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Metastatic Breast Cancer

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SAN ANTONIO BREAST CANCER SYMPOSIUM

Hannelore Denys

January 30th - 2021

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Triple Negative MBC

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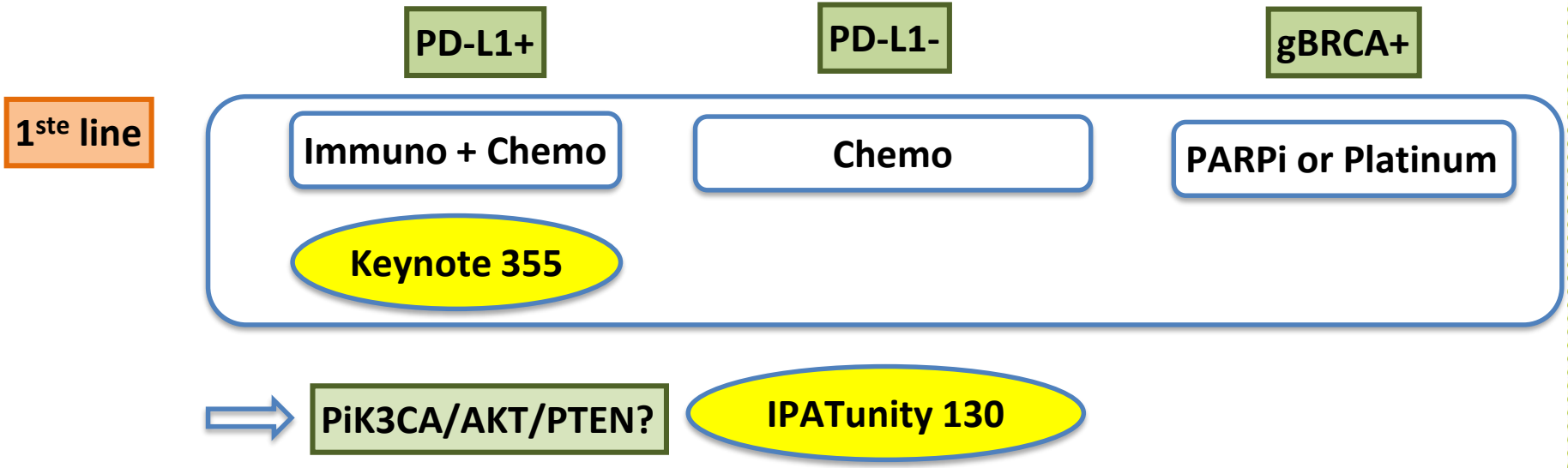
mTNBC: upfront PDL1 test
gBRCA testing



Additional Efficacy Endpoints from the Phase 3 KEYNOTE-355 Study of Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy as First-Line Therapy for mTNBC

Rugo HS et al: Abstract nr GS3-01.

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KEYNOTE-355 Study Design

Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease

R 2:1

- Pembrolizumab[a] + Chemotherapy[b]
- Placebo[c] + Chemotherapy[b]

Progressive disease[d]/cessation of study therapy

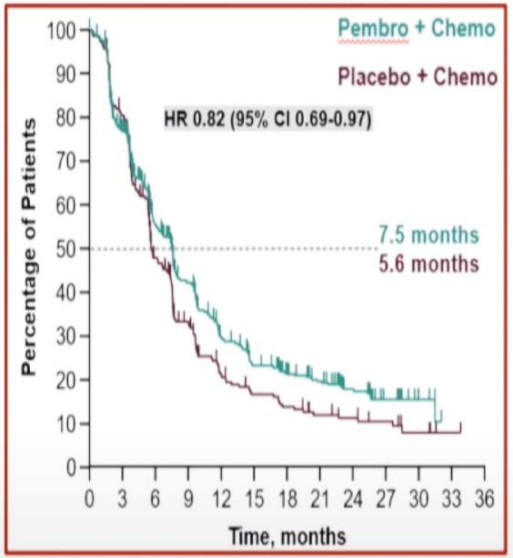
Nab-Pac: 31%
Pac: 13%
Carbo-Gem: 55%

Current analysis: PFS outcomes for each chemotherapy partner and key secondary efficacy endpoints

* Primary Endpoints: PFS and OS in patients with PD-L1–positive tumors[b] (CPS ≥10 and CPS ≥1) and in the ITT population
* Secondary Endpoints: ORR, DCR, DOR
* Exploratory Endpoint: Consistency of treatment effect in all patients and in those with PD-L1–positive tumors[b] (CPS ≥10 and CPS ≥1) according to on-study chemotherapy partner

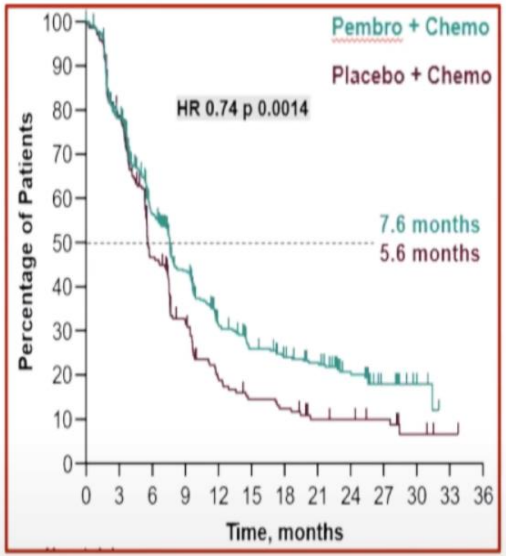
KEYNOTE-355 PFS

ITT



Statistical significance was not tested due to the prespecified hierarchical testing strategy

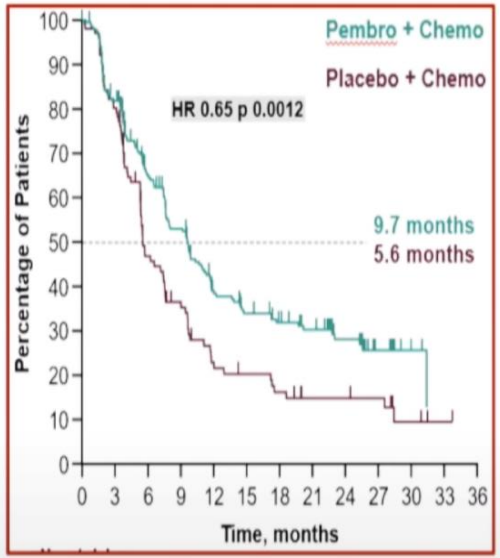
PD-L1 CPS ≥1



Prespecified *P* value boundary of 0.00111 not met

75% of pts

PD-L1 CPS ≥10



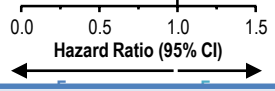
Prespecified *P* value boundary of 0.00411 met

38% of pts

PFS in Subgroups by Chemotherapy regimen

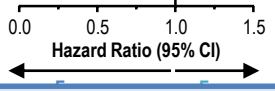
PD-L1 CPS ≥10

Subgroup	N	Median PFS (mo) Pembro + Chemo	Median PFS (mo) Placebo + Chemo	HR
Overall	323	9.7	5.6	0.65 (0.49 to 0.86)
On-study chemotherapy				
Nab-Paclitaxel	99	9.9	5.5	0.57 (0.34 to 0.95)
Paclitaxel	44	9.6	3.6	0.33 (0.14 to 0.76)
Gemcitabine-Carboplatin	180	8.0	7.2	0.77 (0.53 to 1.11)



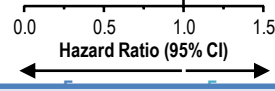
PD-L1 CPS ≥1

Subgroup	N	Median PFS (mo) Pembro + Chemo	Median PFS (mo) Placebo + Chemo	HR
Overall	636	7.6	5.6	0.74 (0.61 to 0.90)
On-study chemotherapy				
Nab-Paclitaxel	204	6.3	5.3	0.66 (0.47 to 0.92)
Paclitaxel	84	9.4	3.8	0.46 (0.26 to 0.82)
Gemcitabine-Carboplatin	348	7.5	7.5	0.86 (0.66 to 1.11)



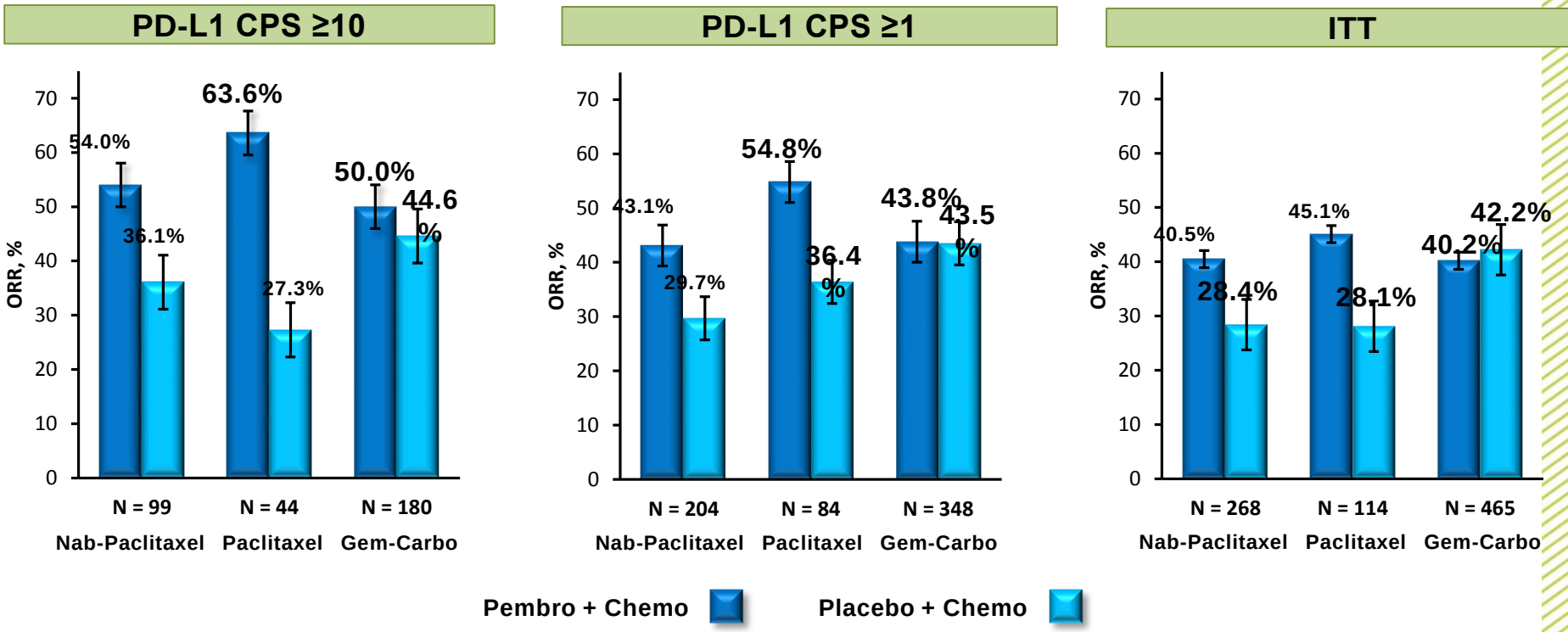
ITT

Subgroup	N	Median PFS (mo) Pembro- + Chemo	Median PFS (mo) Placebo + Chemo	HR
Overall	847	7.5	5.6	0.82 (0.69 to 0.97)
On-study chemotherapy				
Nab-Paclitaxel	268	7.5	5.4	0.69 (0.51 to 0.93)
Paclitaxel	114	8.0	3.8	0.57 (0.35 to 0.93)
Gemcitabine-Carboplatin	465	7.4	7.4	0.93 (0.74 to 1.16)



