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Progresses in Breast Cancer therapies changing Clinical Practice or Emerging

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BSMO-Bordet meeting - November 2020

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Disclosures

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Roche, Lilly, Amgen, EISAI, BMS, Pfizer, Novartis, MSD, Genomic Health, Ipsen, AstraZeneca, Bayer, Leo Pharma

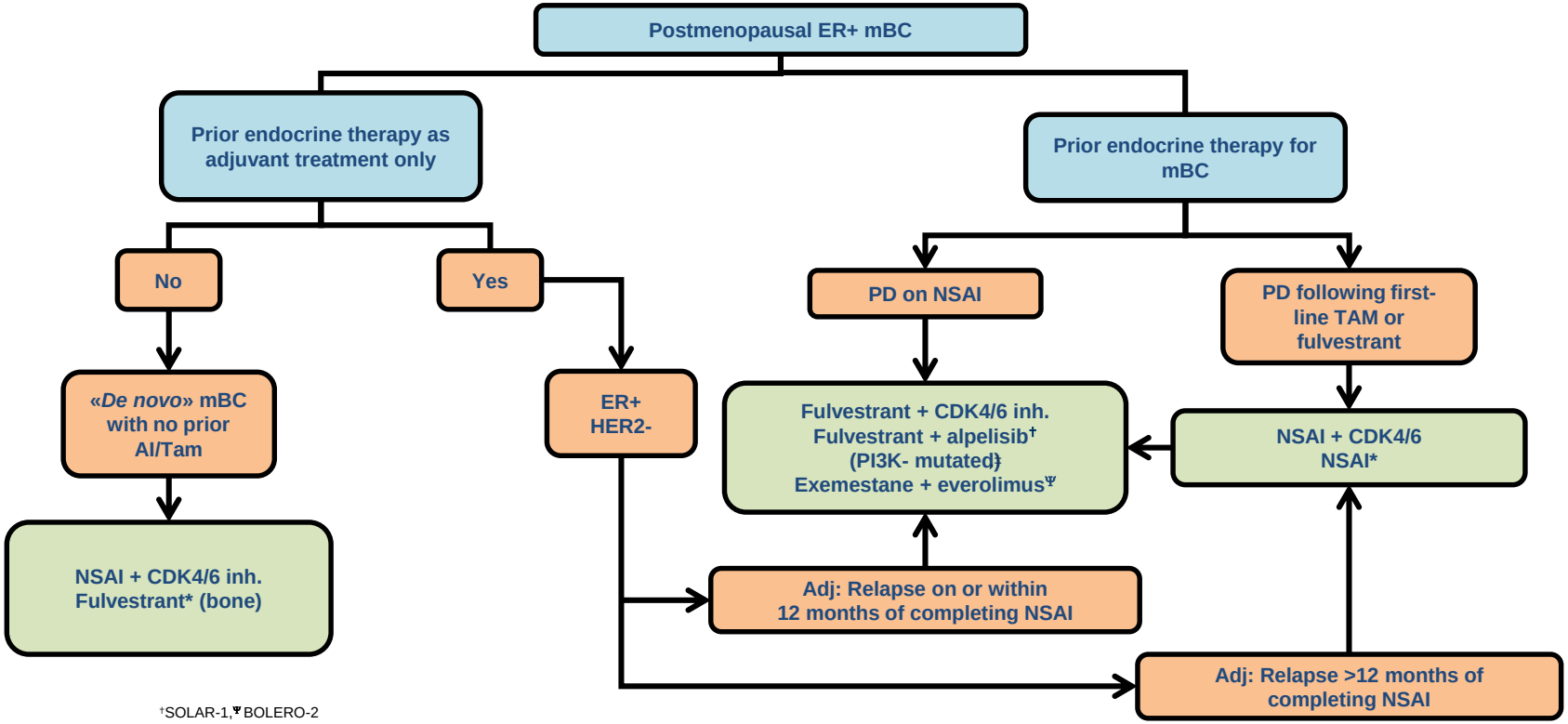
Ten different molecular subtypes of Breast Cancer with therapeutic implications

- ER+ and/or PgR+ (70% of pts)
- ER+ and/or PgR+ and HER-2+ (triple positive)
- ER+ and/or PgR+ and PI3K-mutated (40% of pts)
- ER+ and/or PgR+ and BRCA-mutated

- HER2+ and HR- ± BRCA-mutated

- TNBC ± BRCA mutation
- TNBC + PD-L1 positive

Proposed therapeutic algorithm for luminal subtype MBC in 2020



†SOLAR-1, ΨBOLERO-2

*Pts with very limited bone disease

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Awada A, et al. ESMO Open. 2019.

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Trials in advanced luminal disease of interest for clinical practice

Aim: Best endocrine partner with CDK4-6 inhibitor ?

Parsifal

First line « End. sensitive » N = 486 — R →
- Fulvestrant (F) + palbo
- Letrozole (L) + palbo

Median PFS 28m (F) vs 33m (L)
- Failed to show superiority or non inferiority of F !
- Same dose intensity

Aim: Does Alpelisib work after CDK4-6 inhibitor ?

BY-lieve

Prior CDK4-6 inh →
- N = 112 Cohort A* Fulv + alpelisib
- N = 112 Cohort B Letrozole + alpelisib

* Median PFS 7.3m
Clinical benefit 45%
Discontinued for AE 20%
Benefit of prophyl antihistaminics (70% w/o rash)
Results cohort B pending

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ASCO 2020 – abst 1007/1006

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CDK4/6i in HR+/HER2+ Disease
MonarcHER Study

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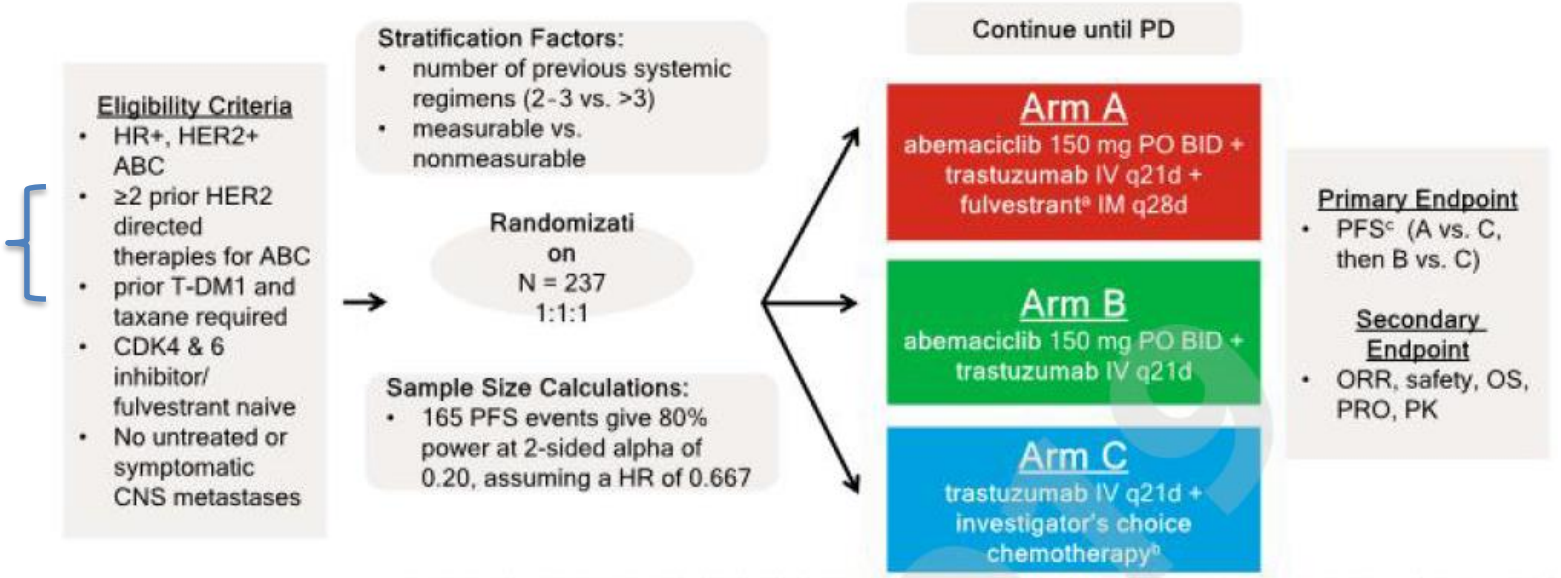
monarcHER STUDY DESIGN



Abbreviations: ABC = advanced breast cancer, HR+ = hormone receptor-positive, HER2(+) = human epidermal growth factor receptor-2 (positive), n = number of patients, PD = progress disease, BID= twice daily, q21d= every 21 days, PFS = Progression Free Survival, ORR = Objective Response Rate, OS = Overall Survival, PRO = Patient Reported Outcomes, PK = pharmac

[a]Dosingper fulvestrant label

[b]Standardof-care single-agent chemotherapy should include approved drug in breast cancer.

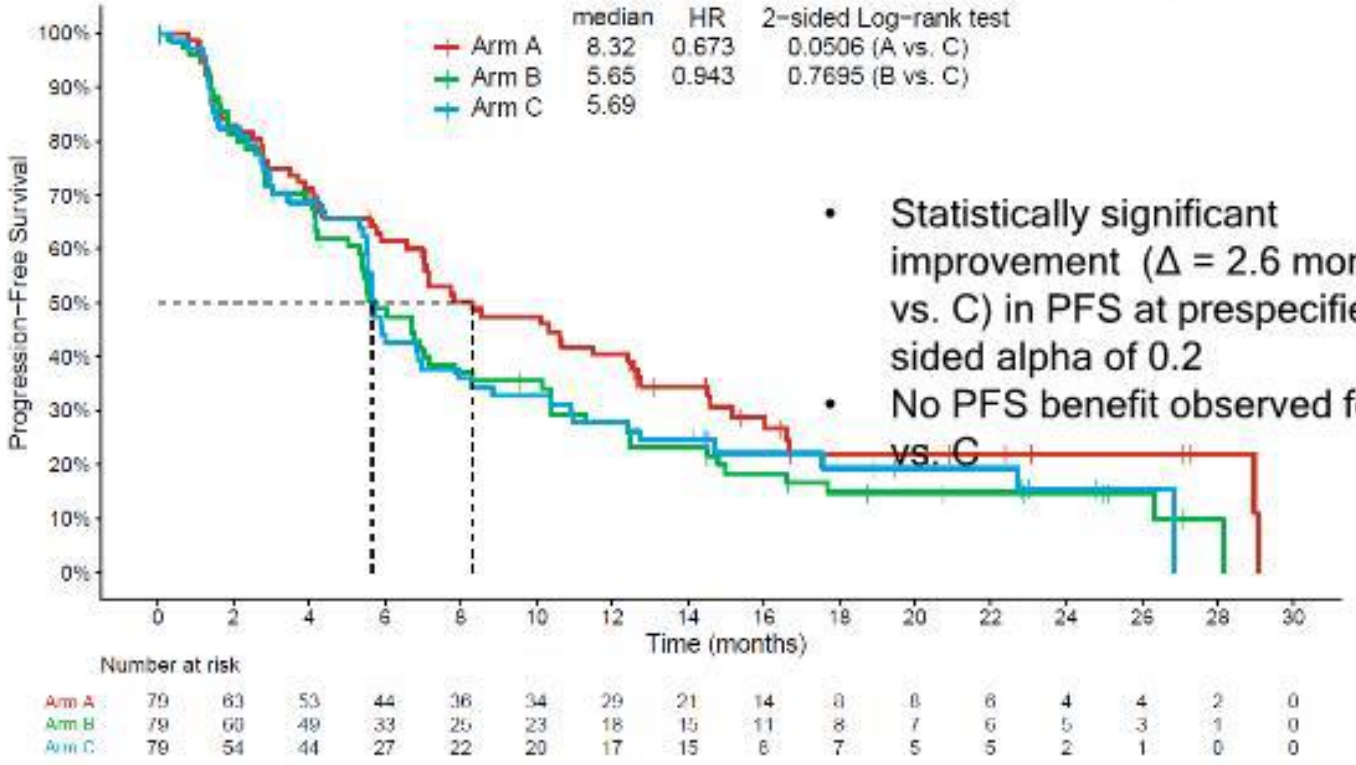
[c]Investigatorassessed

ESMO congress BARCELONA 2019

Tolaney S et al. 2019

MONARCHER PRIMARY ENDPOINT: PFS

Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy

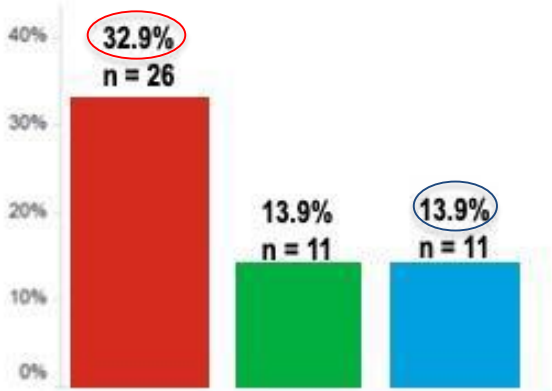


- Statistically significant improvement (Δ = 2.6 months A vs. C) in PFS at prespecified 2-sided alpha of 0.2
- No PFS benefit observed for B vs. C

