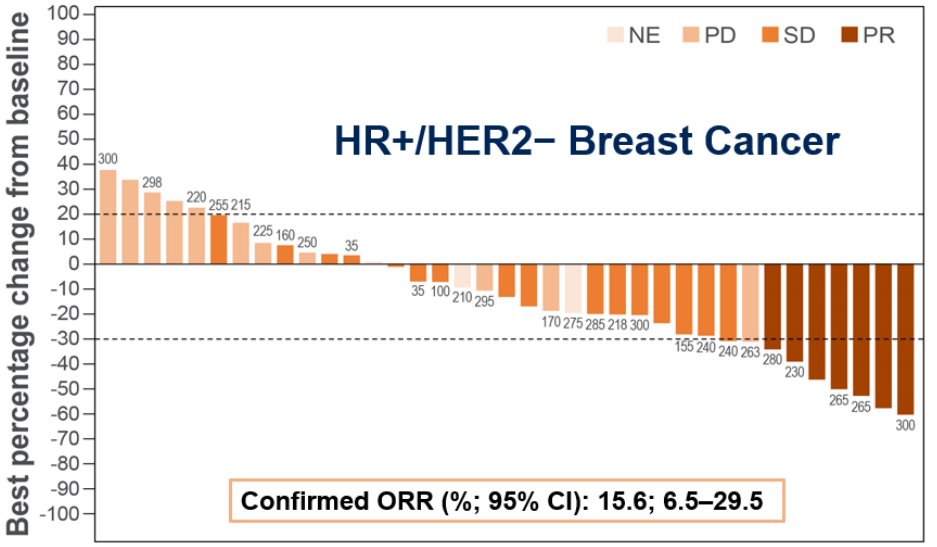
Enfortumab Vedotin in TNBC & ER+ MBC (EV-202)

LBA005: Antonio Giordano, MD, PhD et al

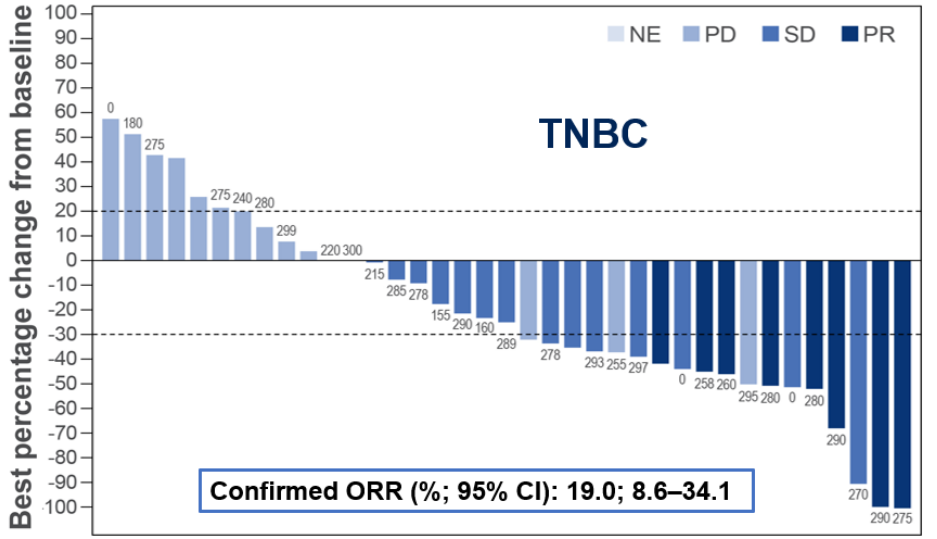
EV-202 Study Design: BC Cohorts (1/2)



Selected TRAEs of special interest, n (%)		
Any rashes or severe cutaneous adverse reactions	28 (62.2)	25 (59.5)
Any peripheral neuropathy	12 (26.7)	11 (26.2)
Any hyperglycemia	5 (11.1)	2 (4.8)



Numbers above and below the bars indicate Nectin-4 H-scores.



Numbers above and below the bars indicate Nectin-4 H-scores.