In subgroup analysis, PFS with pembrolizumab + CT was improved regardless of CT partner

Response Rate in Subgroups by Chemotherapy



Summary

- In subgroup analysis, PFS with pembro + CT was improved regardless of CT partner

- Insufficient evidence of optimal CT backbone
  - trial not powered for comparison (small numbers to draw conclusions)
  - CT not randomized

  Underlying chemo sensitivity seems to be required for IO efficacy in mTNBC

- Key secundairy endpoints of ORR, DCR and DOR favored pembro + CT, with the treatment effect increasing with PDL-1 enrichment

- OS data Keynote 355 eagerly awaited

PFS	OS
IMP 130: 2,5m	IMP130: 7,5m
IMP 131: 9 days	IMP 131: no benefit
K355: 4,1m	K355: ?

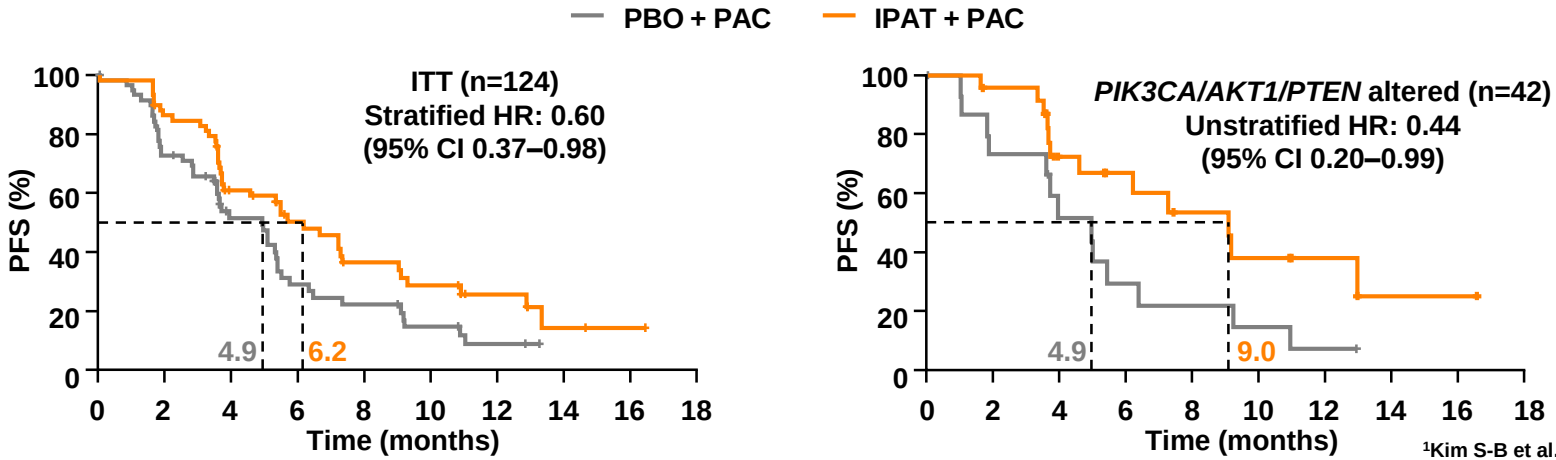
Double-blind placebo-controlled randomized phase 3 trial evaluating first-line ipatasertib combined with paclitaxel for *PIK3CA/AKT1/PTEN*-altered mTNBC: Primary results from IPATunity130 Cohort A

Dent R et al: Abstract nr GS3-04.

PI3K/AKT pathway inhibition in mTNBC

- As ~35% of TNBCs harbor *PIK3CA/AKT1/PTEN* alterations, AKT-inhibition is an appealing strategy
- Ipatasertib is a highly selective ATP-competitive AKT-inhibitor
- In the randomized phase 2 LOTUS-trial, first-line paclitaxel + ipatasertib increased PFS vs placebo + paclitaxel in an unselected population of patients with mTNBC

  Effect on PFS more pronounced in patients with *PIK3CA/AKT1/PTEN*-altered tumors, providing rationale for phase 3 evaluation in biomarker-selected mTNBC



[1]Kim S-B et al. Lancet Oncol 2017

IPATunity130 Cohort A

- Measurable mTNBC
- *PIK3CA/AKT1/PTEN* alteration[a]
- No prior chemotherapy for mTNBC (≥12 months since last [neo]adjuvant chemotherapy)
- Candidate for taxane therapy
- ECOG performance status 0/1

R 2:1

- **PAC 80 mg/m² days 1, 8 & 15 + IPAT 400 mg qd days 1–21 q28d**
- **PAC 80 mg/m² days 1, 8, & 15 + PBO days 1–21 q28d**

255 patients enrolled between Feb 6, 2018 and Apr 8, 2020

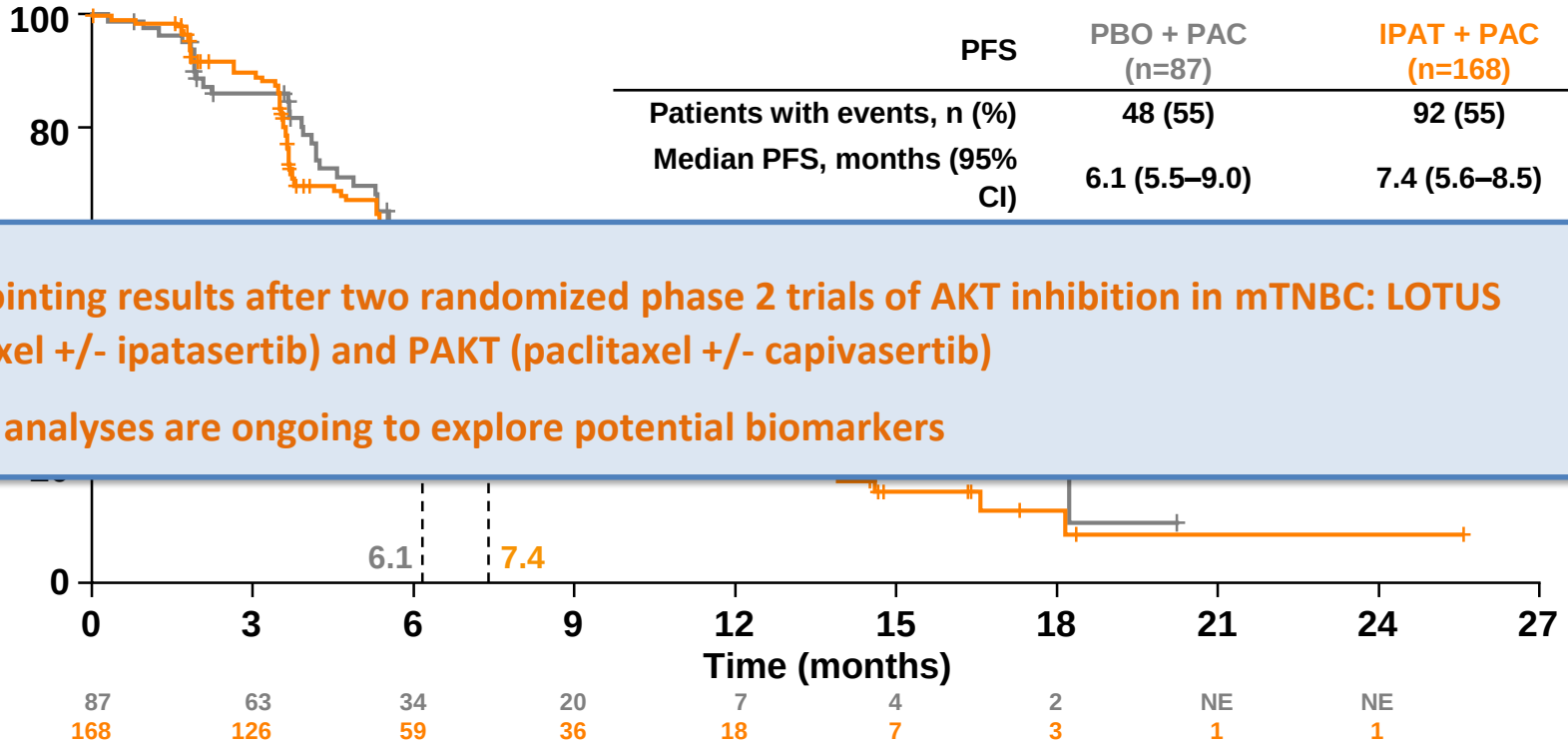
Stratification factors:

- **Prior (neo)adjuvant chemotherapy**
- **Geographic region**
- **Tumor alteration status (*PIK3CA/AKT1*-activating mutation vs *PTEN* alteration without *PIK3CA/AKT1*-activating mutation)**

Analysis of primary endpoint (investigator-assessed PFS) planned after 125 PFS events

- 95.5% power to detect an increase in median PFS of 6 → 12 months with addition of IPAT to PAC
- Target HR = 0.50 at 2-sided 5% significance level

Primary endpoint: Investigator-assessed PFS
Data cut-off: May 7, 2020 (median follow-up: 8.3 months)



PFS	PBO + PAC (n=87)	IPAT + PAC (n=168)
Patients with events, n (%)	48 (55)	92 (55)
Median PFS, months (95% CI)	6.1 (5.5–9.0)	7.4 (5.6–8.5)

- Disappointing results after two randomized phase 2 trials of AKT inhibition in mTNBC: LOTUS (paclitaxel +/- ipatasertib) and PAKT (paclitaxel +/- capivasertib)
- Further analyses are ongoing to explore potential biomarkers