Tolaney S et al. 2019

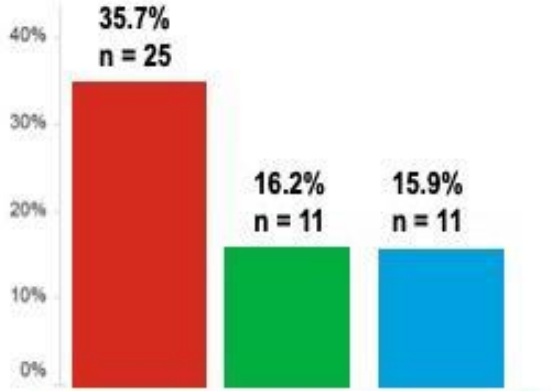
CONFIRMED BEST OVERALL RESPONSE RATE

Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy



ITT Population
Total N = 237

	Arm A N=79	Arm B N=79	Arm C N=79
95% CI (%)	(22.5-43.3)	(6.3-21.6)	(6.3-21.6)
Stratified 2-sided p-value (vs Arm C)	0.0042	1.0000	-
Duration of Response, months	12.5	9.5	not reached



Measurable Disease
Total N = 207

	Arm A N=70	Arm B N=68	Arm C N=69
95% CI (%)	(24.5-46.9)	(7.4-24.9)	(7.3-24.6)
Stratified 2-sided p-value (vs Arm C)	0.0111	1.0000	-
Duration of Response, months	10.4	9.5	not reached

BARCELONA 2019 ESMO congress

Tolaney S et al.
2019

ALPELISIB + Fulvestrant in HR+, HER2- MBC
Results of the phase III SOLAR-1 Trial

André F. et al
ESMO 2018 - NEJM 2019

Men or postmenopausal women, with HR+, HER2– ABC

- Recurrence/progression on/after prior AI
- Identified *PIK3CA* status (in archival or fresh tumor tissue)
- Measurable disease or ≥1 predominantly lytic bone lesion
- ECOG performance status ≤1

(N=572)

PIK3CA-mutant cohort (n=341)

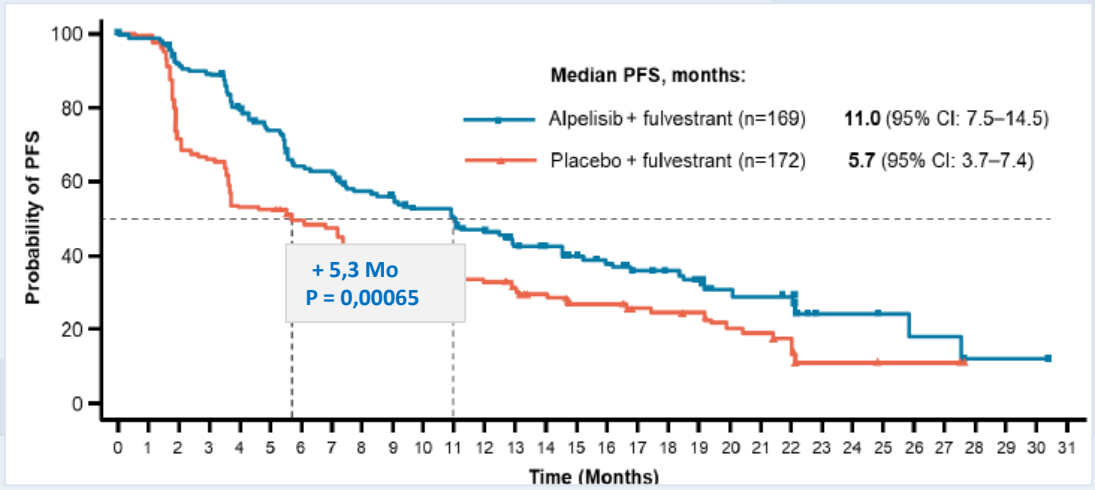
R

ALP 300 mg QD PO + FUL 500 mg IM* n=169

PBO + FUL 500 mg IM* n=172

Primary endpoint

- **PFS in *PIK3CA*-mutant cohort**



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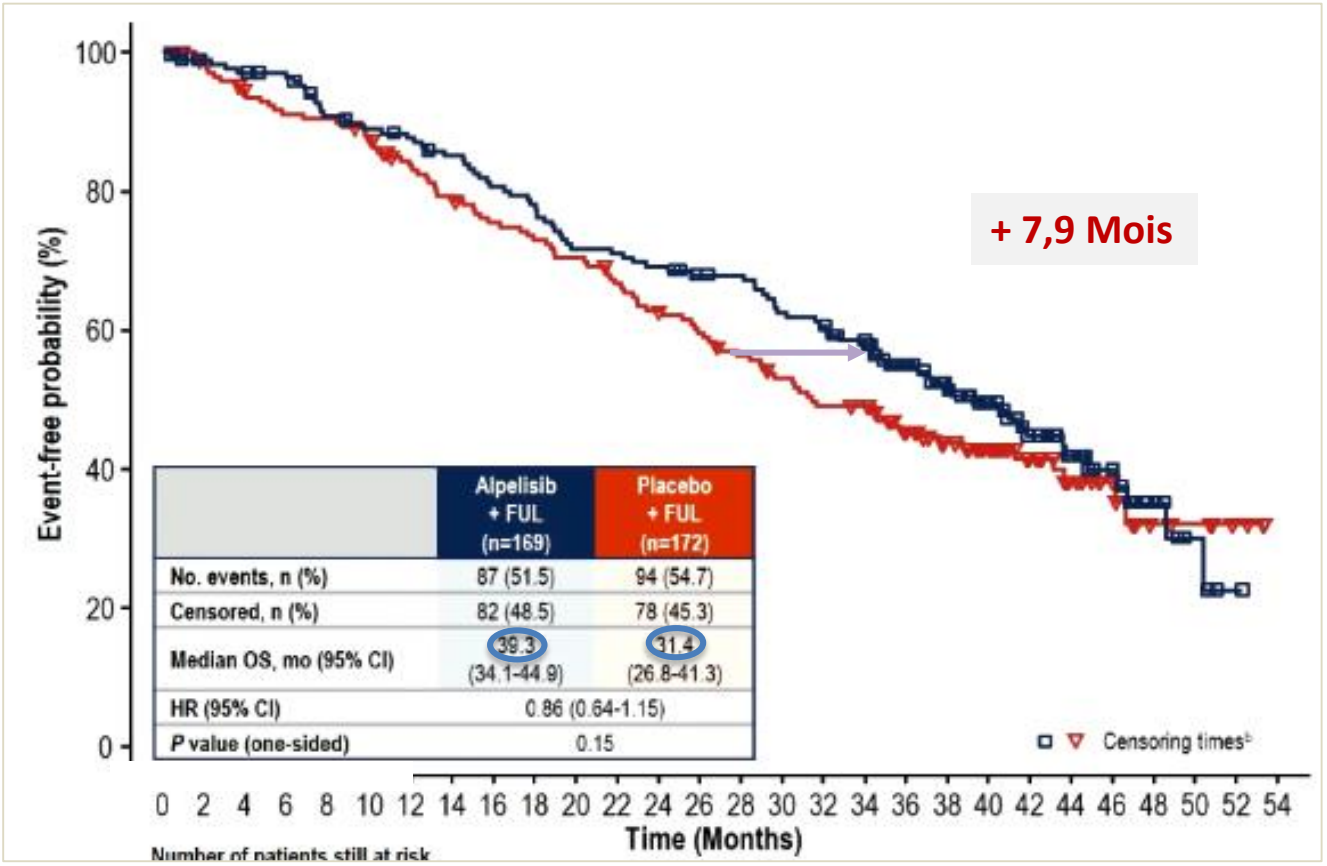
VIRTUAL 2020 ESMO congress

Overall Survival Results From SOLAR-1, a Phase 3 Study of Alpelisib + Fulvestrant for HR+, HER2– Advanced Breast Cancer



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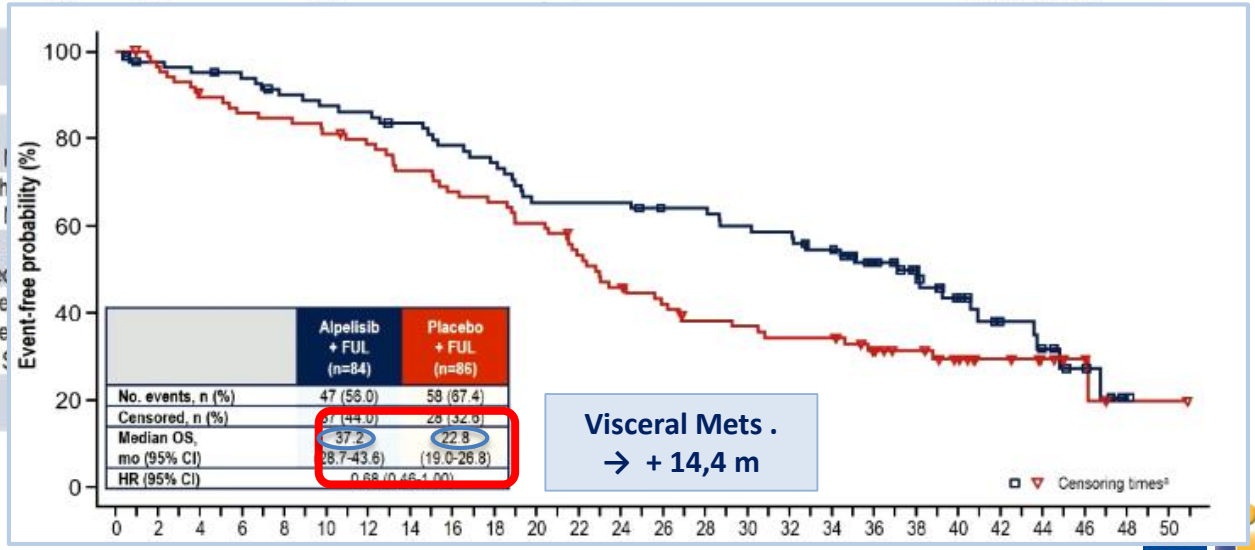
VIRTUAL 2020 ESMO congress

Overall Survival Results From SOLAR-1, a Phase 3 Study of Alpelisib + Fulvestrant for HR+, HER2– Advanced Breast Cancer

SOLAR-1: OS by Subgroups

Subgroup		No. of Patients	No. Patients with Events	Hazard Ratio (95% CI)
All subjects		341	181	0.86 (0.64-1.15)
Lung/liver metastases[a]	Yes	170	105	0.68 (0.46-1.00)
	No	171	76	1.18 (0.74-1.86)
Bone-only disease	Yes	77	31	1.74 (0.83-3.68)
Prior CDK4/6 inhibitor treatment[a]				
ER status				
PR status				
ER and PR status	Both			
	Positive -			
Line of advanced anti-cancer treatment	Sec			
Endocrine status	Primary re			
	Secondary re			
ECOG status				

