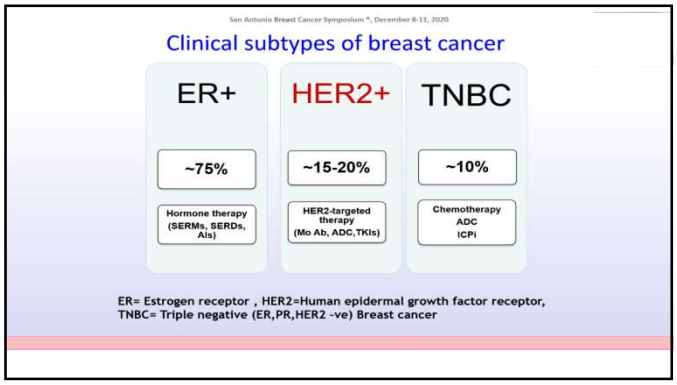


National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2021
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression		HER2-Positive and Postmenopausal[g,h,i] or Premenopausal Receiving Ovarian Ablation or Suppression
Preferred Regimens **First-Line Therapy** • Aromatase inhibitor + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1) • Selective ER down-regulator (fulvestrant, category 1)[b] ± non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[b] • Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1) • Non-steroidal aromatase inhibitor (anastrozole, letrozole) • Selective estrogen receptors modulator (tamoxifen or toremifene) • Steroidal aromatase inactivator (exemestane)	**Preferred Regimens** **Second- and Subsequent-Line Therapy** • Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CDK4/6 inhibitor not previously used (category 1)[c] • For *PIK3CA*-mutated tumors, see additional targeted therapy options (see BINV-R)[c,d] • Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[c,f] • Non-steroidal aromatase inhibitor (anastrozole, letrozole) • Steroidal aromatase inactivator (exemestane) • Selective ER down-regulator (fulvestrant) • Selective estrogen receptors modulator (tamoxifen or toremifene)	• Aromatase inhibitor ± trastuzumab • Aromatase inhibitor ± lapatinib • Aromatase inhibitor ± lapatinib + trastuzumab • Fulvestrant ± trastuzumab • Tamoxifen ± trastuzumab
Useful in Certain Circumstances[d] • Megestrol acetate • Estradiol • Abemaciclib[c,e]		

CDK 4/6 Inhibitors in endocrine-sensitive and resistance metastatic breast cancer

PFS in 1st and 2nd line ER+ MBC with CDK 4/6i

	1st LINE TREATMENT					≥ 2nd LINE TREATMENT		1st AND 2nd LINE TREATMENT
	PALOMA-2	MONALEESA-2	MONARCH-3	MONALEESA-7	PARSIFAL	PALOMA-3	MONARCH-2	MONALEESA-3
Design	Phase III placebo control	Phase III placebo control	Phase III placebo control	Phase III placebo control (pre-menopausal patients only)	Phase II open label	Phase III placebo control	Phase III placebo control	Phase III placebo control
Endocrine partner	Letrozole	Letrozole	Letrozole	Letrozole (or Tamoxifen) + LHRH agonist	Letrozole or Fulvestrant	Fulvestrant	Fulvestrant	Fulvestrant
CDK4/6 Inhibitor	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Palbociclib (control arm)	Palbociclib	Abemaciclib	Ribociclib
Patients on study, n	666	668	493	672	486	521	669	726
Primary Endpoint = PFS (CDK4/6 inhibitor + ET vs. ET)								
HR	0.58	0.56	0.54	0.55	1.13	0.46	0.55	0.59
Median PFS, months	24.8 vs 14.5 (10.3 mo)	25.3 vs 16 (9.3 mo)	28 vs 14.7 (13.3 mo)	23.8 vs 13 (10.8 mo)	27.9 vs 32.8 (5 mo)	9.5 vs 4.6 (4.9 mo)	16.4 vs 9.3 (7.1 mo)	20.5 vs 12.8 (7.7 mo)

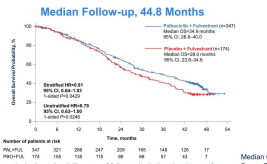
Cristofanilli et al. Lancet Oncology 2016; Finn et al. NEJM 2016; Hortobagyi et al. NEJM 2016; Tripathy et al. Lancet 2018; Sledge et al. JCO 2017; Goetz et al. JCO 2017; Slamon et al. JCO 2018; Llombart-Cussac et al. ASCO 2020