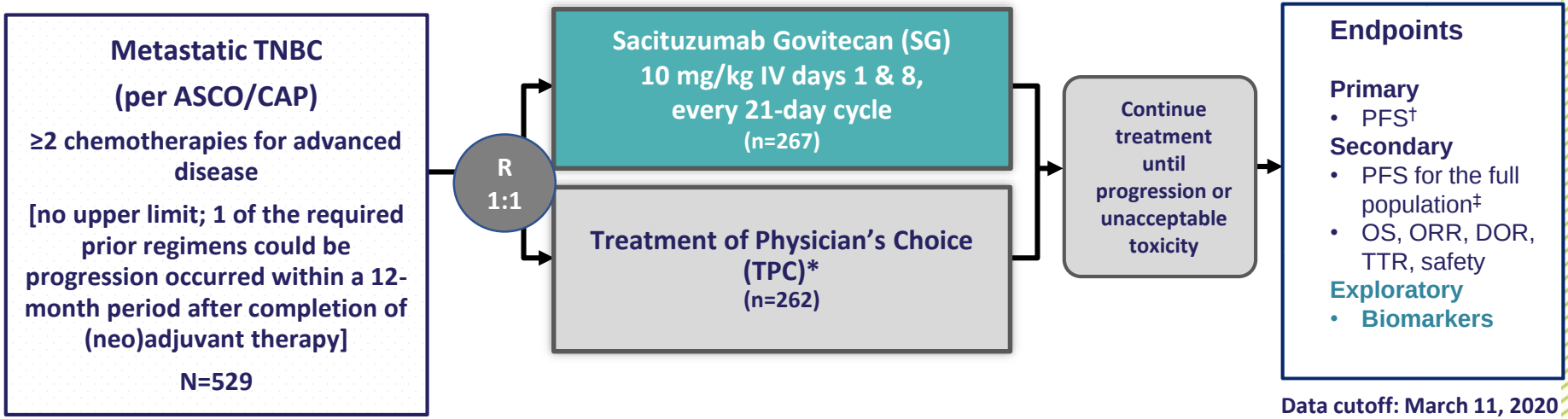
mTNBC

	PD-L1+	PD-L1-	gBRCA+
1st line	Immuno + chemo Keynote 355	Chemo IPATuxity 130 ✗	PARPi or platinum No data on best approach if PDL1+ and gBRCA+
≥2lines	Chemo		PARPi
≥3lines	Chemo ADC ASCENT		PARPi

Biomarker Evaluation in the Phase 3 ASCENT Study of Sacituzumab Govitecan Versus Chemotherapy in Patients With mTNBC

Hurvitz SA, Tolaney S, Punie K et al: Abstract nr GS3-06.

ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC

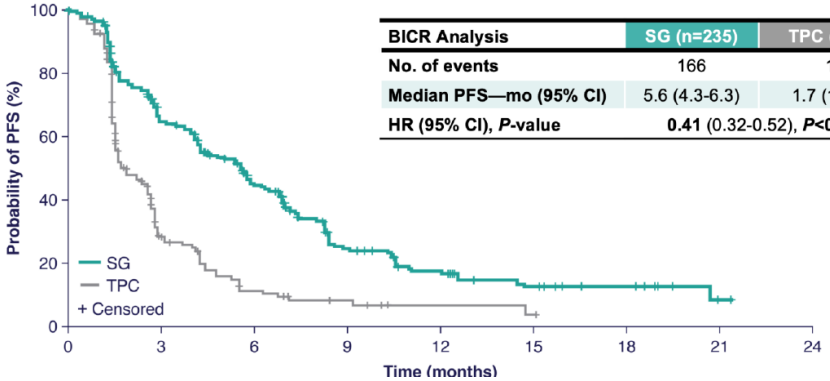


Data cutoff: March 11, 2020

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation

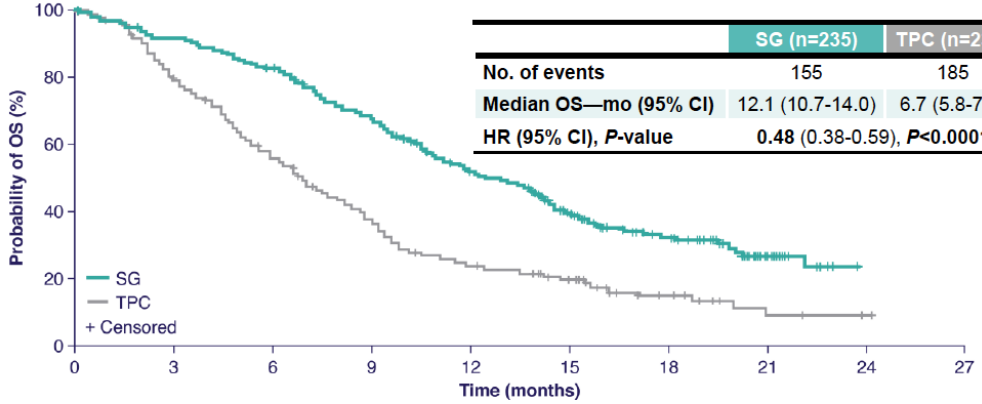
ASCENT PFS and OS

Progression-Free Survival (BICR Analysis)



BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

Overall Survival



	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

Bardia A et al, ESMO 2020

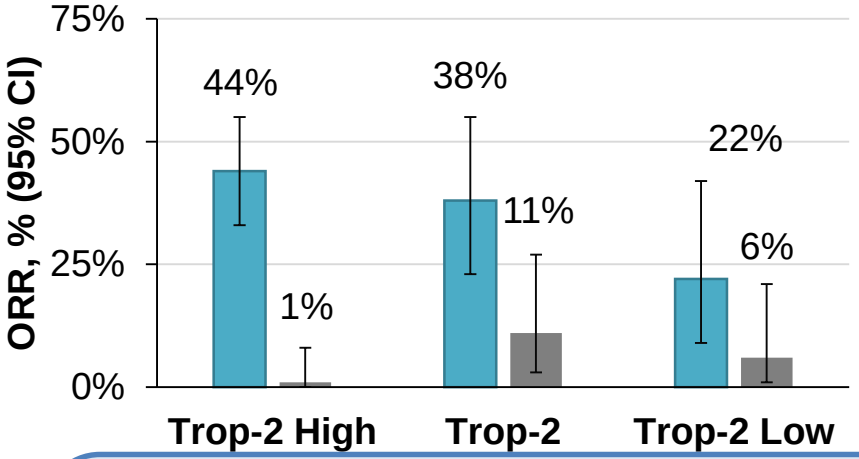
ASCENT SABCS 2020: An exploratory biomarker assessment to evaluate the association between Trop-2 expression or g*BRCA1/2* mutation status and efficacy

- **Primary or metastatic** archival biopsy or surgical specimens were requested at study entry Trop-2 expression was assessed using a validated immunohistochemistry assay and categorized based on a H-score, a numerical value (0 to 300) representing a weighted summation of percent staining
  - H-score <100 (including H-score 0): Trop-2 Low
  - H-score 100-200: Trop-2 Medium
  - H-score 200-300: Trop-2 High

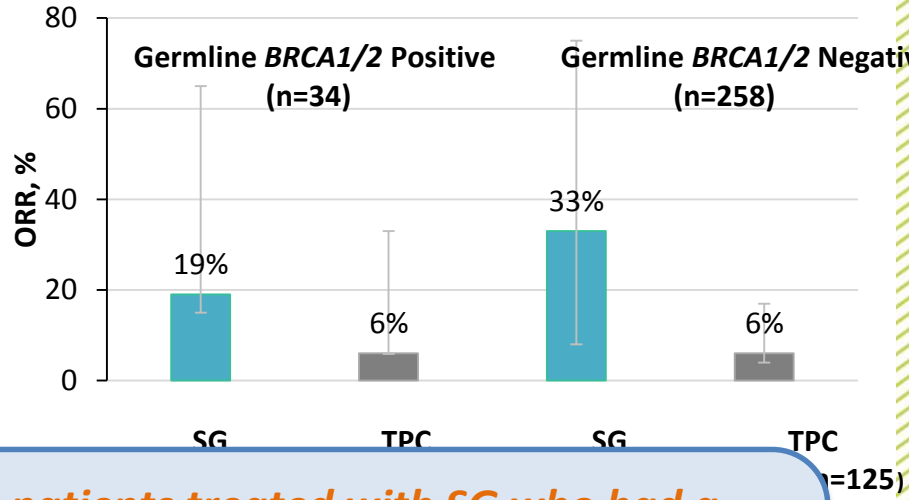
- **Status of germline *BRCA1/2* mutations was collected at baseline, if known**

ORR by

Trop-2 Expression



BRCA 1/2 status



Higher efficacy outcomes were observed in patients treated with SG who had a medium/high Trop-2 H-score (vs low Trop-2 H-score) versus those treated with TPC

SG outperformed TPC regardless of germline BRCA1/2 mutation status (caution small numbers)

Take home messages mTNBC (1)

- **Immunotherapy**
  - * Real progress but only subset of patients benefits and far from turning mTNBC into a chronic disease
  - * PD-L1 is an imperfect biomarker, but the best we have so far
  - * Use the CT partner and the companion diagnostic according to the trial

Future directions:

- Predictive biomarker research (immunogram?)
- How to tackle the dysfuntional tumor microenvironment in MBC?
- Novel agents and novel combinations in testing, sequence?