PART 3: Exploring New Partnerships in HER2+ Disease

Discussant: Ciara O'Sullivan, MD, MBBCh (Mayo Clinic)

Abstract #	Presenter	Title	Data Presented	"One Liner"
1007	Toshinari Yamashita, MD, PhD (Kanagawa Cancer Center)	JBCRG-M06/EMERALD: Phase III 1L trastuzumab & pertuzumab (HP) w/ eribulin mesylate or a taxane (n=446)	Primary objective of non-inferiority (margin HR 1.33) 58% "de novo" MBC	HR 0.95 (95% CI, 0.76-1.19) & not inferior; but not less toxic (esp, neurotox)
1008	Eva Maria Ciruelos, MD, PhD (Hospital 12 de Octubre)	PATRICIA, SOLTI-1303: Phase II study of trastuzumab plus ET/palbociclib vs TPC ≥1L in HER2+ PAM50 luminal (n=73 randomized)	Primary results of cohort C (n=264 screened; n=114 luminal A/B); integral biomarker trials are tough to do	Promising signal, must be confirmed
1009	Fabrice Andre, MD, PhD (Gustave Roussy)	DESTINY-Breast07: Phase Ib/II 1L T-DXd alone (n=75) and T-DXd + pertuzumab (n=50)	Dose-expansion interim analysis (DB-09 T-DxD vs T-DXd/P vs THP)	Appear equally active (ORR 76% & 84%) w/ no incremental tox

JBCRG-M06/EMERALD: Design

Multicenter non-inferiority phase III trial (NCT03264547)

Eligibility:
- HER2+ LABC or metastatic BC
- No prior chemo for MBC (except T-DM1)
- ≥ 6 months since (neo)adjuvant chemo
- LVEF ≥ 50%

(N = 446)

R 1:1

Study Arm (21-day cycle)

Eribulin 1.4 mg/m² day D1,8 + Trastuzumab + Pertuzumab* D1 (n= 224)

Control Arm (21-day cycle)

Docetaxel 75mg/m² D1 or Paclitaxel 80mg/m² D1,8,15 + Trastuzumab + Pertuzumab* D1 (n=222)

Docetaxel =186, paclitaxel =36

Primary endpoint:
- PFS

Secondary endpoints:
- OS
- ORR
- QoL
- Safety
- PROs

Translational Endpoints
- Biomarker discovery

Registration : 8/2017→ 4/2020
Median follow-up : 35.7 months
Data cut off: 6/30/2023

Stratification factors
- Perioperative taxane
- Treatment with HER2 targeted ADC post recurrence
- Visceral metastases

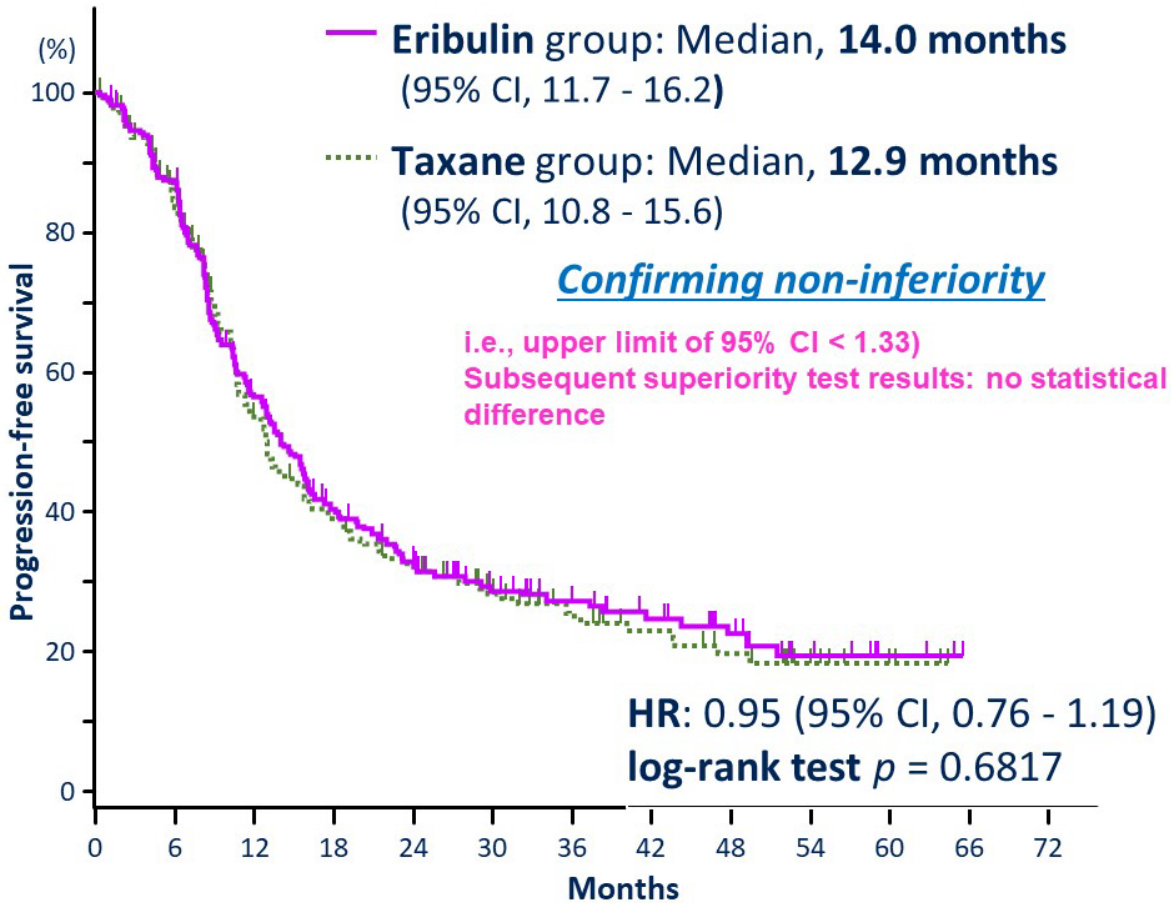
*Trastuzumab: 8mg/kg loading dose, 6 mg/kg subsequent doses + pertuzumab: 840mg loading dose, 420 mg subsequent doses