1st and 2nd Line Rx of HR+ MBC with CDK4/6i

	1st LINE TREATMENT					≥ 2nd LINE TREATMENT		1st AND 2nd LINE TREATMENT
	PALOMA-2	MONALEESA-2	MONARCH-3	MONALEESA-7	PARSIFAL	PALOMA-3	MONARCH-2	MONALEESA-3
Design	Phase III placebo control	Phase III placebo control	Phase III placebo control	Phase III placebo control (pre-menopausal patients only)	Phase II open label	Phase III placebo control	Phase III placebo control	Phase III placebo control
Endocrine partner	Letrozole	Letrozole	Letrozole	Letrozole (or Tamoxifen) + LHRH agonist	Letrozole or Fulvestrant	Fulvestrant	Fulvestrant	Fulvestrant
CDK4/6 Inhibitor	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Palbociclib (control arm)	Palbociclib	Abemaciclib	Ribociclib
Patients on study, n	666	668	493	672	486	521	669	726
OS (CDK4/6 inhibitor + ET vs. ET)								
HR				0.71	1	0.81	0.75	0.72
Median OS, months	Not yet reported (Aug 2023)	Not yet reported (Aug 2021)	Not yet reported (Jul 2021)	NR vs 40.9	3- year OS ~ 78%	34.9 vs 28 (7 mo)	46.7 vs 37.3 (9 mo)	NR vs 40

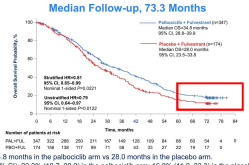
Updated OS analyses from PALOMA-3

Final Protocol-Specified Overall Survival Analysis[1]



Median OS was 34.9 months in the palbociclib arm vs 28.0 months in the placebo arm.[1]

Updated Overall Survival Analysis

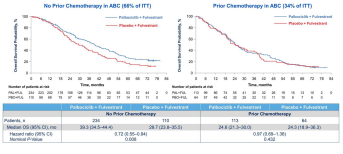


Median OS was 34.9 months in the palbociclib arm vs 28.0 months in the placebo arm.
5-year OS rate (95% CI): 23.3% (18.7–28.2) in the palbociclib arm; 16.8% (11.2–23.3) in the placebo arm.

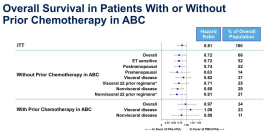
Cristofanilli M, et al, ASCO 2021, abstract 1000

Overall Survival in Patients with prior CT in ABC

Overall Survival in Patients With Prior Chemotherapy in ABC

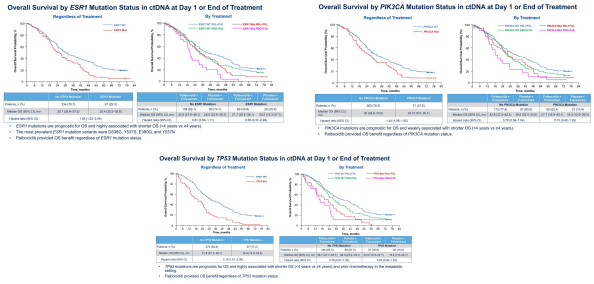


Overall Survival in Patients With or Without Prior Chemotherapy in ABC



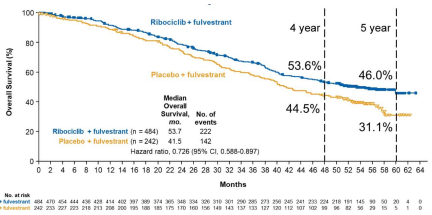
Cristofanilli M, et al, ASCO 2021, abstract 1000

ESR1, *PIK3CA* and *TP53* gene mutations by ctDNA analysis



Cristofanilli M, et al, ASCO 2021, abstract 1000

Monalessa 3: Updated overall survival



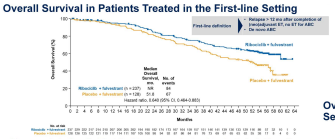
- With an extended follow-up of > 4 years, ribociclib + fulvestrant continued to demonstrate a clinically relevant > 1 year OS benefit compared with placebo + fulvestrant

Data cutoff: October 30, 2020.

Slamon D, et al, ASCO 2021, abstract 1001

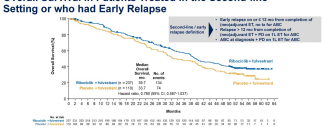
Monalessa 3: Updated overall survival

Overall Survival in Patients Treated in the First-line Setting



- A larger magnitude of benefit of ribociclib + fulvestrant over placebo + fulvestrant in the first-line setting was observed compared with the prior reported data cutoff for OS (HR, 0.70; 95% CI, 0.48-1.02)[1]

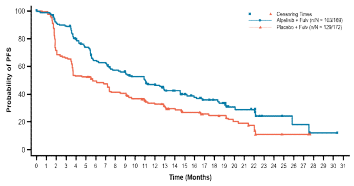
Overall Survival in Patients Treated in the Second-line Setting or who had Early Relapse



- Ribociclib + fulvestrant demonstrated a 6-month longer median OS over placebo + fulvestrant in the second-line setting