Take home messages mTNBC (2)

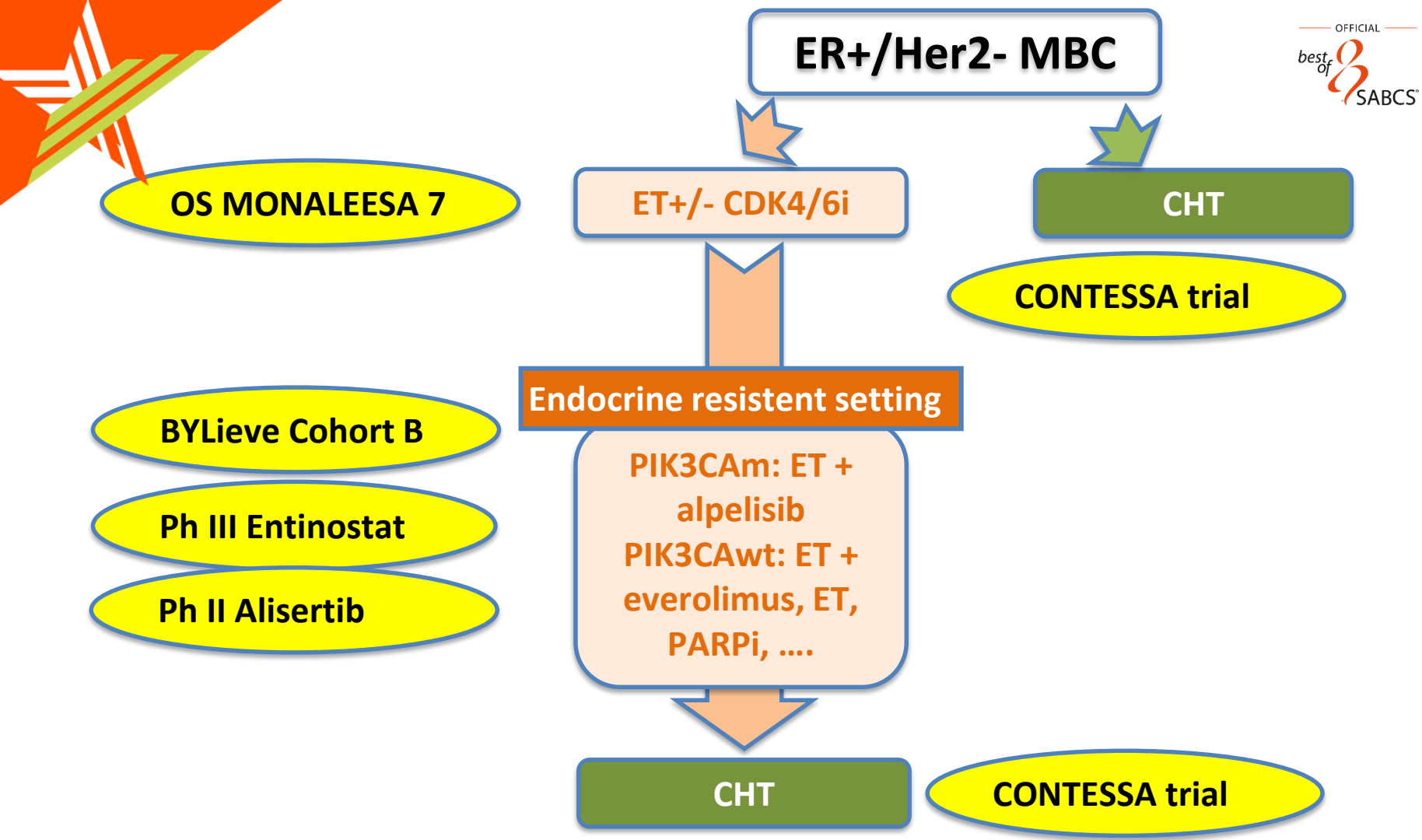
- **PiK3CA pathway:** After two positive phase 2 trials (LOTUS and PAKT) a negative phase 3 trial with ipatasertib. The end for AKTi in mTNBC? Wait for phase 3 Capitello trial in 1st line mTNBC (N=800), pac +/- capivasertib

- **PARPi:** PFS benefit, no OS benefit but QoL better compared to chemo
  - Sequencing of agents under investigation
  - Benefit beyond BRCA carriers, promising data in PALB2 mutant patients

- **ADC:** exciting new class of drugs in mTNBC
  - SG new SOC option for mTNBC >2 lines, no need to measure TROP-2 levels
  - Treatment in earlier lines?

- **Promising new combinations under investigation** (ladiratizumab vedotin + pembro, olaparib + durvalumab, …)

Luminal Breast Cancer


ER+/Her2- MBC
OS MONALEESA 7
ET+/- CDK4/6i
CHT
CONTESSA trial
Endocrine resistent setting
BYLieve Cohort B
Ph III Entinostat
Ph II Alisertib
PIK3CAm: ET + alpelisib
PIK3CAwt: ET + everolimus, ET, PARPi, ….
CHT
CONTESSA trial

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Results from CONTESSA: A phase 3 study of tesetaxel plus a reduced dose of capecitabine versus capecitabine alone in patients with HER2-, HR+ MBC who previously received a taxane

O'Shaughnessy J et al, Abst nr GS4-01.

Tesetaxel: a novel oral taxane

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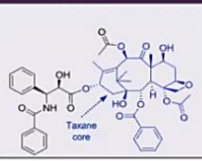
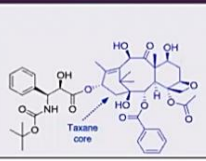
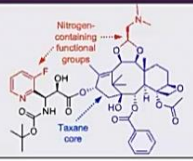
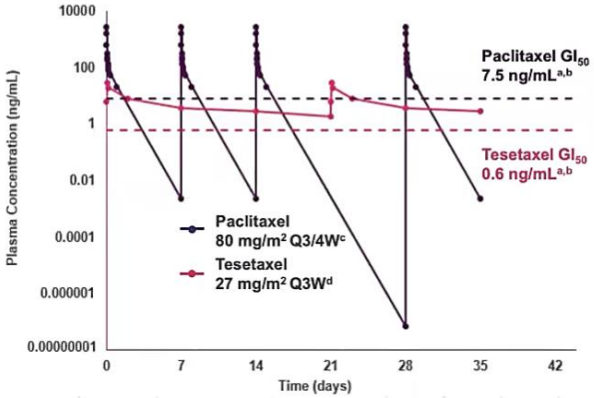
Molecule	Paclitaxel	Docetaxel	Tesetaxel
Structure			
Substantially effluxed by P-gp pump*	Yes	Yes	No
Oral bioavailability in preclinical studies	8%[a]	18%[b]	56%
Solubility (μg/mL)[c]	0.3[d]	0.5[e]	41,600
Terminal plasma half-life in humans ($t_{1/2}$)	0.5 days[f]	0.5 days[g]	8 days[h]

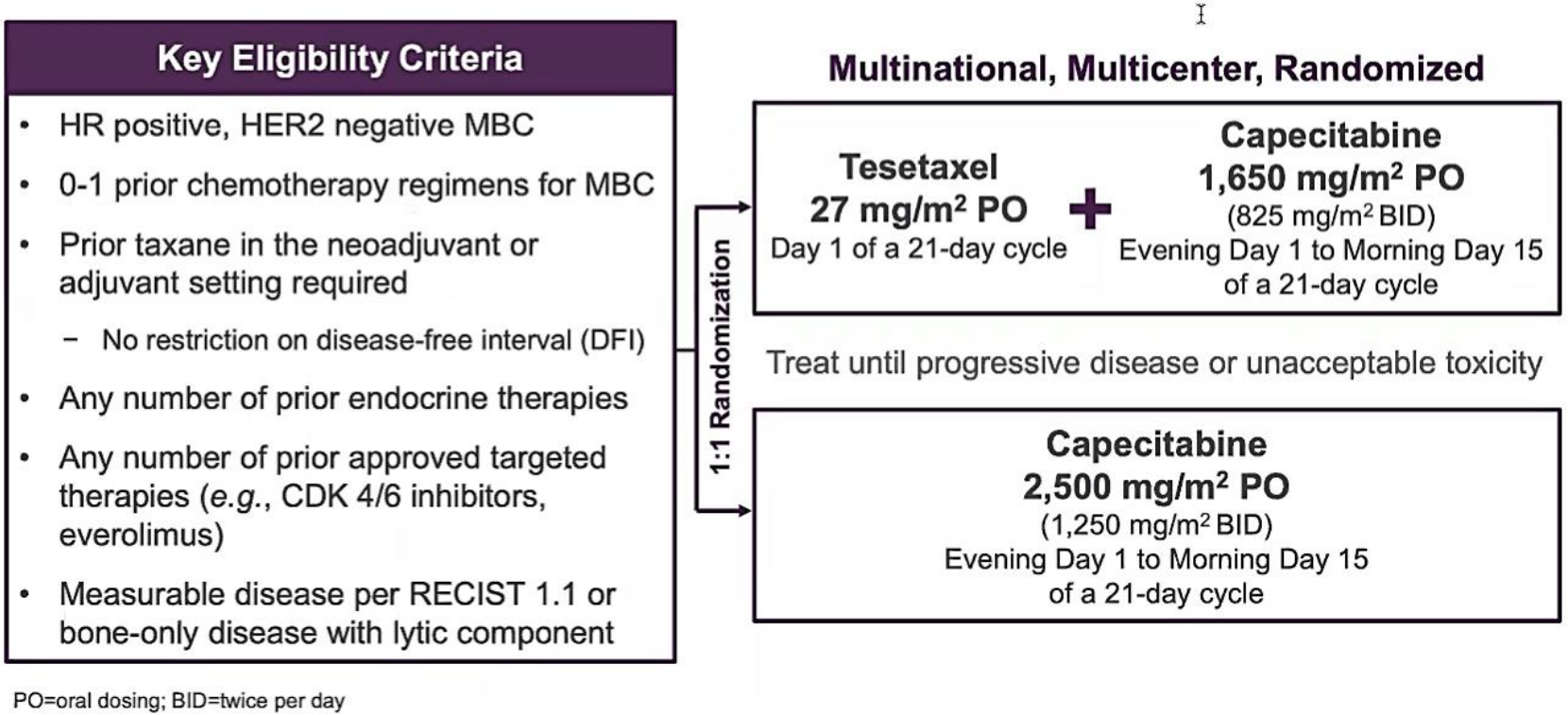


	Paclitaxel[e]	Tesetaxel
Route	Intravenous	Oral
Frequency	Once every 7 days	Once every 21 days
Dose	80 mg/m^2	27 mg/m^2 (2-5 capsules)
Anti-allergy Premedication	Yes[f]	No

- Not effluxed by P-gp pump
- Orally
- Longer half life
- No hypersensitivity reactions
- Low rates of alopecia and neuropathy
- Encouraging results of tesetaxel monotherapy phase 2 trial: ORR 45%

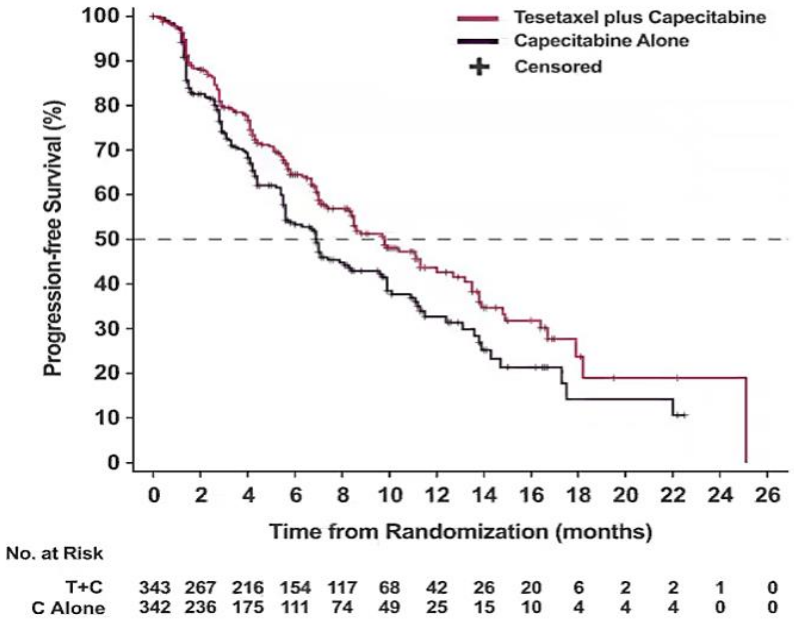
Shanmugam et al, Drug Devel Industrial Pharm 2015; Tan et al, Br J Can 2014