Abbreviations: HER2, human epidermal growth factor receptor 2; BC, breast cancer; MBC, metastatic breast cancer; LABC, locally advanced breast cancer; chemo, chemotherapy; LVEF, left ventricular ejection fraction; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; D, day; DoR, duration of response; PRO, patient-reported outcomes; QoL, quality of life

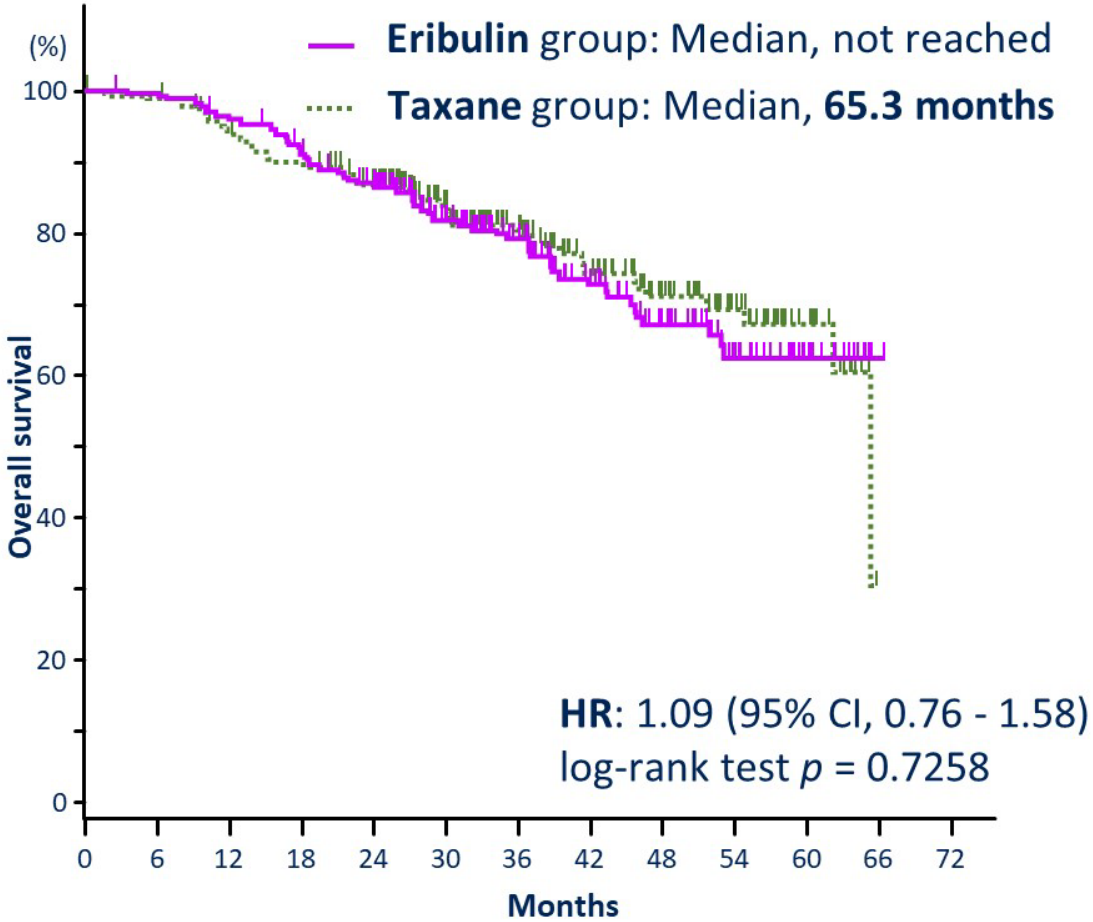
PRESENTED BY: Ciara C. O'Sullivan

JBCRG-M06/EMERALD: median PFS & OS

Progression-Free Survival



Overall Survival



More neuropathy with eribulin

Yamashita *et al.*, ASCO 2024

Phase II Study of Trastuzumab plus ET/palbociclib vs TPC ≥1L in HER2+ PAM50 Luminal ABC(PATRICIA, SOLTI-1303)

1008: Eva Maria Ciruelos, MD, PhD et al

PATRICIA Cohort C: Study design

SOLTI

Open-label, multicenter, randomized phase II trial

- ✓ Male or Pre and postmenopausal women
- ✓ **HR+/HER2+ ABC**
- ✓ **PAM50 Luminal A or B subtype** by Prosigna® (research use only)
- ✓ **At least 1L for ABC**[1]
- ✓ **Baseline LVEF** ≥ 50%
- ✓ **Stable CNS metastasis allowed**[2]
- ✓ **No prior CDK4/6i**

Pre-screening

PAM50 Luminal A/B[3] → R 1:1

- **Palbociclib 125 mg QD 3W + Trastuzumab* + Endocrine therapy****
- **Treatment of physician's choice (TPC)*****

Re-randomization[4] → R 1:1

Stratification factors:

- Number of previous regimens (1-2 vs ≥ 3)
- Visceral disease (yes vs no)

* Trastuzumab: loading dose of 8mg/kg followed by 6 mg/kg IV or 600 mg SC administration.
** Aromatase inhibitor, fulvestrant or tamoxifen +/- gonadal suppression
*** T-DM1, any endocrine therapy or chemotherapy (gemcitabine, vinorelbine, capecitabine, eribulin, paclitaxel or docetaxel) plus trastuzumab.

Primary endpoint

- Investigator-assessed PFS (RECIST 1.1)

Secondary endpoints

- Overall response rate (ORR)
- Disease control rate (DCR)
- Duration of response
- Safety profile

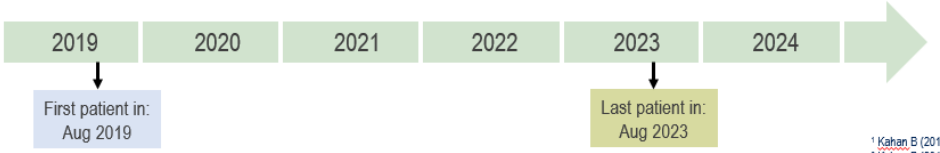
Protocol assumptions

- **Sample size** of **102** patients
- One-sided stratified log-rank test (0.1 alpha)
- **Target** PFS **hazard ratio (HR)**: **0.62**
- To achieve **80% statistical power**, 80 PFS events were needed

Feb 2021: Re-randomization design

- **Patients allocated** in the **TPC arm** could be **re-randomized** after disease progression if the inclusion criteria were met
- **Mixed effects Cox** models were used to adjust for intra-patient correlation
- The re-randomization approach led to unbiased treatment estimation, correct type I error and **potentially reduce number of patients** to be pre-screened[1-2]. **Overall survival** was not assessed as a trial endpoint.