Full Analysis Set, *PIK3CA*-mutant cohort



Visceral Mets .
→ + 14,4 m

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MonarchE and PALLAS : Study characteristics

CHARACTERISTICS	MONARCHE	PALLAS
Study drug (2y) Inclusion period	Abemaciclib 07/17 – 08/19	Palbociclib 09/15 – 11/18
Stratification factors	Previous chemo Menopausal status Region	Stage II A vs IIB/III Chemo yes/no Age (50), Region
Pts eligibility	LN + (≥4) or LN + (1-3) + T≥5cm or gr3 or ki67 ≥ 20%	Stage II – III
Statistics	85% power for HR 0.73 5y IDFS 82,5% in control Arm (390 IDFS events)	85% power for HR 0.75 (IDFS)
Interim analysis	50% of required events	1st futility (167 events) 2d futility (313 events) 469 IDFS for final analysis

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Johnston et al, JCO, 38, 2020
Mayer et al, ESMO 2020

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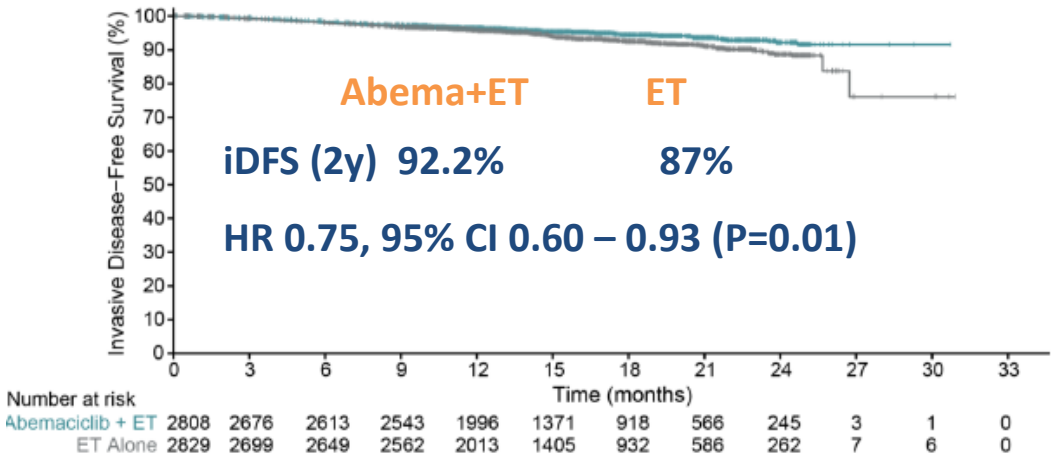
Abemaciclib (MONARCHE) and Palbociclib (PALLAS) in the Adjuvant Setting: Primary end point results

MonarchE IDFS (med FU: 15,5 mo.)



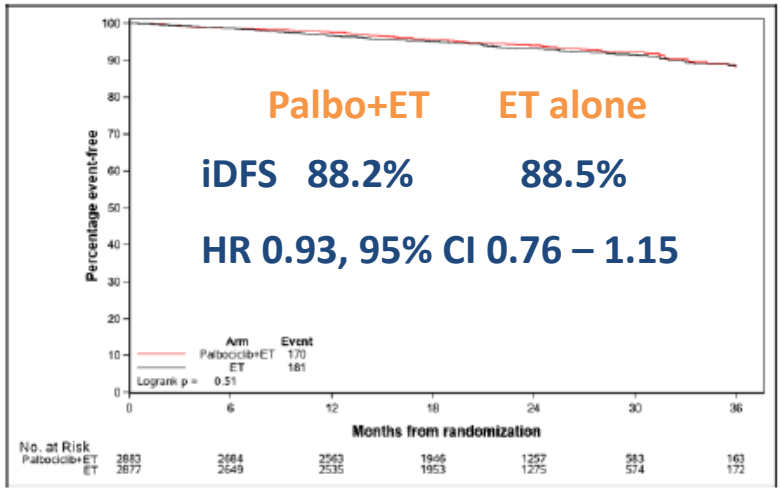
Abema+ET **ET**

iDFS (2y) 92.2% 87%

HR 0.75, 95% CI 0.60 – 0.93 (P=0.01)

Johnston SRD et al, JCO 2020, LBA5

PALLAS IDFS (med FU: 23.7 mo)



Palbo+ET **ET alone**

iDFS 88.2% 88.5%

HR 0.93, 95% CI 0.76 – 1.15

Mayer, EL et al, ESMO 2020, LBA 12

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Why do MonarchE and PALLAS results differ?

	MONARCHE	PALLAS
Selection of pts	More selective (100% high risk pts)	Less selective (60% high risk pts)
CDK 4/6 inh. features	Continuous therapy; Pan CDK inhibitor	Intermittent therapy CDK4/6
CDK4/6 discontinuation	16.6%	42%
CDK4/6 reduction	41%	89%
Sites of recurrence	Bone: 30 (Abem.) vs 53% (ET alone)	NA
	Visceral: 69 (Abem.) vs 59%	NA

Is abemaciclib a standard of care in EBC?

The decision to use adjuvant CDK4/6 inhibitor (Abemaciclib) therapy is more complex than the obtained results of iDFS with a median FU of only 15 months.

- **OS data are important (awaited)**
- **More mature data of iDFS are important (at SABCS?)**
- **QoI and PROs are important**
- **Financial aspect is important**

Nevertheless the results of Abemaciclib in high risk population are very encouraging.

HER-2 Positive Breast Cancer: Understanding the present, Moving to cure this disease ?!

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Biomarkers (early FDG–PET) in HER2+ early disease : who can forego chemotherapy ?

« Excellent responders » to

↓

Trastuzumab + Pertuzumab

↓

identified by

FDG-PET

↓

« Phergain » neoadjuvant trial

PET response (SUV ↓ by ≥ 40%)

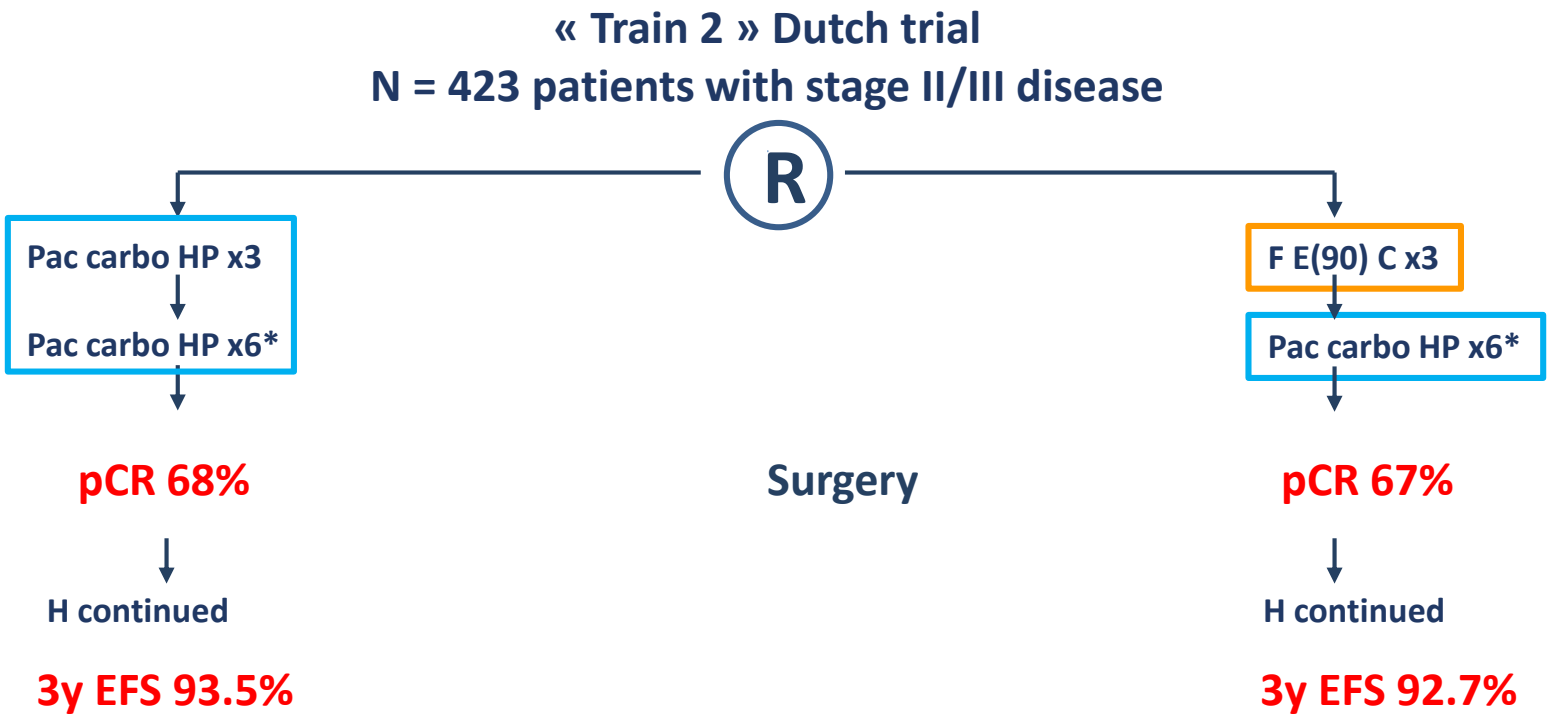
after 2# (= 80% of pts)

↓

pCR ≈ 40%

ASCO 2020, abst 503

HER2+ BC: Optimizing neoadjuvant therapy Anthracyclines needed?



More ↓ in LVEF with 11% stopping H early

***and** 2 acute leukemias*

ASCO 2020 – abst 501

** Paclitaxel weekly d1+8; carbo AUC 6 q3wks*

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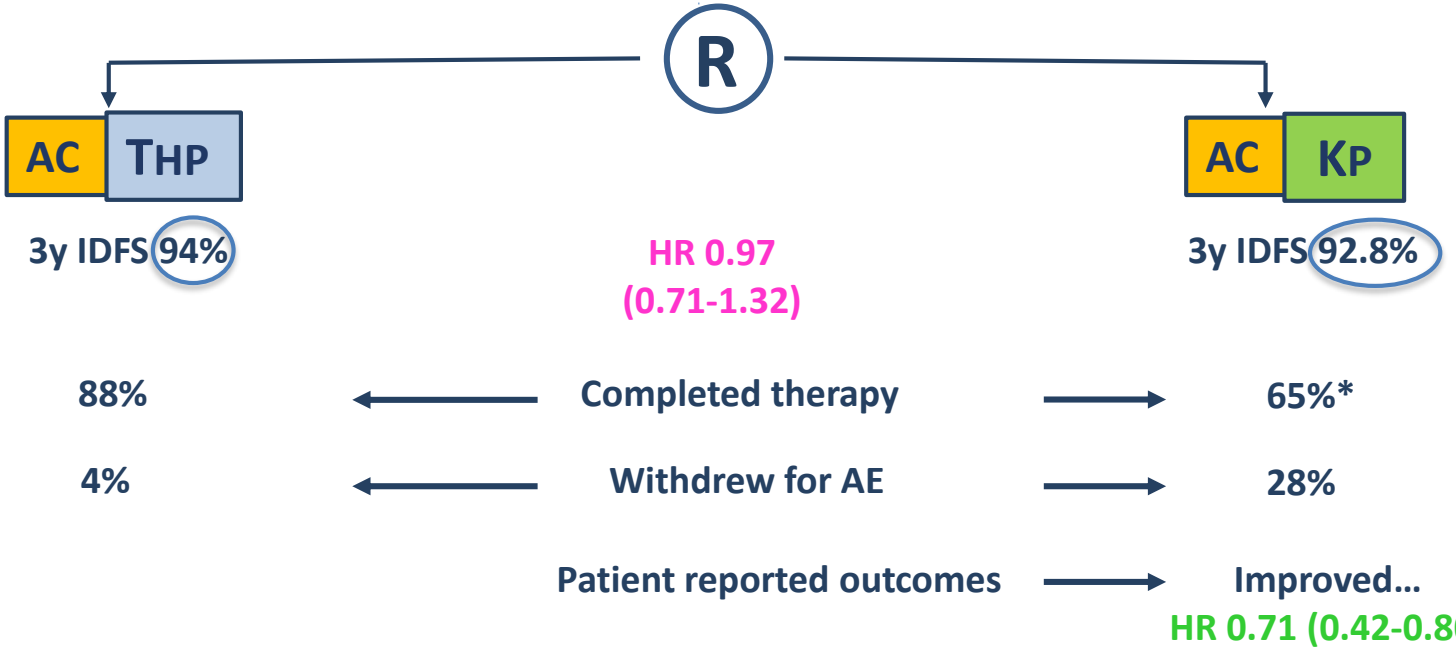
KATHERINE STUDY: Role of T-DM1 in residual disease following neoadjuvant therapy = Standard of care