CONTESSA: Phase 3 trial in HR+/HER2- MBC



PO=oral dosing; BID=twice per day

CONTESSA PFS (Primary Endpoint)



	Tesetaxel plus Capecitabine (N=343)	Capecitabine Alone (N=342)
Events	155	169
Median Months (95% CI)	9.8 (8.4 – 12.0)	6.9 (5.6 – 8.3)
	2.9-Month Improvement	
Hazard Ratio (95% CI)	0.716 (0.573 – 0.895)	
P-value	0.003	

CI=confidence interval

- *Overall RR were better with tesetaxel/capecitabine vs capecitabine alone*
- *All subgroups received benefit from tesetaxel/capecitabine*
- *OS data immature, final analysis expected in 2022*

Grade ≥ 3 treatment related AEs

(occurring in >5% of patients)

System Organ Class	TEAE	Tesetaxel plus Capecitabine (N=337) (%)		Capecitabine Alone (N=337) (%)	
		Grade 3	Grade 4	Grade 3	Grade 4
Hematologic	Neutropenia	32.6	38.3	7.4	0.9
	Febrile neutropenia	10.4	2.7	0.3	0.9
	Anemia	8.0	0.0	2.4	0.0
	Leukopenia	6.8	3.0	0.6	0.3
Gastrointestinal	Diarrhea	12.5	0.6	8.9	0.0
	Nausea	6.2	0.0	2.1	0.0
Other	Fatigue	8.6	0.0	4.5	0.0
	Hypokalemia	8.0	0.6	2.7	0.0
	Hand-foot syndrome	6.8	0.0	12.2	0.0
	Neuropathy[a]	5.3	0.6	0.9	0.0

No treatment-related hypersensitivity reactions

- Treatment discontinuation due to any AE was 23.1% in the Tesetaxel arm vs 11.9% for Capecitabine alone.
- Treatment discontinuation due to neutropenia or febrile neutropenia was 4.2% for Tesetaxel plus Capecitabine versus 1.5% for Capecitabine alone.

CONTESSA conclusions:

- All oral, no hypersensitivity reactions, less neuropathy and alopecia
- Doublet Tesetaxel plus Capecitabine not surprisingly improved PFS vs Capecitabine alone but modest improvement (2.9m) and more toxicity
- No OS data

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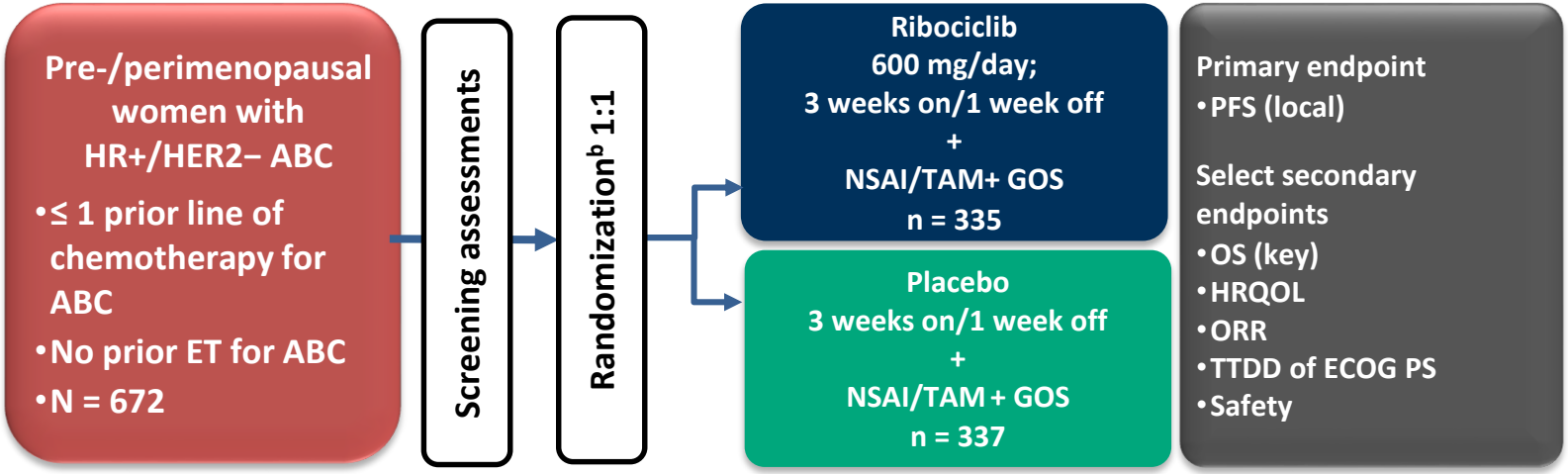
MONALEESA-7 trial of pre- or perimenopausal patients with HR+/HER2– advanced breast cancer treated with endocrine therapy ± ribociclib

Tripathy D et al, PD 02-04.

MONALEESA7 Study Design and Eligibility

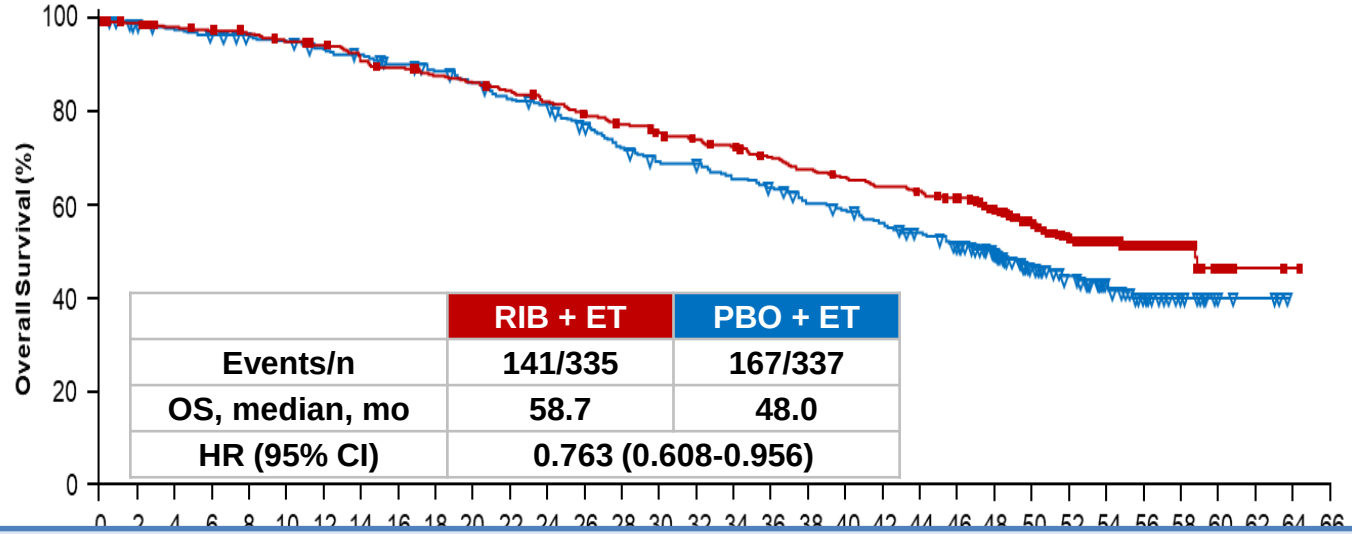


Special notes:

- Median OS had not been reached in the Ribociclib group at the time of the initial analysis median FU of 34.6m
- After prior analysis, patients were unblinded and 15 patients in the placebo group crossed over to Ribociclib

Exploratory updated OS Analysis with median FU of 53.5 months

Updated Overall Survival in ITT, mFU 53.5m



	RIB + ET	PBO + ET
Events/n	141/335	167/337
OS, median, mo	58.7	48.0
HR (95% CI)	0.763 (0.608-0.956)	

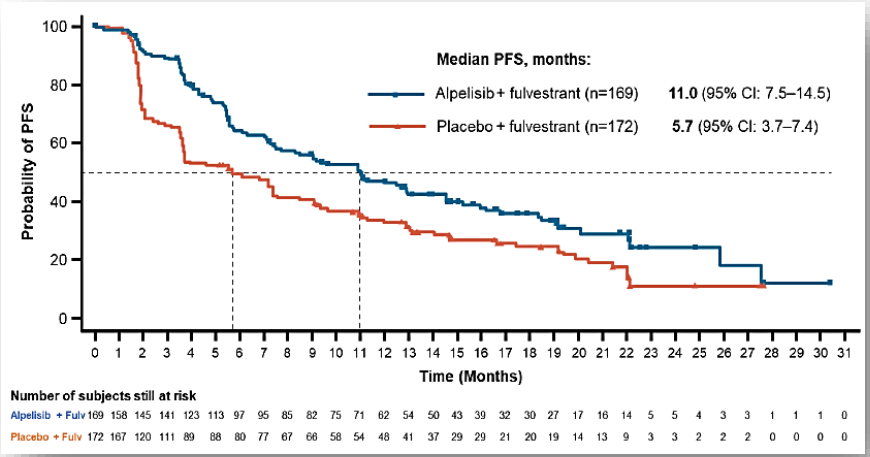
- *OS benefit is sustained with longer follow up, encouraging results for younger patients*
- *Addition of Ribociclib also lengthens time to chemotherapy and chemotherapy-free survival*