- The trial was **closed earlier** after 73 patients were randomized due to **low recruitment**. At data cut-off, 51 PFS events were observed. The study was **underpowered** based on the protocol assumptions (64% statistical power)

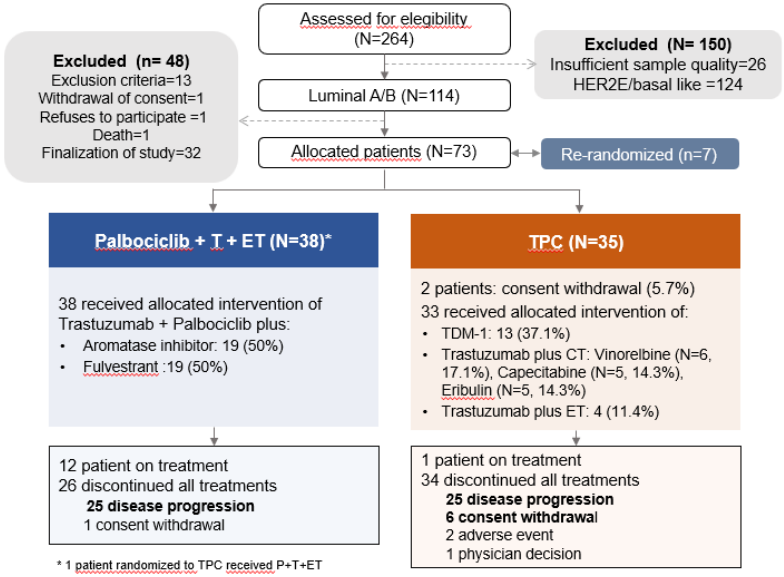


[1] Kahan B (2015). BMC Med Res Methodol
[2] Kahan B (2016). Trials

Phase II Study of Trastuzumab plus ET/palbociclib vs TPC ≥1L in HER2+ PAM50 Luminal ABC(PATRICIA, SOLTI-1303)

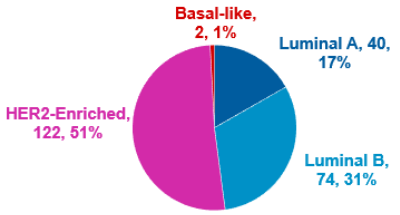
1008: Eva Maria Ciruelos, MD, PhD et al

Patient´s disposition



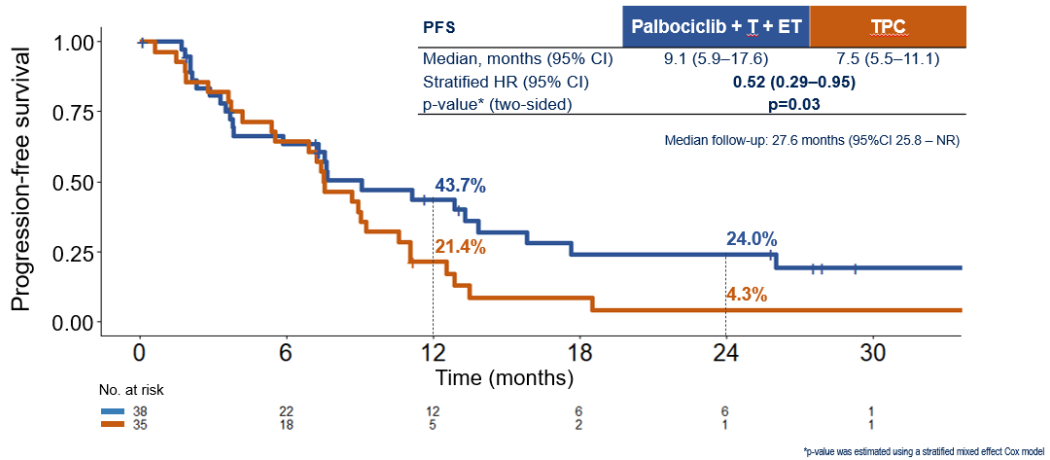
PAM50 subtype distribution

Pre-screened tumors (N = 238)
Tissue type: primary tumor 54.8%; metastatic 45.2%

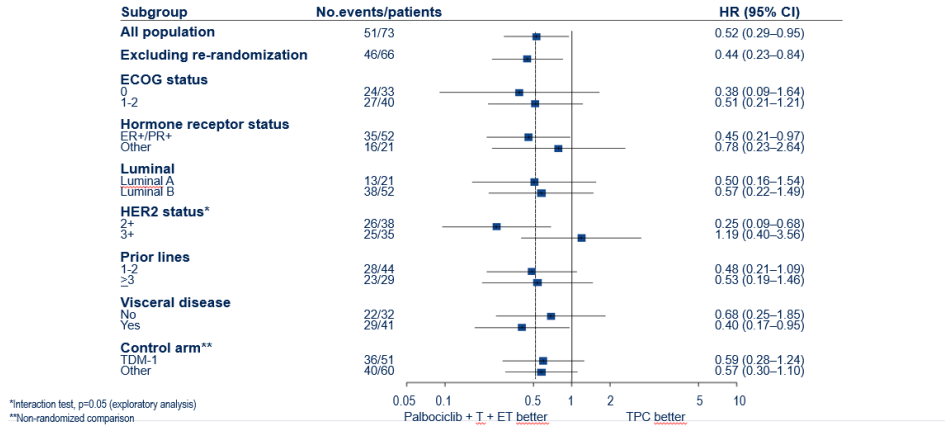


Molecular screening failure rate: 52.1%

Primary objective: Investigator-assessed PFS



Subgroup analysis (PFS)