HER2+ BC: Results of Adjuvant T-DM1 replacing taxane

« Kaitlin » : N = 1846 « high risk patients » (90% N+)
Median fup 57 months



** ! 18 cycles of T-DM1 planned*

T = taxane, K = T-DM1

ASCO 2020 – abst 500

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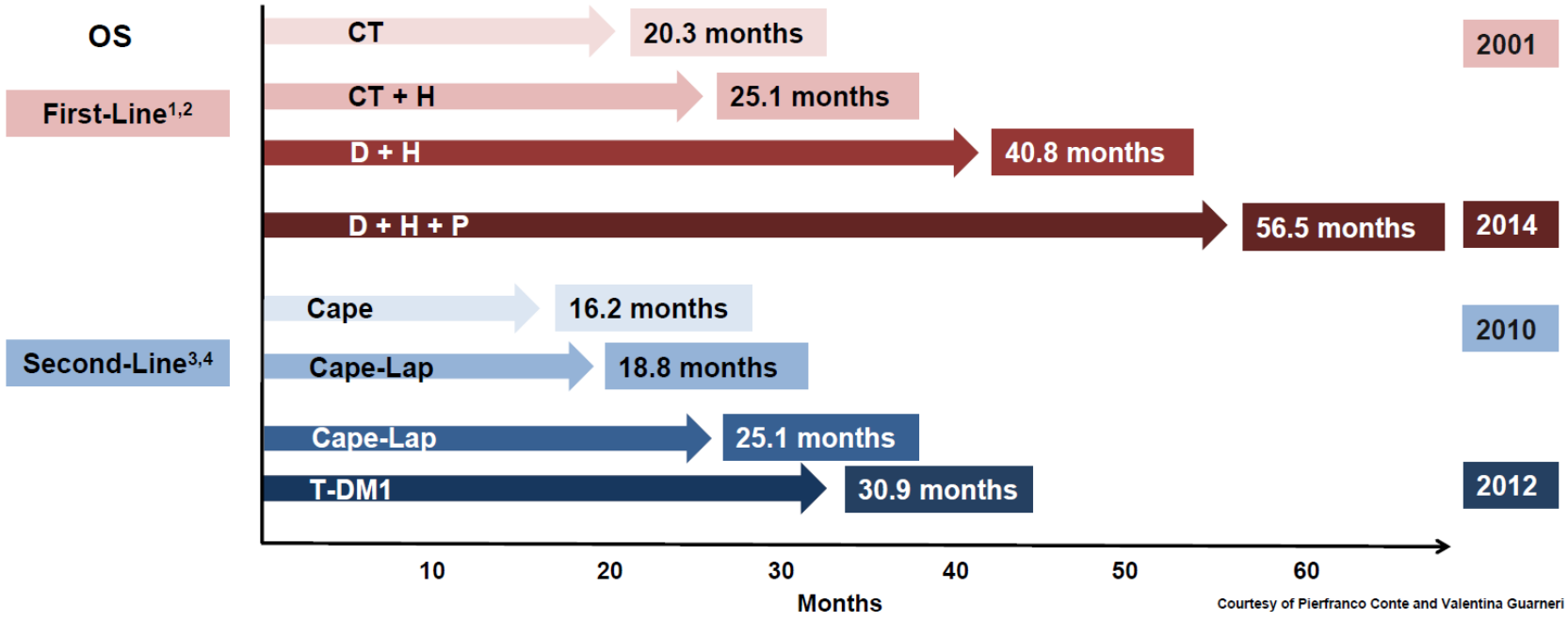
Treatment of HER2-positive MBC
Progress Over Time



Cape, capecitabine; CT, chemotherapy; D, docetaxel; H, trastuzumab; Lap, lapatinib; OS, overall survival; P, pertuzumab; T-DM1, trastuzumab emtansine

1. Slamon D, et al. *N Engl J Med.* 2001;15(1);344:783-792. 2. Swain S, et al. *N Engl J Med.* 2015;372(8):724-734. 3. Geyer C, et al. *N Engl J Med.* 2006;355:2733-2743. 4. Verma S, et al. *N Engl J* Med. 2012;367(19):1783-1791.

Investigational agents

Progress on the clinical Management of HER2 Positive advanced Breast cancer in 2020

- New HER2 agents in ABC
  - Neratinib (NALA)
  - Tucatinib
  - Pyrotinib
  - Trastuzumab Deruxtecan (DS-8201)
- Perspectives
  - Antibody drugs conjugates (high and low HER2 expressors!)

New HER2-TKIs for advanced disease

Tucatinib

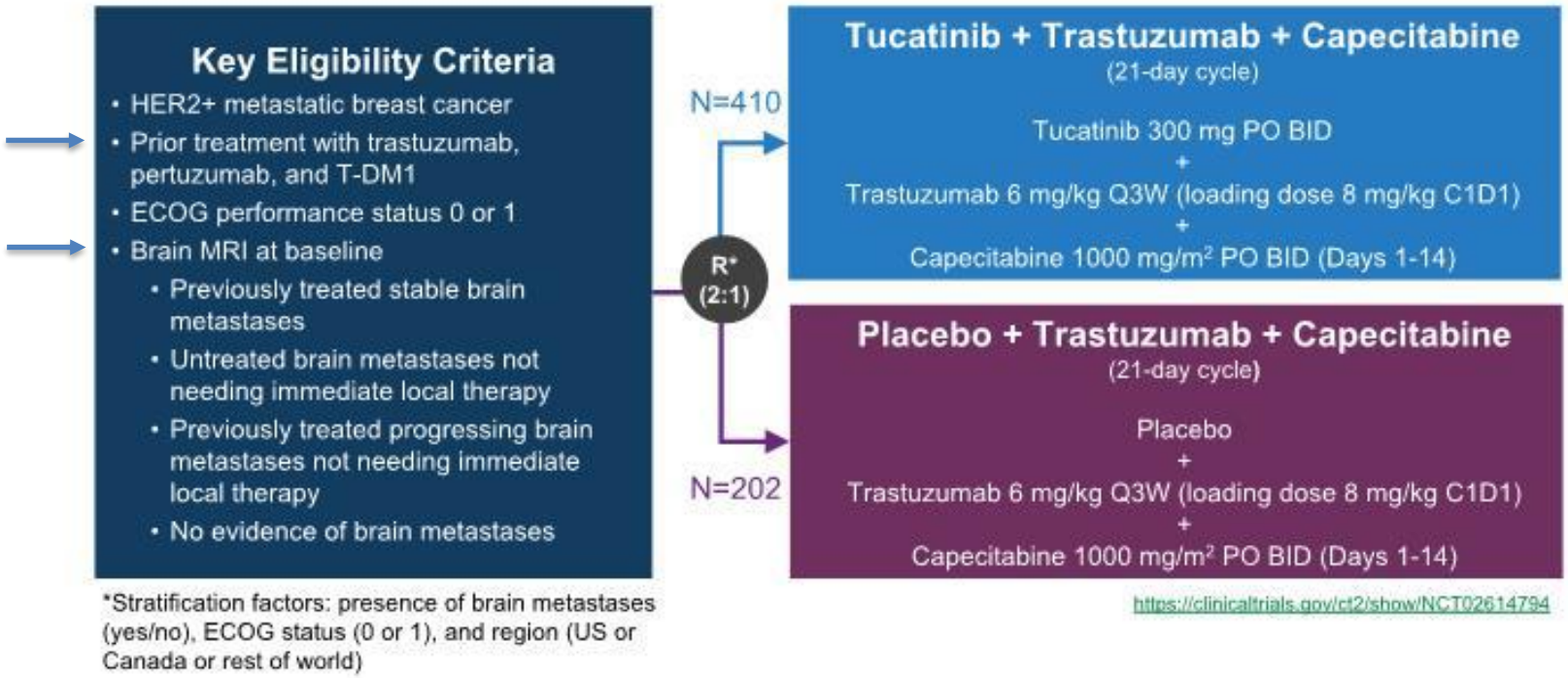
Potent HER2 TKI with minimal EGFR inhibition

Pyrotinib

Potent Pan-ErbB receptor TKI (HER1-2-4)

Tucatinib in HER2+ MBC ± Brain metastases

HER2CLIMB Trial Design



*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

https://clinicaltrials.gov/ct2/show/NCT02614794

HER2 CLIMB

Key Baseline Demographics and Disease Characteristics

Characteristic, n (%)		Total Population, N=612 TUC+Tras+Cape n=410	 Pbo+Tras+Cape n=202
Female		407 (99)	200 (99)
Age (years), median (range)		55.0 (22, 80)	54.0 (25, 82)
ECOG performance status	0	204 (50)	94 (47)
	1	206 (50)	108 (54)
Stage IV at initial diagnosis		143 (35)	77 (39)
Hormone receptor status	ER and/or PR-positive	243 (60)	127 (63)
	ER and PR-negative	161 (40)	75 (37)
Prior lines of therapy, median (range)	Overall	4.0 (2, 14)	4.0 (2,17)
	Metastatic setting	3.0 (1, 14)	3.0 (1, 13)
Presence/history of brain metastases		198 (48)	93 (46)
Treated, stable		118 (59.6)	55 (59.1)
Untreated		44 (22.2)	22 (23.7)
Treated, progressing		36 (18.2)	16 (17.2)

Baseline characteristics were balanced between endpoint populations and treatment arms

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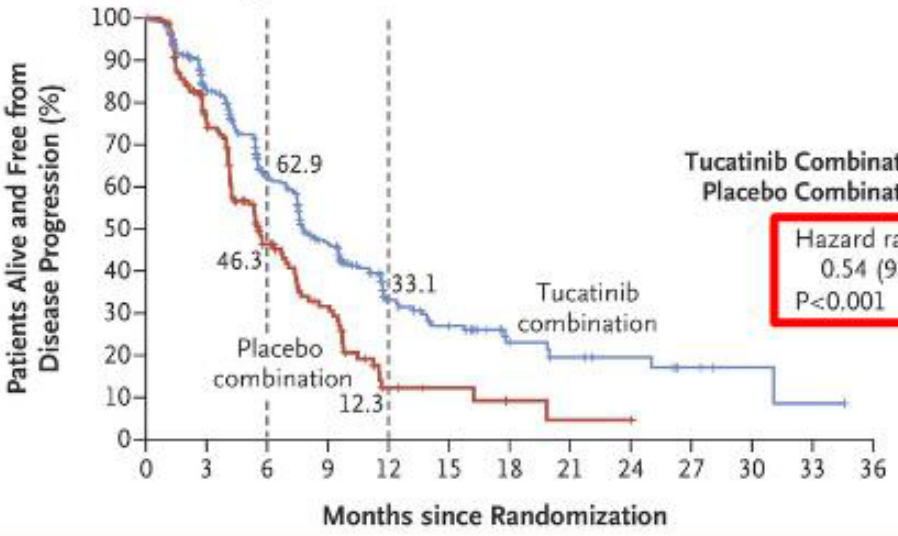
Progression–free Survival