Results of BYLieve Cohort B

Rugo H et al, PD 2-07

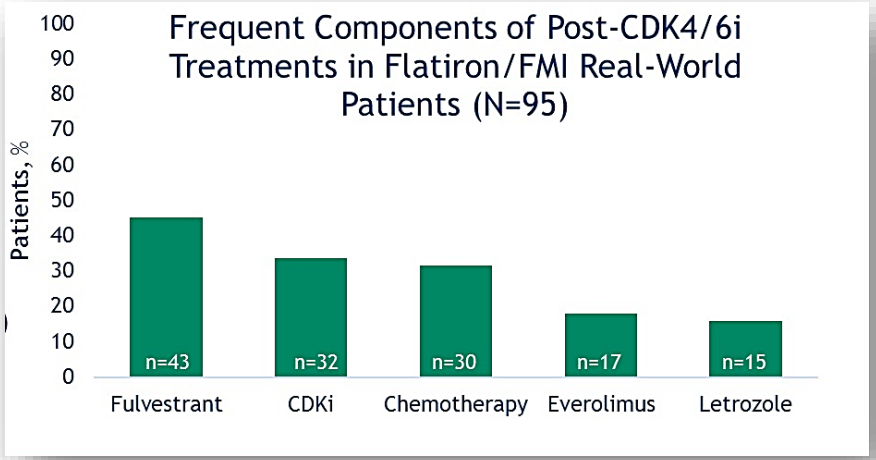
SOLAR-1: PFS and OS results in *PIK3CA*mut cohort

PFS



Median PFS 11.0 vs 5.7 months
HR 0.65 (0.50-0.85)
P=0.00065

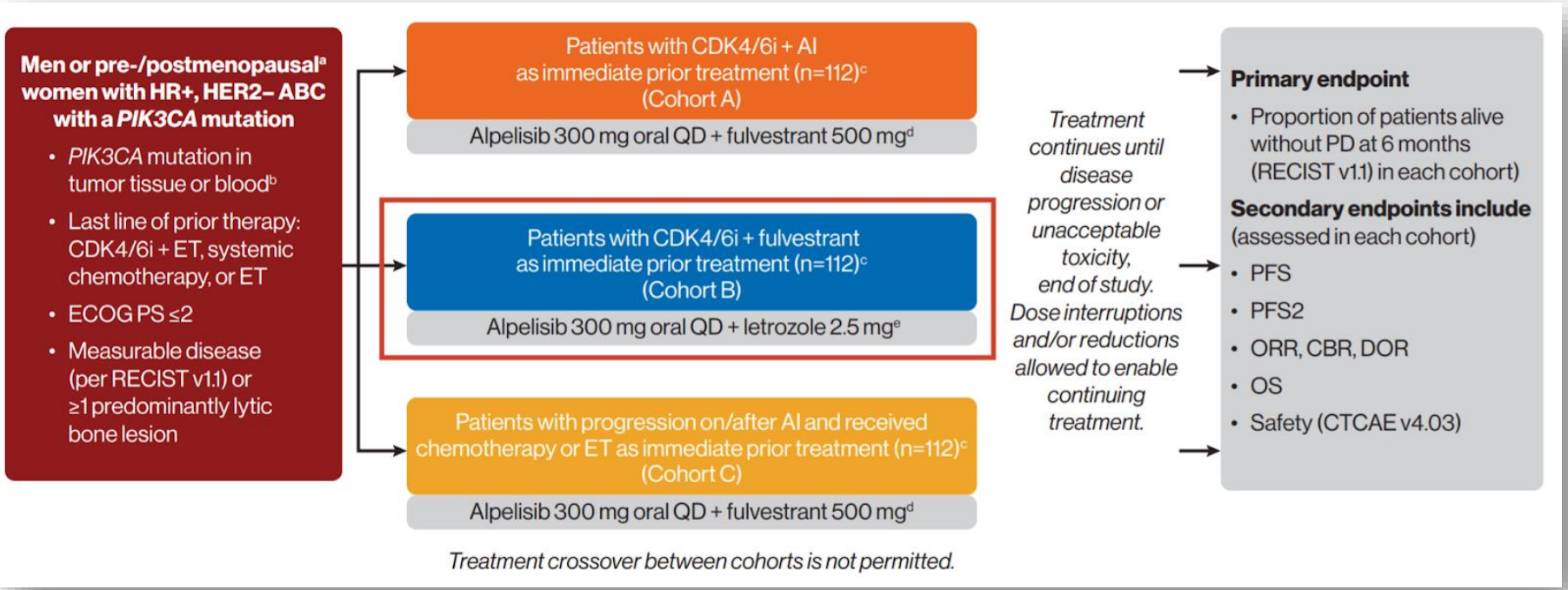
Only 5,9% prior CDK4/6i



Median PFS (unadjusted):
3.6 months (95% CI 3.1-6.1)

André F, NEJM 2019; André F, ESMO 2020

SABCS BYLieve: Cohort B



BYLieve cohort B results into context

	SOLAR-1 Fulv + Alp	BYLieve cohort A Fulv + Alp	BYLieve cohort B Let + Alp
1st line 2nd line 3rd line	52% 47% -	11.8% 70.1% 16.5%	1.6% 52.4% 44.4%
Prior CDK4/6i	5.9%	100%	100%
mPFS (months)	11.0	7.3	5.7
ORR%	36%	21%	18%
CBR%	57%	42%	32%
Decrease in best % change from baseline	75.6%	70.1%	66.3%
AEs leading to discontinuation	25%	20.5%	14.3%

>80% progressed on prior AI

5.7 months mPFS compares favorably with available data on post-CDK4/6i tx

Improvement in toxicity management with increasing experience?

André F, NEJM 2019; Rugo H et al, ASCO 2020; Rugo H et al, SABCS 2020

BYLieve: conclusion

- **BYLieve cohorts A and B** support Alpelisib + ET as a treatment option after CDK4/6i for *PIK3CA*-mut patients.
- **In cohort B**, efficacy of Alpelisib + Letrozole was demonstrated despite >80% of pts progressed on prior AI.
  - Reasonable to expect substantial rate of ESR1 mutations
  - Any role for combining Alpelisib with new SERDs in this context?
- **Careful safety management** is key to maintain dose intensity.

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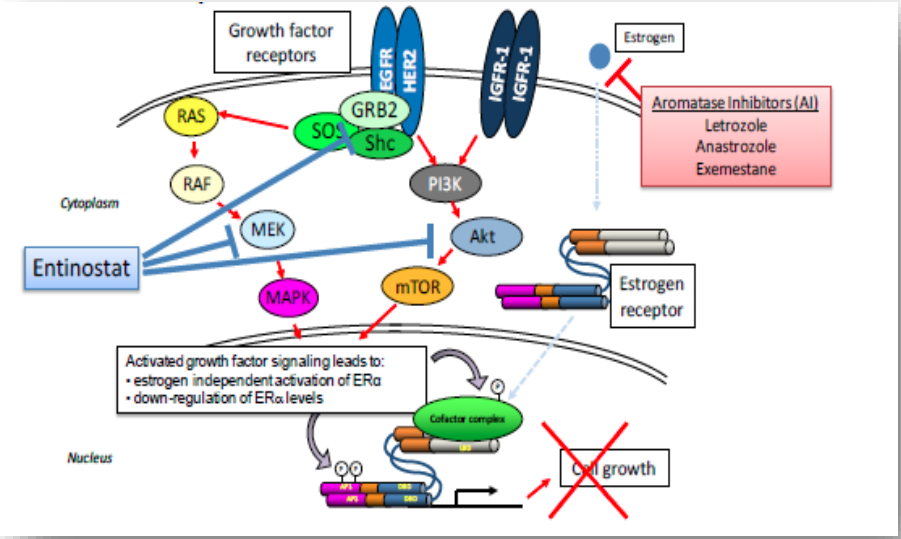
Results from E2112: Randomised phase 3 trial of endocrine therapy plus entinostat/placebo in patients with HR+ MBC.

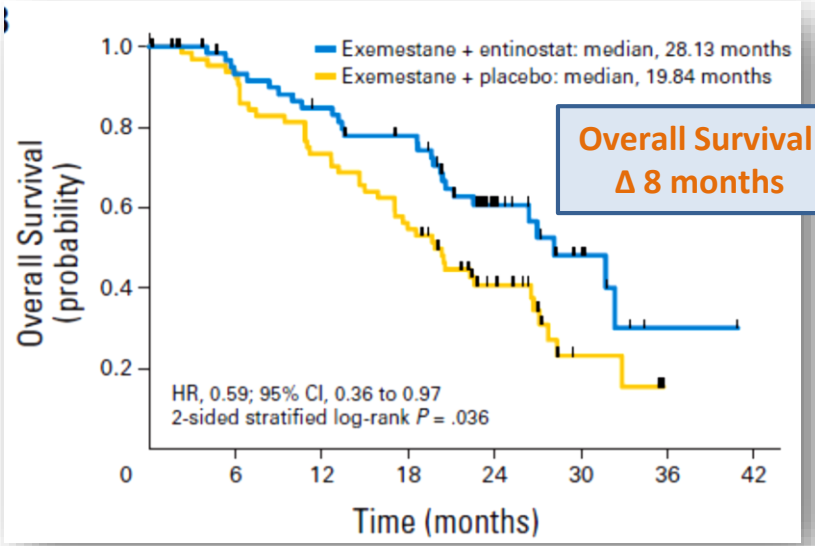
Connolly RM et al, Abstract nr GS4-02.

Rationale for E2112

Entinostat: selective oral class I histone deacetylase (HDAC) inhibitor
Overcomes endocrine therapy resistance in Letrozole-resistant mouse models

Phase 2 ENCORE 301 trial: Improvement in progression-free (PFS) and overall survival (OS) with addition of Entinostat to Exemestane, versus placebo





Yardley DA. JCO 2013, Yardley DA. SABCS 2011, Sabnis G. Mol Canc Ther 2013

E2112 Study Design

N=600
NCT02115282

Eligible:

Advanced breast cancer

HR+, HER2-

Pre/peri/post-menopausal women and men

Progression on prior non-steroidal AI

≤ 1 prior chemo for metastatic disease

RANDOMIZE

Exemestane 25mg po daily plus ENTINOSTAT 5mg po weekly*

Exemestane 25mg po daily plus PLACEBO 5mg po weekly*

Stratification

1) Prior AI (adjuvant/metastatic)
2) USA, versus elsewhere
3) Visceral disease, versus not
4) Prior fulvestrant, versus not

Blood sampling: Baseline (C1D1), 2 weeks (C1D15)