Slamon D, et al, ASCO 2021, abstract 1001

SOLAR-1:Primary endpoint -Locally assessed PFS in the PIK3CA-mutant cohort

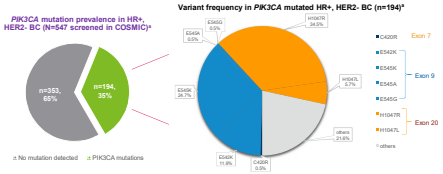


Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (N=169)	Placebo + fulvestrant (N=172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5–14.5)	5.7 (3.7–7.4)
HR (95% CI)	0.65 (0.50–0.85)	
p-value	0.00065	

~ 5.5 months benefit in PFS
Only ~ 7% pretreated with CDK 4/6i

André F ESMO 2020; Annal Oncol 2020

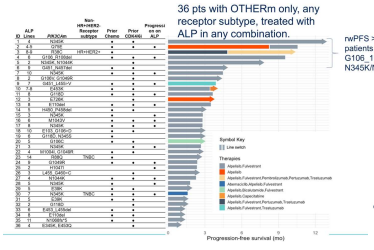
Prevalence and Distribution of *PIK3CA* Mutation in HR+/HER2- Breast Cancer (COSMIC)



- Of 547 HR+, HER2- BC patients screened, 194 (35%) cases with *PIK3CA* mutations were identified in COSMIC database[a]
  - Among the *PIK3CA* mutated population (n=194), the most frequent mutation variants were found in exons 9 and 20

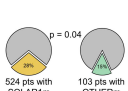
BC, breast cancer; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.
ª COSMIC data filtered to HER2-, HR+ breast carcinoma taken from the Catalogue of Somatic Mutations in Cancer; www.sanger.ac.uk/genetics/CGP/cosmic/. Accessed April 16, 2019. COSMIC is the world's largest and most comprehensive resource for exploring the impact of somatic mutations in human cancer. Forbes et al. *Nucleic Acids Res.* 2017 Jan 4;45(D1):D777-D783.

Some patients with OTHERm show sustained rwPFS on alpelisib



36 pts with OTHERm only, any receptor subtype, treated with ALP in any combination.

rwPFS > 6 months was observed in 5 patients bearing: N345K, Q75E, R38C, G106_108del (a p85 BD indel), and N345K/N1044K.



Of a cohort of 627 HR+/HER2- patients with *PIK3CA*m who received a clinical report with alpelisib listed (report date after 5/2019): 147/524 (28%) pts with a SOLAR1m were treated with alpelisib compared to 15/103 (15%) pts who had OTHERm only

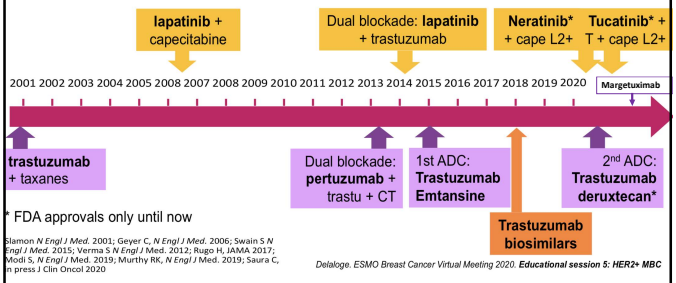
Rugo H, et al, ASCO 2021, poster abstract 1068

Select Oral SERDs in Development

Drug	Ongoing Studies	Reference	Status
Elacestrant (RAD1901)	EMERALD Phase III	NCT03778931	Enrollment complete
Amcenestrant (SAR439859)	AMEERA1 (Ph 1/2 1st line + palbo, 2nd line +alpelisib)[1]	NCT03284957; Campone M., et al. *J Clin Oncol* 2020;38:15_suppl, 1070-1070.	Ongoing
	AMEERA-3 Phase II am vs TPC	NCT04059484	Ongoing
	AMEERA-5 Phase III (1st line + palbo)	NCT04478266	Ongoing
	AMEERA-4 Window of Opportunity Neoadj	NCT04191382	Terminated
Camizestrant (AZD9833)	SERENA-1 Phase I mono or + palbo	NCT03616587 Baird et al. SABCS 2020. PS11-05	Ongoing
	SERENA-2 Phase II randomized open label vs fulvestrant	NCT04214288	Ongoing
	SERANA-4 Phase III randomized in combination with palbo vs anastrozole + palbo	NCT04711252	Ongoing
Giredestrant (GDC-9545)	Phase II randomized open label vs fulvestrant or AI	NCT04576455	Ongoing
	Phase III GDC/palbo vs. letroz/palbo	NCT04546009	Ongoing
	TRIO 038/WO42133: Phase II neoadjuvant AI/palbo vs gire/palbo	NCT04436744	Ongoing
H3B-6545	Phase I/II	NCT03250676 Hamilton et al. SABCS 2020. PD8-06.	Ongoing
ARV-471	Phase I/II mono or +palbo	NCT04072952	Ongoing
Rintodestrant (GLT48)	Phase I mono or +palbo	NCT03455270	Enrollment complete