Conclusions

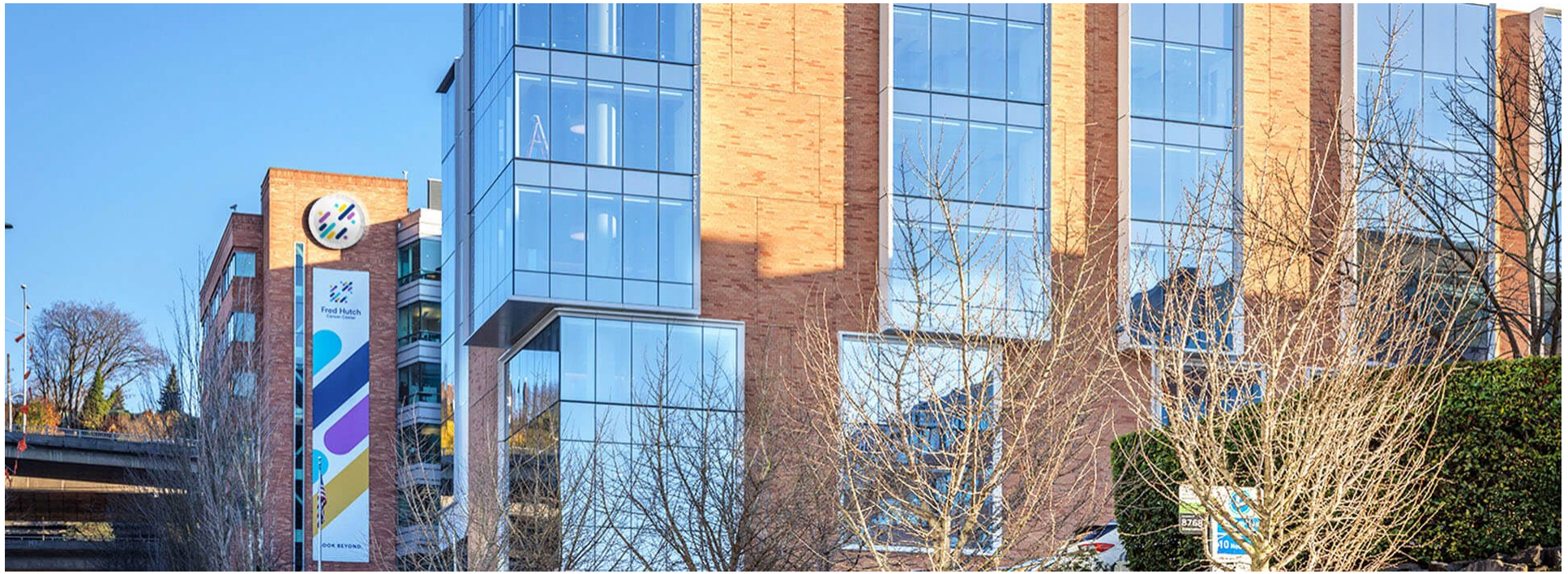
- In patients with advanced HR+/HER2+ breast cancer with **PAM50 Luminal A or B intrinsic subtype tumors**, the combination of **palbociclib, trastuzumab and endocrine therapy** showed a statistically significant improvement in PFS compared to treatment of physician choice:
  - **HR PFS**= 0.52 (95%CI 0.29-0.95) and 24m PFS (24.0% vs 4.3%)

PRESENTED BY: Antonio C. Wolff, MD, FACP, FASCO

Take Home Messages for Advanced Breast Cancer

- Role for continuing CDK4/6i after disease progression on CDK4/6i?
- FDA approval of a new PIKC3A inhibitor with endocrine + CDK4/6i—role in era of adjuvant CDK4/6i?
- Role of new drugs eg enfortumab or old drugs eg taxane and eribulin
- Continued focus on biologically- driven combination approaches

Thank you!



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