***Treatment until Progression/Intolerance.**

Premenopausal/male receive goserelin on C1D1 and q28 days

AI, aromatase inhibitor; HR, hormone receptor

E2112 Study Design

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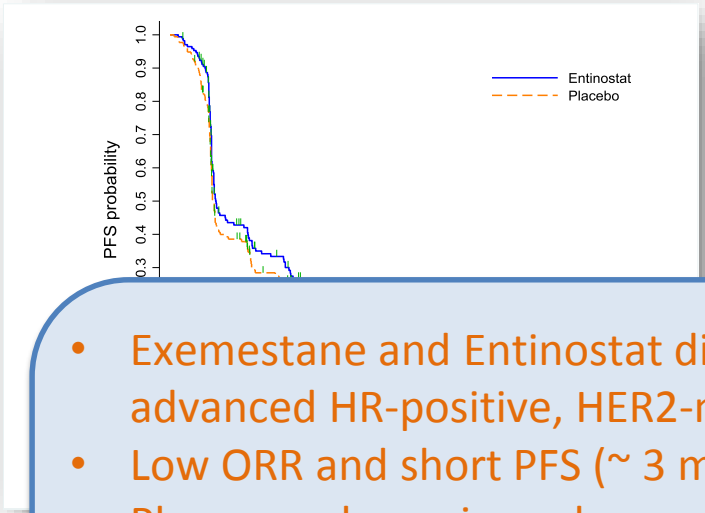
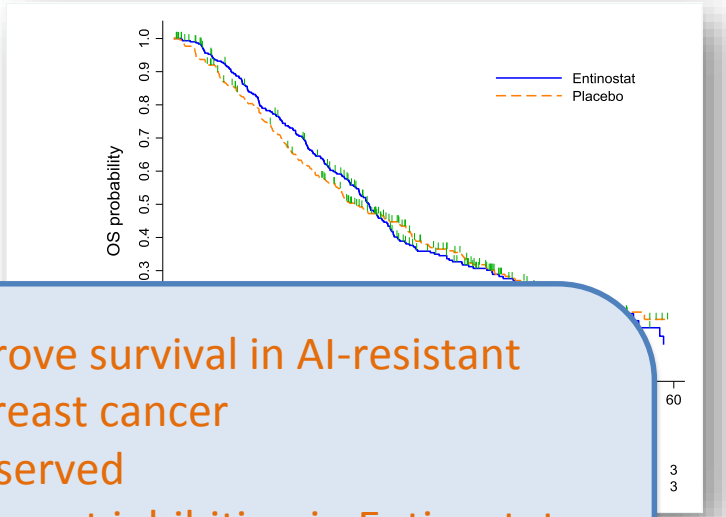
PFS



OS



- Exemestane and Entinostat did not improve survival in AI-resistant advanced HR-positive, HER2-negative breast cancer
- Low ORR and short PFS (~ 3 months) observed
- Pharmacodynamic analyses confirmed target inhibition in Entinostat-treated patients (lysine acetylation but no correlation with PFS)

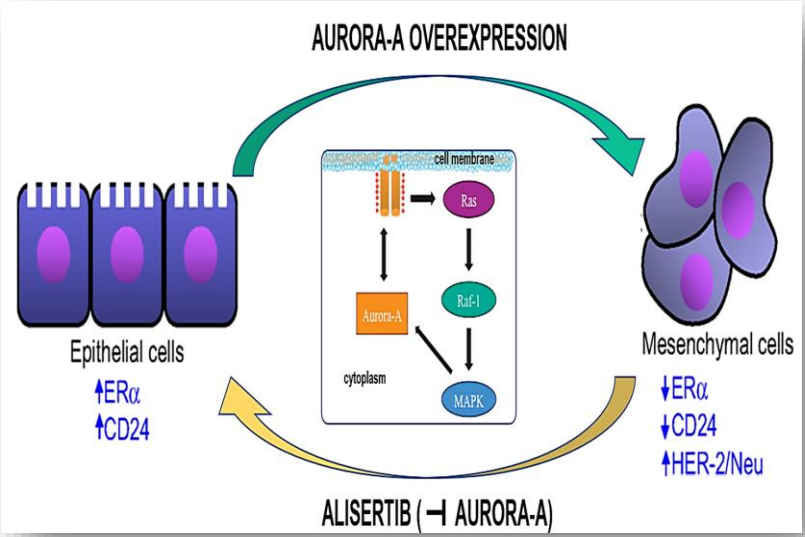
Results highlight importance of phase 3 confirmation of promising phase 2 data

Results of TBCRC 041

Haddad T et al, PD 2-05

TBCRC 041: Background

Rationale



In ER+ BC models AURKA activation induces EMT and expansion of tumor-initiating cells→ loss of ER expression, endocrine resistance[1,2].

Randomized phase 2 trial

90 Post-menopausal women

ECOG 0-1

Prior Fulvestrant ≤2 CT lines

R 1:1

Alisertib
pulse dose (50 mg twice on dd 1-3, 8-10, 15-17 q28 dd)

Alisertib + Fulvestrant
fixed dose

Modified from D'Assoro AB et al, Oncogene 2014 and Niu H et al, Frontiers in Oncol, 2015

1. Opyrchal M, Plos One 2014; 2. **D'Assoro AB et al, Oncogene 2014; 3**. Melichar B, Lancet Oncol 2015; 4. Haddad TC, Br Canc Res and Treat 2018

TBCRC041: results

Clinical Outcomes		
	Alisertib (n=45)	Alisertib + Fulvestrant (n=45)
Confirmed Responses	8 PR	1 CR; 8 PR
Objective Response Rate	17.8% (90% CI: 9.2-29.8%)	20.0% (90% CI: 10.9-32.3%)
Clinical Benefit Rate (24-week)	42.2% (90% CI: 29.7-55.6%)	28.9% (90% CI: 18.0-42.0%)
Median PFS (months)	5.6 (95%CI: 3.9 – 9.3)	5.1 (95%CI: 3.8 – 7.6)
Deaths	n=10	n=14
6-month OS rate	90. 6% (95% CI: 82.2-99.8%)	75.6% (95% CI: 63.9-90.2%)

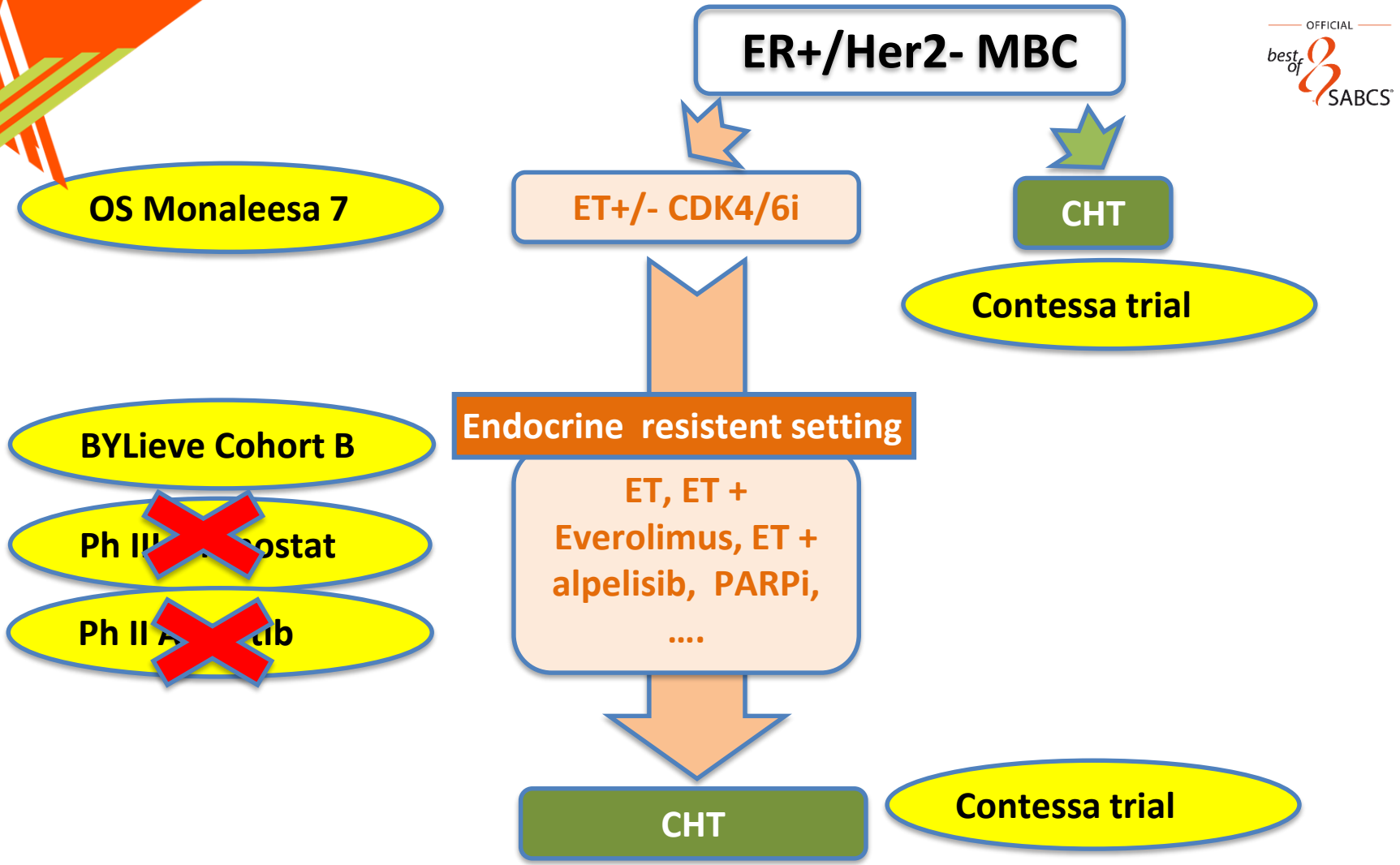
Grade 3-4 neutropenia: 42% in both arms

Addition of fulvestrant to alisertib did not improve efficacy:

- combination arm was enriched for more heavily pre-treated patients
- ~100% of patients received previous Fulvestrant in the advanced setting

Alisertib alone showed a promising efficacy in the post-CDK4/6i setting:

- mPFS of 5.6m compares favorably with available data on post-CDK4/6i therapies


ER+/Her2- MBC
OS Monaleesa 7
ET+/- CDK4/6i
CHT
Contessa trial
Endocrine resistent setting
BYLieve Cohort B
ET, ET +
Everolimus, ET +
alpelisib, PARPi,
....
CHT
Contessa trial

Luminal MBC

- CDK4/6i are SOC, all patients with metastatic disease should receive these drugs
- Drug activity of post CDK4/6i therapy is not good enough

Goals: improving OS, improving QoL, palliation of symptoms

- Agents under investigations:

SERDs
- EMERALD: Elacestrant vs choice ET
- AMEERA: SAR439859 vs let + Pal
- GDC9545 + Pal vs Let+ Pal
- SERENA-2: AZD9833vs Fulvestrant

AKT i
- CAPitello-291: Ful +- capivasertib
- IPATunity 150: Pal/Ful +/- ipatasertib