A Kaplan–Meier Estimates of Progression-free Survival



	No. of Events/ No. of Patients	Median Duration (95% CI)
		mo
Tucatinib Combination	178/320	7.8 (7.5–9.6)
Placebo Combination	97/160	5.6 (4.2–7.1)

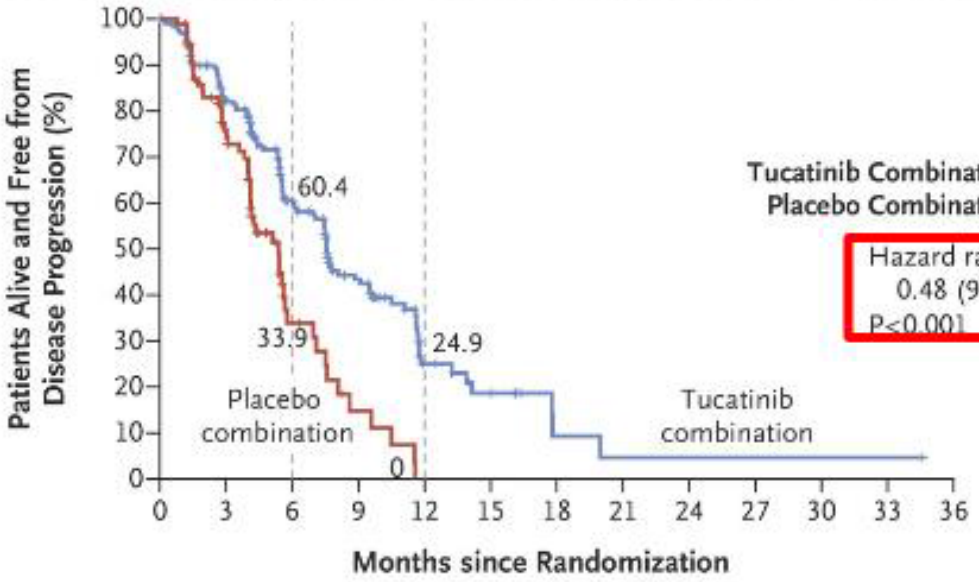
Hazard ratio for disease progression or death, 0.54 (95% CI, 0.42–0.71)
P<0.001

- ORR: 41% (tucatinib) vs. 23% (placebo)

The NEW ENGLAND JOURNAL of MEDICINE
RK Murthy et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914609

Progression–free Survival among the Patients with Brain Metastases

A Kaplan–Meier Estimates of Progression-free Survival among Patients with Brain Metastases



	No. of Events/ No. of Patients	Median Duration (95% CI)
		mo
Tucatinib Combination	106/198	7.6 (6.2–9.5)
Placebo Combination	51/93	5.4 (4.1–5.7)

Hazard ratio for disease progression or death, 0.48 (95% CI, 0.34–0.69)
P<0.001

The NEW ENGLAND JOURNAL of MEDICINE
RK Murthy et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914609

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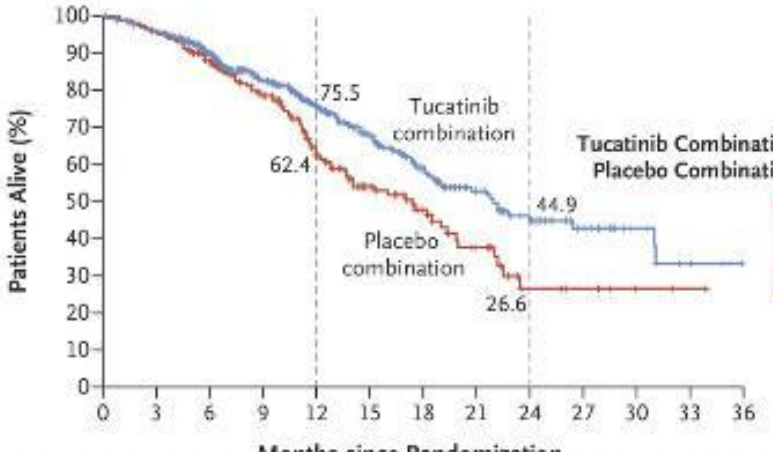
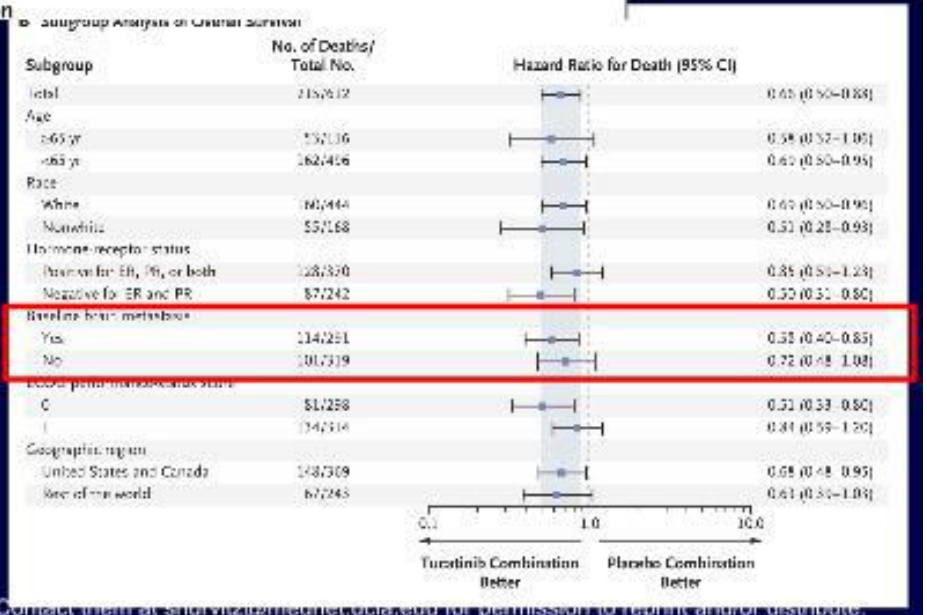
Overall Survival in the Total Population and Prespecified Subgroups.

A Kaplan–Meier Estimates of Overall Survival



	No. of Deaths/ No. of Patients	Median Duration (95% CI) mo
Tucatinib Combination	130/410	21.9 (18.3–31.0)
Placebo Combination	85/202	17.4 (13.6–19.9)

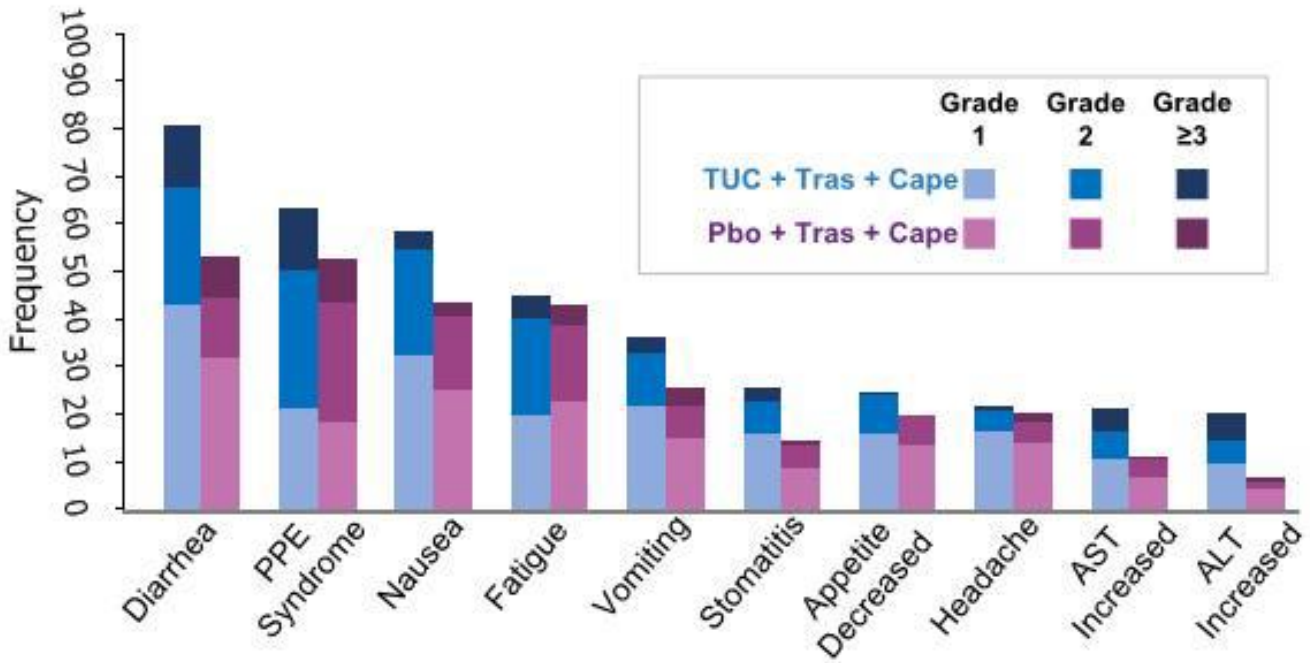
Hazard ratio for death, 0.66 (95% CI, 0.50–0.88)
P=0.005



The NEW ENGLAND JOURNAL of MEDICINE

RK Murthy et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914609

Most Common Adverse Events (≥20% in the Tucatinib Arm)



PPE: palmar-plantar erythrodysesthesia, AST: aspartate transaminase, ALT: alanine transaminase

New Antibody drug conjugates (ADCs) targeting HER2

Agent	Target	Phase of development	Initial Phase I Results	Main Side Effects
DS8201a[1]	Humanized HER2 antibody + topoisomerase-I inhibitor exatecan	Ongoing phase II (DESTINY-Breast01) and III (NCT03529110)	RR: 64.2% PFS:10.4 mo. (heavily pre-treated patients)	Gastrointestinal and haematological
SYD985[2]	Trastuzumab + duocarmazine	Ongoing phase III (TULIP)	RR: 33%[2] PFS: 9.4 mo.	Ophthalmologic effects (conjunctivitis and keratitis)
RC48- ADC[3]	HER2 antibody + MMAE	Ongoing phase II (NCT03500380)	RR: 36.7%	Transaminases elevations Neutropenia

[1] Iwata H et al. J Clin Oncol. 2018, [2] Saura C et al. J Clin Oncol. 2018, [3] Xu B et al. J Clin Oncol. 2018

Trastuzumab Deruxtecan (DS-8201) is a Novel ADC Designed to Deliver an Optimal Antitumor Effect

Trastuzumab deruxtecan is an ADC composed of 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker

- Payload MOA: topoisomerase I inhibitor
- High potency of payload
- High drug to antibody ratio ≈ 8
- Payload with short systemic half-life
- Stable linker-payload
- Tumor-selective cleavable linker
- Membrane-permeable payload

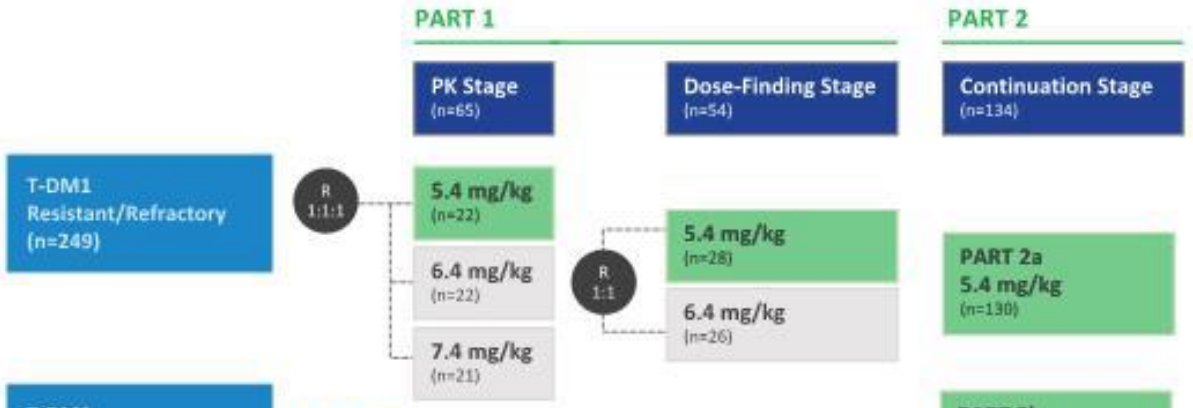
The clinical relevance of these features is under investigation.