SER/SERM
- ELAINE: Lasofoxifene vs Fulvestrant
- Enobosarm mono

ADC's
- Sac Gov
- Tras Deruxtecan
- Ladiratuzumab vedotin (Liv1a)

HER2+ Metastatic Breast Cancer

SABCS
SAN ANTONIO BREAST CANCER SYMPOSIUM

HER2+ MBC

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Taxane + HP

T-DM1

Tuc + Cape + H

HER2CLIMB consistent benefit by HR status

T-DXT

Update DESTINY01

Nera + Cape

NALA CNS activity

Margetuximab

SABCS SAN ANTONIO BREAST CANCER SYMPOSIUM

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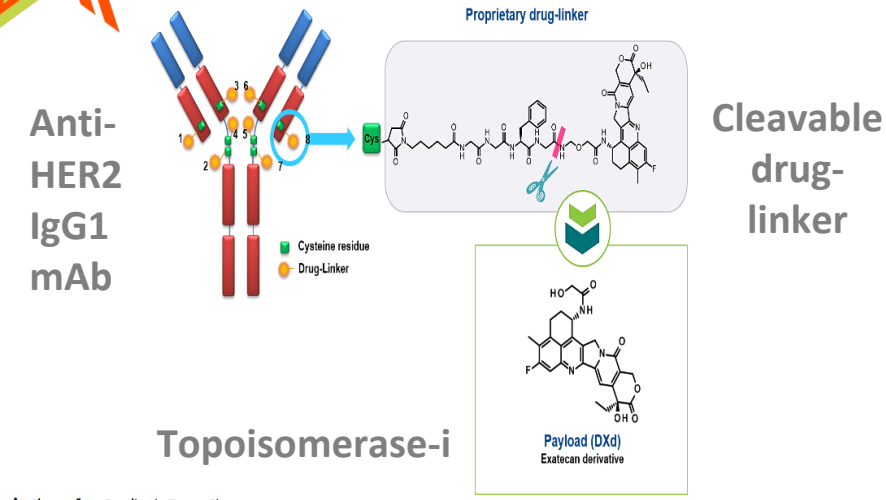
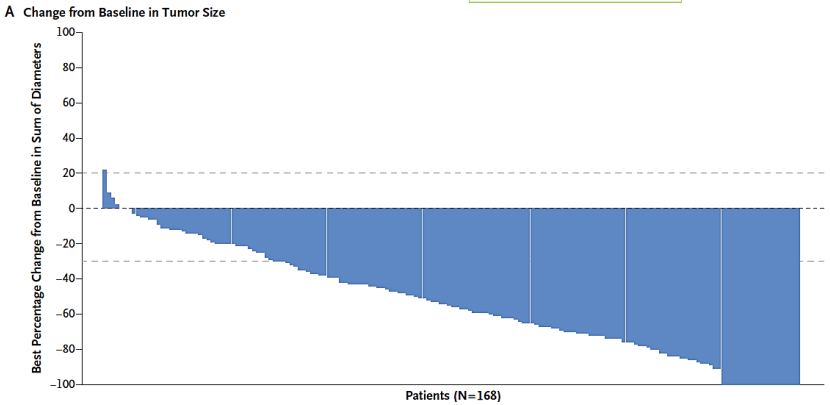
Updated Results From DESTINY-Breast 01, a Phase 2 Trial of Trastuzumab Deruxtecan (T-DXd) in HER2-Positive MBC

Modi et al, et al. Abstract 1199

Trastuzumab Deruxtecan: a HER2 ADC





DESTINY-Breast01:

Ph II T-DXd in patients with HER2+ MBC

Median lines of therapy = 6 (range: 2-27)

- 100% received prior trastuzumab & TDM1
- 66% received prior pertuzumab
- 54% received other HER2 therapies

Results: N=184, median follow up ~11 mo

ORR 61%

mPFS 16.4 mo; mPFS in brain mets 18.1 mo

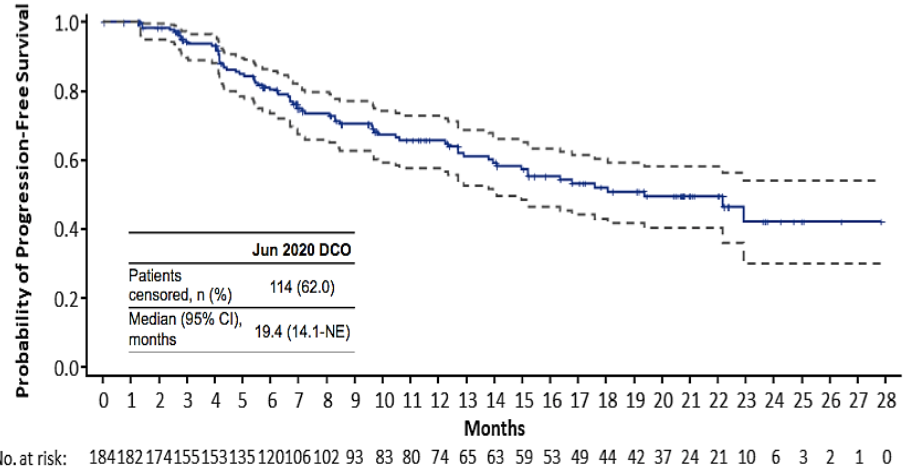
mOS Not Reached

FDA approval 12/20/19:
≥2 anti-HER2 based lines

Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185.
Pondé N, et al. *Curr Treat Options Oncol*. 2019;20(5):37. Modi et al *NEJM* 2020

DESTINY-Breast01 mFU 20,5m

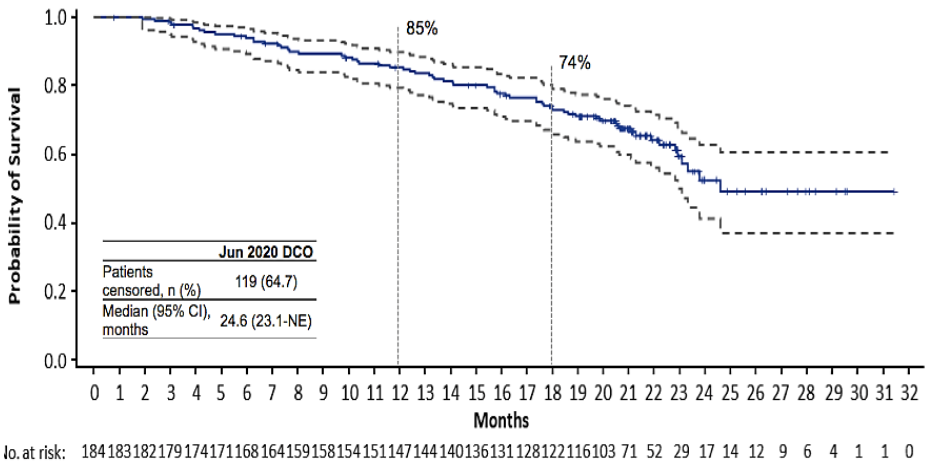
Median PFS 19.4 mo (14.1 – NE)



Median OS 24.6 mo (23.1 - NE)

Only 35% of events

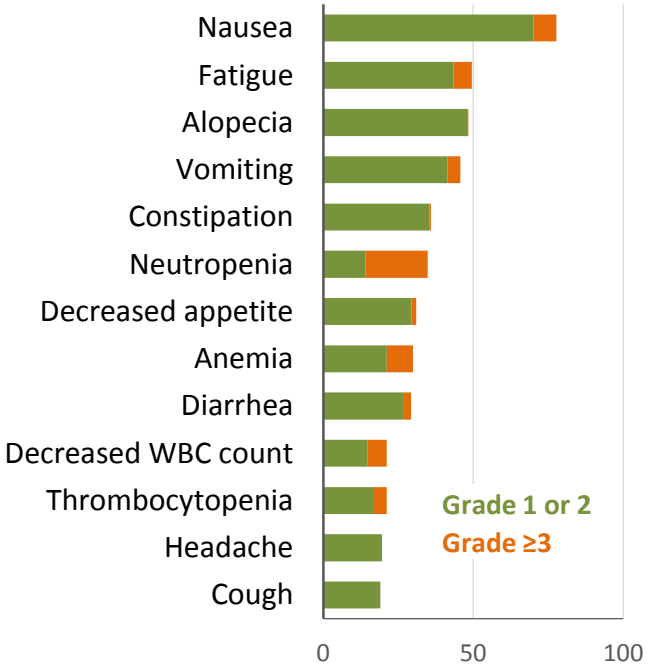
74% of patients alive at 18m



T-DXT continues to demonstrate clinically meaningful and durable efficacy

Modi et al, Abstract #1190 SABCS 2020

DESTINY Breast01: TEAEs in >15% of Patients

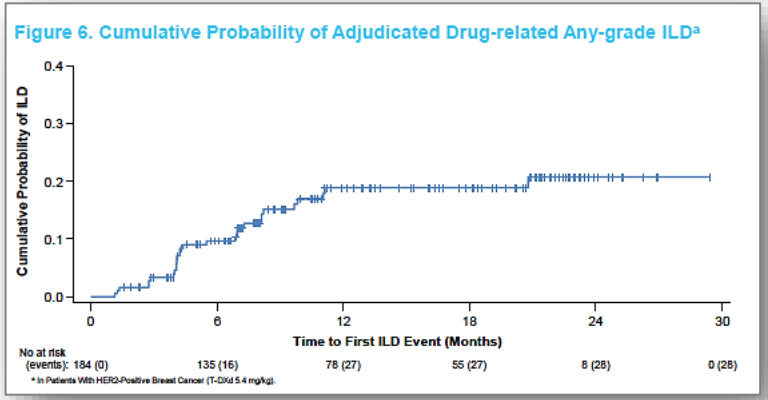


* Interstitial lung disease: 3 additional cases

Interstitial lung disease , n (%)	T-DXd 5.4 mg/kg (N=184)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade/ Total
Aug 2019 data cutoff	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**
June 2020 data cutoff	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	**28 (15.2)**

[a] As determined by an independent ILD adjudication committee. At data cutoff, 1 grade 1 event and 1 grade 3 event were pending adjudication.

* Median to onset of ILD was 27.6 weeks (range, 6-76 weeks)



ILD requires awareness via monitoring, dose interruptions and modification and adherence to management guidelines

Modi et al, NEJM 2019; SABCS 2020

Conclusions HER2+ MBC

- **Major progress in OS**
- **New therapeutics with CNS activity**
- **Still many challenges:**
  - Prevention of CNS
  - Resistance mechanism? Prevention?
  - HER2 TKI, value of continuation? Switch?
  - Immunotherapy?
  - Long responders: are we curing patients? Stop R/?

Questions?

Is Doctor Vogel on the line?