ADC, antibody-drug conjugate; MOA, mechanism of action.

1. Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. Clin Cancer Res. 2016;22(20):5097-5108. 3. Trail PA, et al. Pharmacol Ther. 2018;181:126-142. 4. Ogitani Y, et al. Cancer Sci. 2016;107(7):1039-1046.

DESTINY-Breast01 Study Design:
An Open-Label, Multicenter, Phase 2 Study

Population
- ≥18 years of age
- Unresectable and/or metastatic BC
- HER2-positive (centrally confirmed on archival tissue)
- Prior T-DM1
- Excluded patients with history of significant ILD
- Stable, treated brain metastases were allowed



Baseline Characteristics of Note
- 53% HR positive
- HER2 IHC 3+ 84%; 1+/2+ (FISH+) 16%
- 92% visceral disease; 13% h/o brain metastases
- Median 6 prior lines of therapy (range 2-27)

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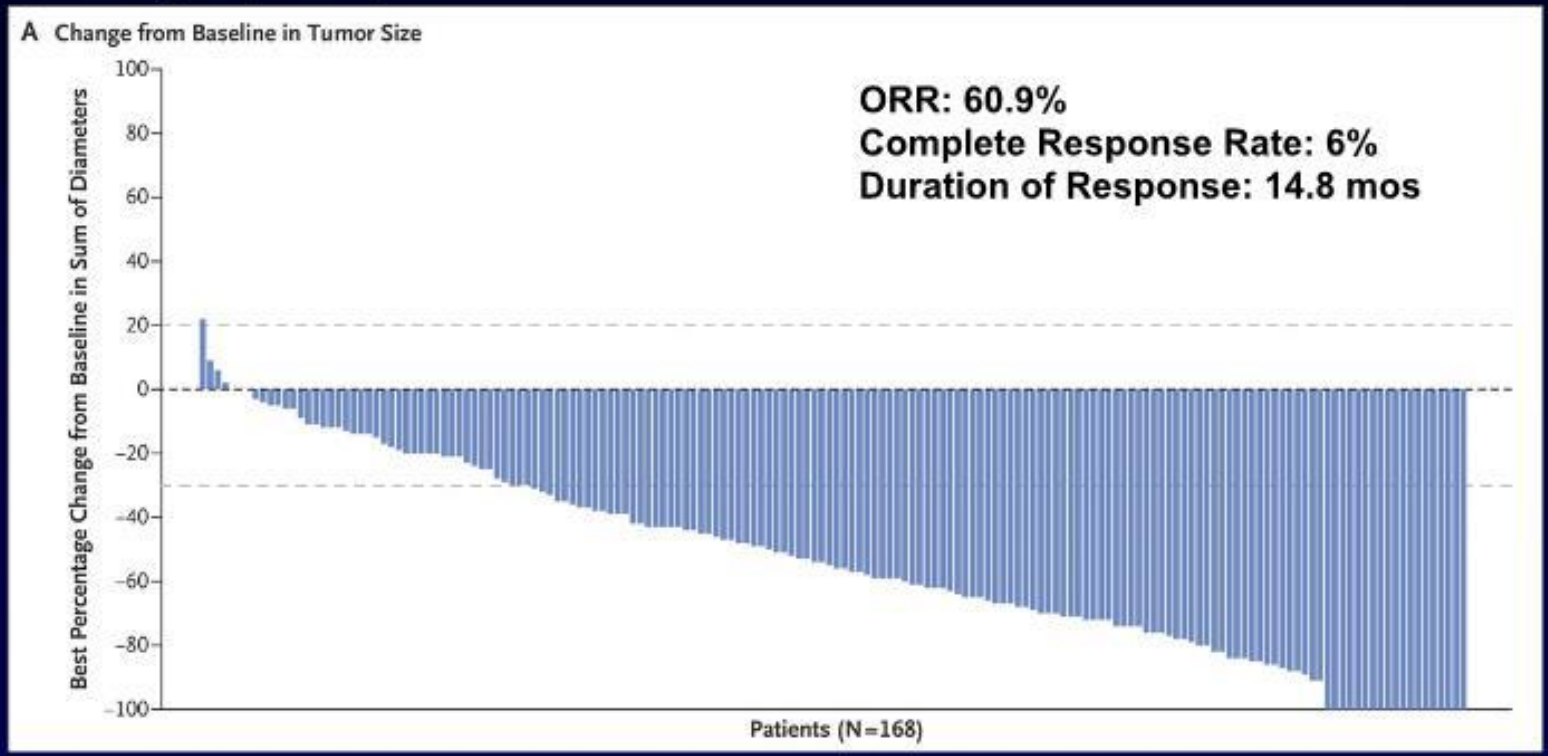
Response to Trastuzumab Deruxtecan, According to Tumor Size and Subgroup Analyses.



The NEW ENGLAND JOURNAL of MEDICINE

S Modi et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914510

Trastuzumab Deruxtecan

Adverse Events of Special Interest: Interstitial Lung Disease

	Patients who received T-DXd 5.4 mg/kg (N=184)					
Preferred Term, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
Interstitial lung disease	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**

Drug related; ILD was determined by the Independent ILD Adjudication Committee based on 44 preferred terms.

Among the 25 total events:

- Median time to investigator-reported onset was **193 days (range, 42-535 days)**
- **Of the 4 fatal cases, onset was from 63-148 days**, 3 received steroids as part of treatment, and death occurred 9-60 days after ILD diagnosis

Recommendations: Monitor for symptoms. Hold T-DXd and start steroids as soon as ILD is suspected

ILD, interstitial lung disease.

III. Triple Negative Breast Cancer Disease

Progresses on the management of Triple Negative Breast Cancer in 2020

- More on the benefit of adjuvant capecitabine in TNBC
- Checkpoints inhibitors-based combination on the neoadjuvant setting
- Update on the role of CPIs in the metastatic setting
- Perspectives
    - Antibody drugs conjugates (Sacituzumab Govitecan)

SYSUCC01 Adjuvant capecitabine trial in early TNBC

Chinese group trial – N = 443 st IIb→IIIc
after completion of « standard » adj CTX/RT
Median follow-up = 57 m

R

« Metronomic » Capecitabine*
650 mg/m 2 continuously
X 1y

Observation

83% ← **5y DFS** → **73%**

HR 0.63 (0.42 – 0.96)
DDFS
HR 0.63 (0.37 – 0.90)

** Completed therapy 91%, med dose intensity 85%, H&F syndrome 45% (17% gr3)*

ASCO 2020 – abst 507

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Neoadjuvant Chemo-Immunotherapy in TNBC
A summary

	KN 522 Pembro / Placebo	Impassion 031 Atezo / Placebo
Patients	n= 602 (pCR Anal.)	n= 333 (after Amendment)
Carboplatin	**yes**	**no**
N+	51.7% / 51.3%	33.9% / 42.9%
T3/T4	26.0% / 25.6%	29.7% / 26.8%
PD-L1 pos.	83.3% / 81.6 % (CPS≥1)	45.2% / 47.3%(IC ≥ 1%)
Primary Endpoints	pCR in ITT, EFS	Co-Primary: pCR in ITT and PD-L1 pos.
pCR ITT	**64,8% / 51;2% Δ13;6%**	**57;6%/41.1% Δ16.5%**
pCR PD-L1pos.	**68.9% / 54.9% Δ 14%**	**68.8% / 49.3% Δ 19.5%**
pCR PD-L1neg.	**45.3% / 30.3% Δ 15%**	**47.7% / 34.3% Δ 13.3%**
LN+	**64.8% / 44.1% Δ 20.7**	**57.1% / 30.6% Δ 26.5%**
LN-	**64.9% / 58.6% Δ 6.3**	**57.8% / 49.0% Δ 8.8%**

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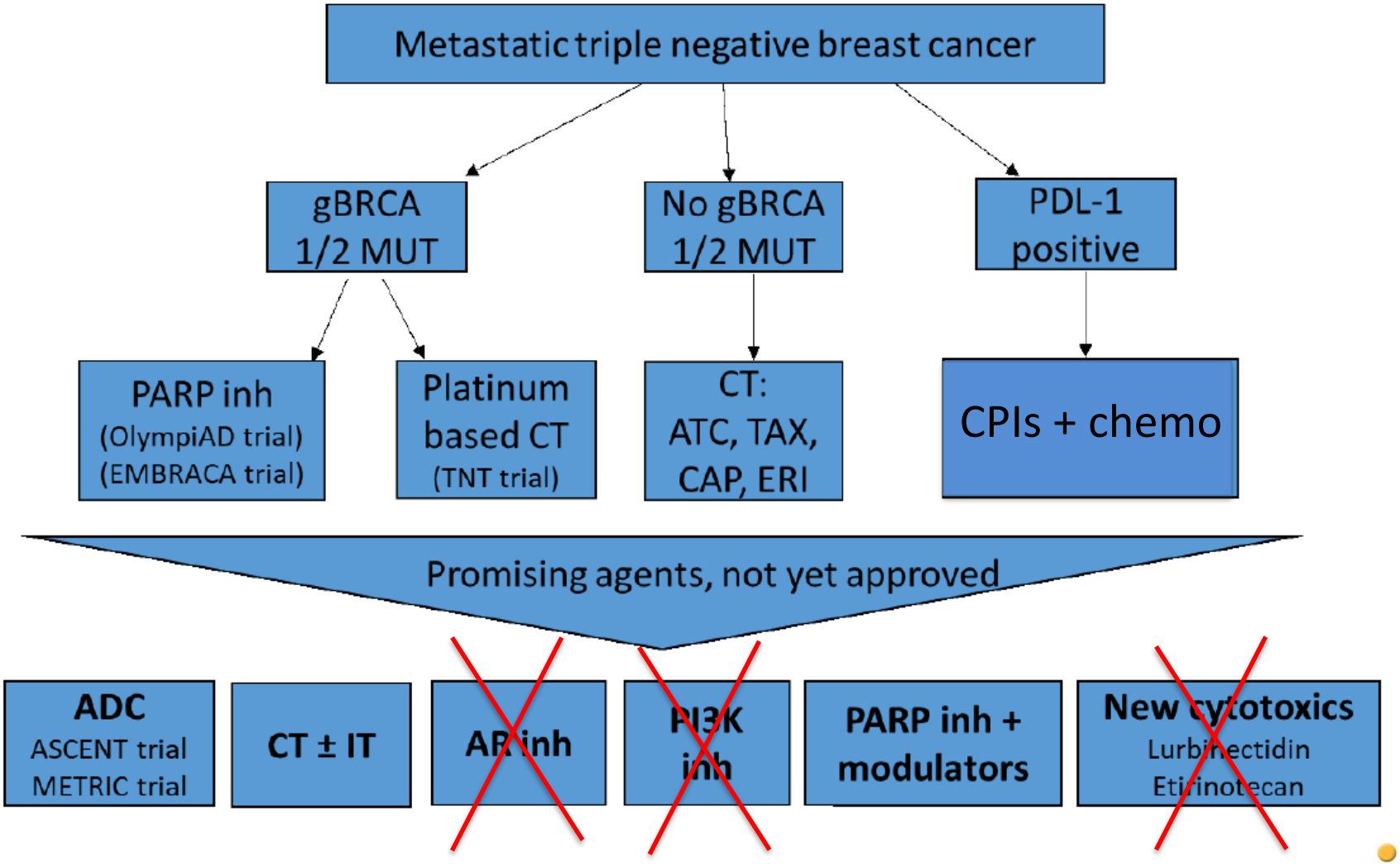
Current standard-of-care treatments in metastatic triple-negative breast cancer and future perspective



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Chemo ± CPIs in metastatic TNBC: A summary

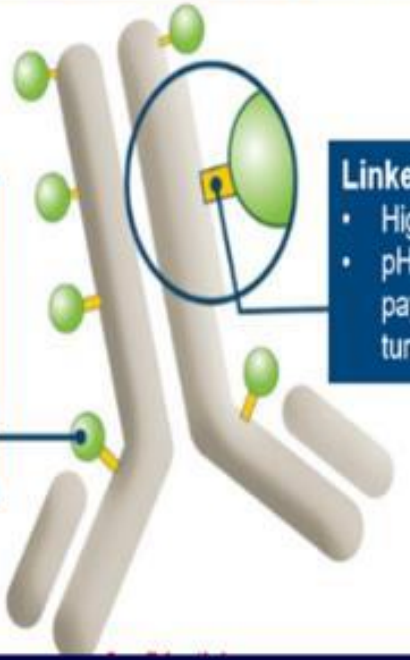
PDL1+ subsets	IMpassion 131 (VIRTUAL ESMO congress 2020)	IMpassion 130 (MUNICH ESMO congress 2018)	KEYNOTE 355 (ASCO20 Virtual)
N	292	369	323 (2:1)
Minimum DFI	12m	12m	6m (20% < 12m)
> 3 involved sites	15%	20%	43% (≥ 3)
Chemo backbone	paclitaxel	nab paclitaxel	nab paclitaxel, paclitaxel, gem/carbo
Prior chemo for EBC	52% taxane	51% taxane	22% prior same class
No prior chemo	29% de novo	35% chemo-naive	32% de novo
PDL1+ rate	45% (SP142, IC≥1%)	41% (SP142, IC≥1%)	38% (22C3, CPS≥10)
	PFS ≈ OS ≤	PFS ↑ « OS ↑ »	PFS ↑

Question de corticoïdes?
Type de chimiothérapie ? Taxol vs Nab PacliT ?

Sacituzumab Govitecan

Sacituzumab Antibody-Drug Conjugate (ADC)

Humanized RS7 antibody
- Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC



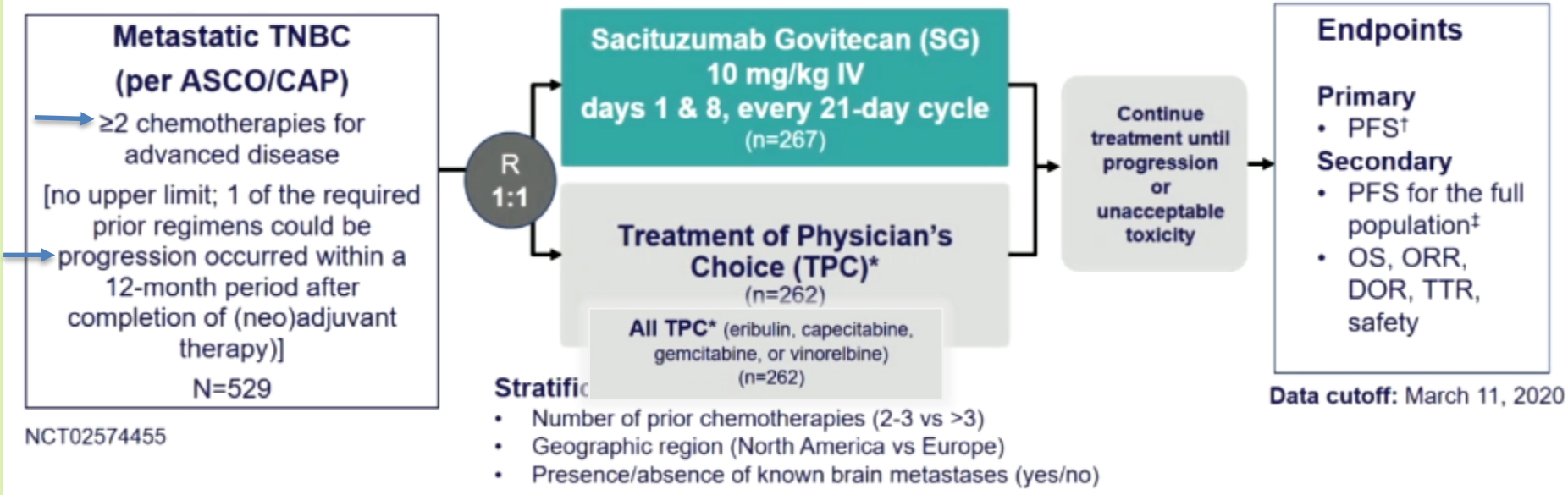
SN-38 payload
- Targets 136-fold more SN-38 than the parent compound, irinotecan (topoisomerase I inhibitor)
- ADCs unique chemistry avoids low solubility and selectively delivers SN-38 to the tumor

Linker for SN-38
- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid payload release at or inside the tumor

5

ASCENT
Clinical Trial

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



NCT02574455

Data cutoff: March 11, 2020

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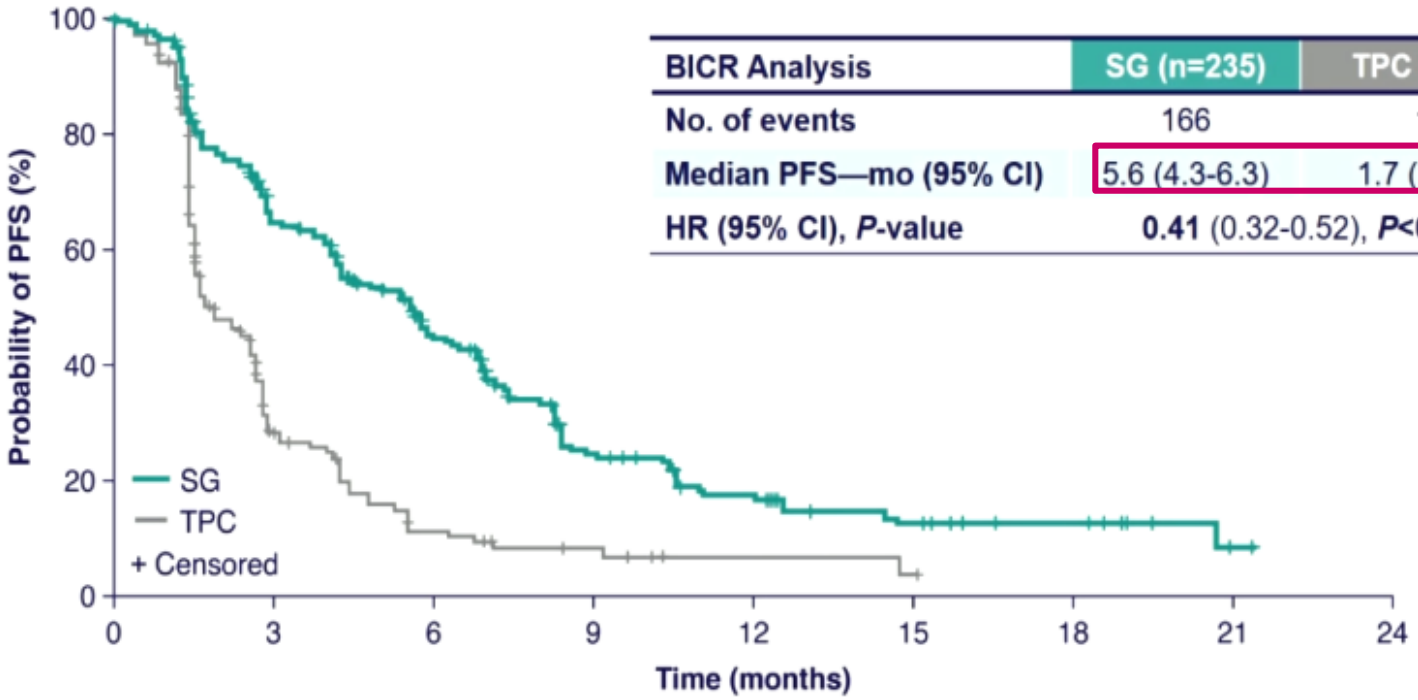
CHL KRIIBSZENTRUM

ASCENT Clinical Trial

(Sacituzumab Govitecan)

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**	

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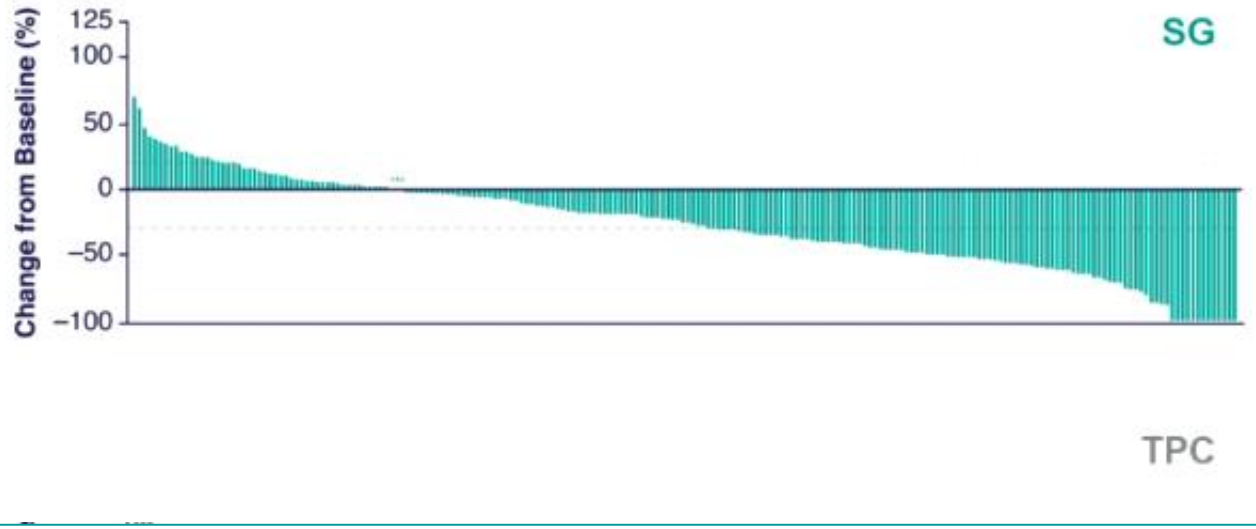
ASCENT Clinical Trial

(Sacituzumab Govitecan)

Overall Response and Best Percent Change From Baseline in Tumor Size



	SG (n=235)	TPC (n=233)
ORR—no. (%)	82 (35)	11 (5)
P-value	<0.0001	
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR—no. (%)	105 (45)	20 (9)
P-value	<0.0001	

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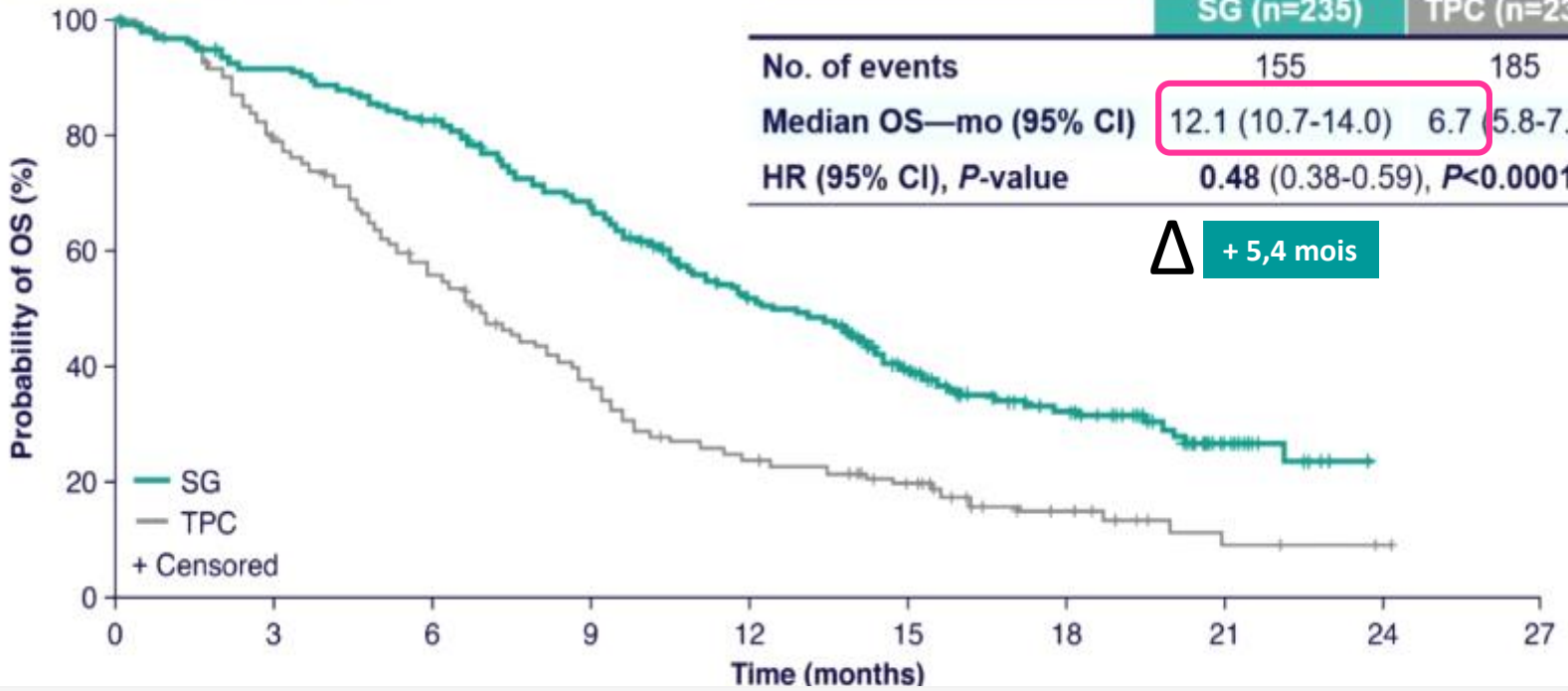
Clinical Trial

(Sacituzumab Govitecan)

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**	

Δ + 5,4 mois

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ASCENT Clinical Trial

(Sacituzumab Govitecan)

TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

		SG (n=258)			TPC (n=224)		
	TRAE*	All grade %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	Neutropenia†	63	46	17	43	27	13
	Anemia‡	34	8	0	24	5	0
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	Diarrhea	59	10	0	12	<1	0
	Nausea	57	2	<1	26	<1	0
	Vomiting	29	1	<1	10	<1	0
Other	Fatigue	45	3	0	30	5	0
	Alopecia	46	0	0	16	0	0

→ **Arrêt = 4,7 %**

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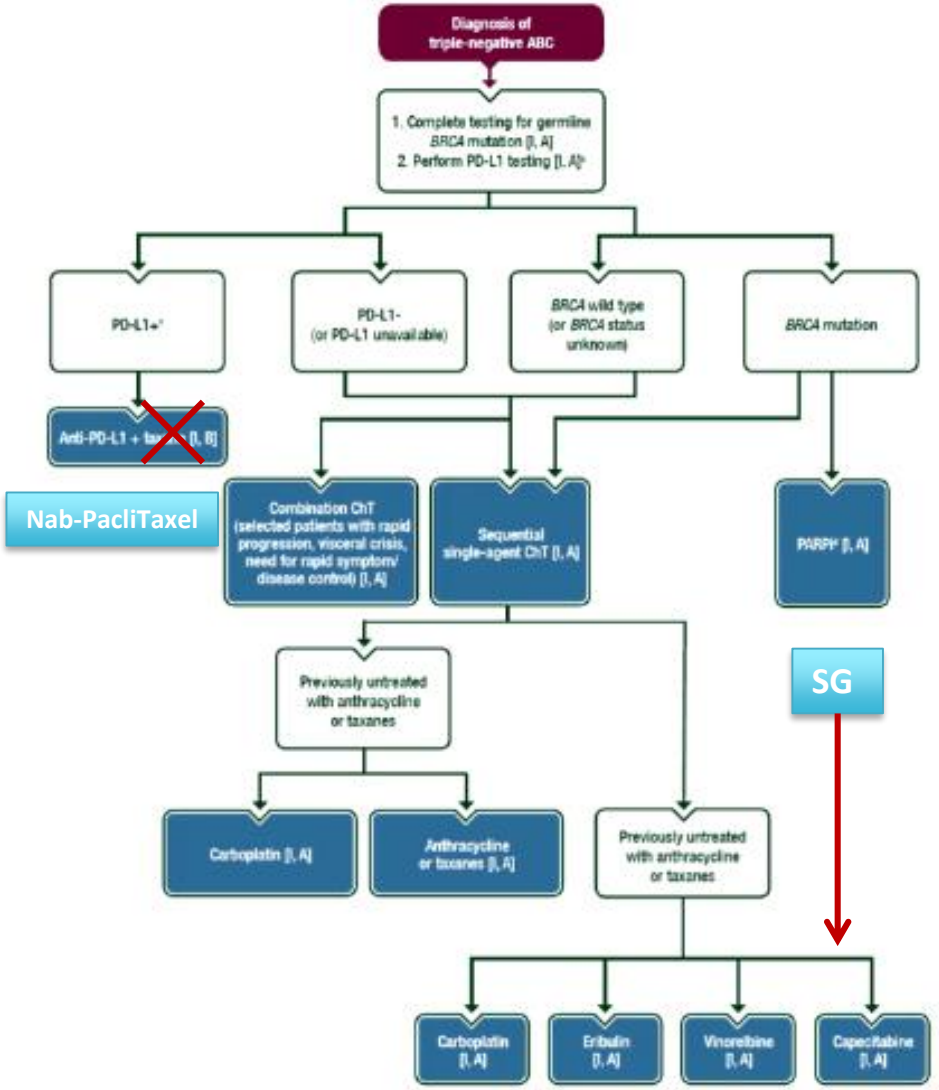
Algorithme mTNBC - ABC 5

Cardoso F , Annals Oncol online



Breast Cancer with mutations in DNA damage response pathway genes

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Progress on the management of gBRCA mutated Breast Cancer in 2020

- Role of PARP inhibitors
  - as single agents (olaparib, talazoparib)
  - in combination (veliparib)
- Therapeutic strategy in gBRCA-mutated breast tumors?

BC with mutations in DNA damage response genes

⇨ **Embraca trial** (Talazoparib vs CTX of physician's choice)
Little impact of any mutation beyond gBRCA1-2 mutation

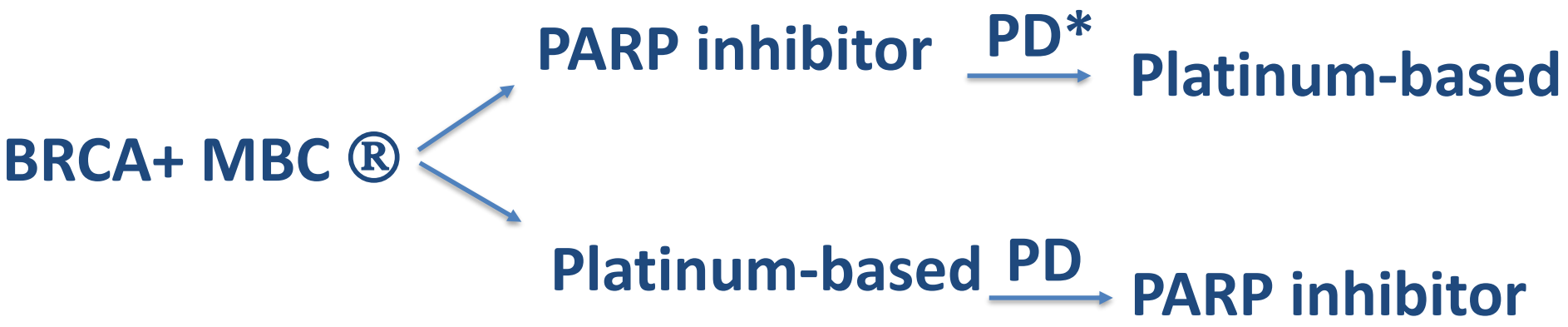
- **P53 mut (gBRCA1) : do worse**
- **PIK3 CA mut (gBRCA2) : no difference**

⇨ **TBCRC 048 « Olaparib expanded »**
Cohort of germline or somatic mutations beyond gBRCA

	PALB2 (N = 13)	ATM/CHEK2 (N = 17)	BRCA1-2 (N = 17)
Germline	82% RR	0/13	-
Somatic	Too few	0/4	50% RR

ASCO 2020 – abst P1018, 1002

Proposition for a clinical trial design including platinum compounds and PARP inhibitors in BRCA+ metastatic breast cancer



* Progressive disease

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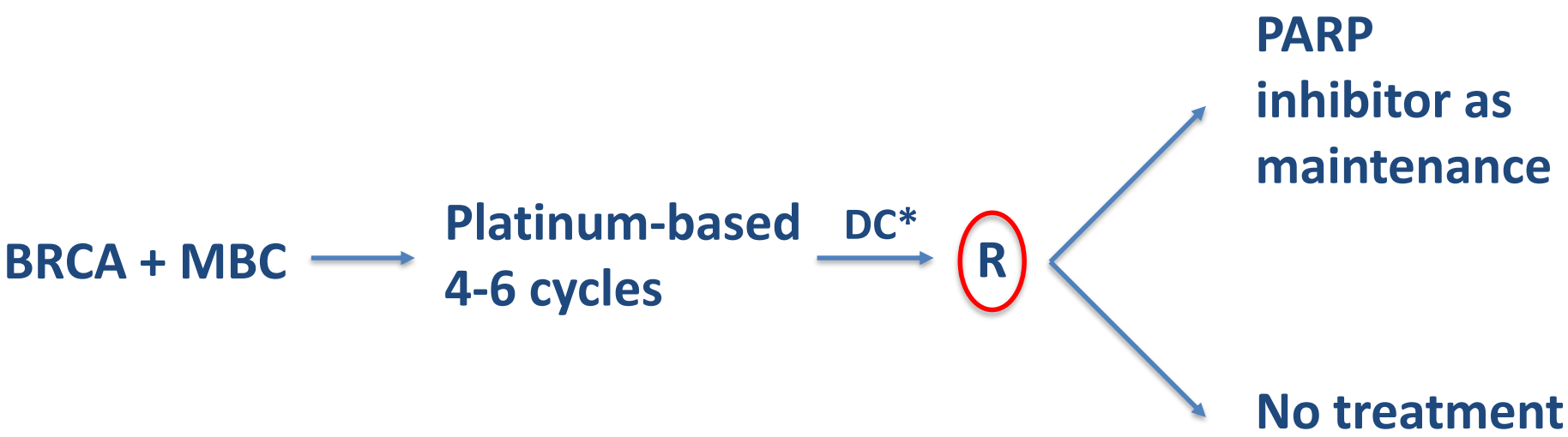
Proposition for a clinical trial design including platinum compounds and PARP inhibitors in BRCA+ metastatic breast cancer (2)



*Disease Control

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Genomic Aberrations in Breast Cancer That Guide Precision Medicine: An Evolving Field

Gene	Aberration	Aberration, %	Targeted Drug(s)
Evidence based (from phase II or III trials)			
HER2	Amplification	20	Trastuzumab, pertuzumab, T-DM1, lapatinib, neratinib
HER2	Activating mutations (nonamplified *HER2*)	2	
PIK3CA	Activating mutations	30-40	Alpelisib
BRCA1/2	Inactivating germline mutations	5	Olaparib, talazoparib
NTRK	Gene fusion	< 1	Larotrectinib
PD-L1	Expression by IHC	40	Atezolizumab + nab-paclitaxel
Emerging			
ESR1	Mutations	30-40	Fulvestrant, other SERDs
PTEN	Inactivating mutations or methylation	20	PI3K, AKT, and mTOR inhibitors
MYC	Amplification	16	BET inhibitors
C-MET	Amplification or mutation	15	MET inhibitors (cabozantinib)
FGFR1-4	Amplification	10	FGFR inhibitors
CDH1	Inactivating mutations	7	Wnt inhibitors
AKT	Activating mutations	2	AKT and mTOR inhibitors (MK-2206, everolimus

Thank you

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