18

HER2+ MBC – Evolution of available treatments

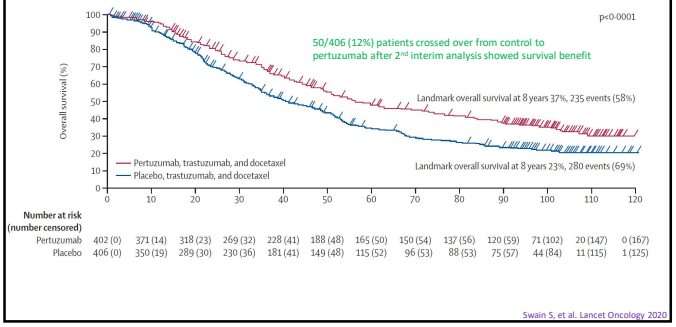


* FDA approvals only until now

Slamon *N Engl J Med.* 2001; Geyer C, *N Engl J Med.* 2006; Swain S *N Engl J Med.* 2015; Verma S *N Engl J* Med. 2012; Rugo H, JAMA 2017; Modi S, *N Engl J* Med. 2019; Murthy RK, *N Engl J* Med. 2019; Saura C, in press J Clin Oncol 2020

Delaloge. ESMO Breast Cancer Virtual Meeting 2020. ***Educational session 5: HER2+ MBC***

Updated Data from CLEOPATRA Trial: Docetaxel + Trastuzumab +/- Pertuzumab in First Line

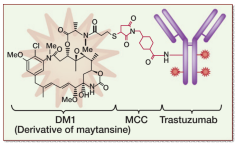


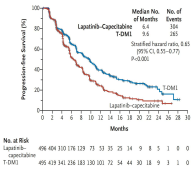
Swain S, et al. Lancet Oncology 2020

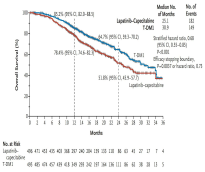
Phase 3 EMILIA: T-DM1 in HER2+ MBC

In EMILIA, T-DM1 was superior to lapatinib + capecitabine in HER2+ MBC

- In 991 randomized patients, median PFS was 9.6 months with T-DM1 vs 6.4 months with lapatinib + capecitabine (HR 0.65; 95% CI, 0.55-0.77; *P* <.001), and median OS was 30.9 months vs 25.1 months (HR, 0.68; 95% CI, 0.55-0.85; *P* <.001)





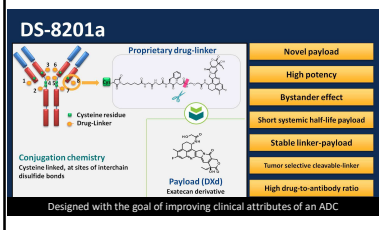


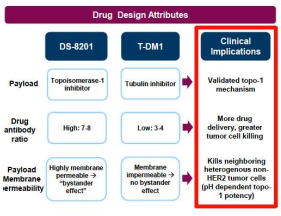
Verma S et al. *N Engl J Med*. 2012;367:1783.

New Therapies After Second Line

Antibody-Drug Conjugates:
Trastuzumab Deruxtecan (DS-8201)

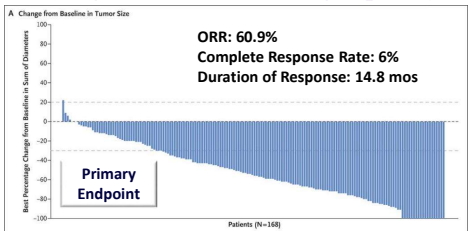
Trastuzumab Deruxtecan (DS-8201a): Structure and Mechanism of Action





Doi T et al. *J Clin Oncol*. 2017;35(suppl 15): abstract 108.

Phase II DESTINY-Breast01: Response to DS-8201, According to Tumor Size and Subgroup Analyses



- Dec 2019 - FDA accelerated approval for HER2+ MBC ≥2 prior lines of antiHER2-based regimens
- Feb 2020 – Added to NCCN Breast Cancer guidelines (V2.2020)

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

UPDATE ON DESTINY-BREAST 01

(n = 184)

ORR	61.4%
Median duration of response	20.8 mo
Median PFS	19.4 mo
Median OS	24.6 mo
Pneumonitis/ILD	15.2%
Grade 5 ILD	2.7%

Modi S et al. SABCS 2020. PD3-06.

Incidence of ILD after implementation of toxicity management guidelines

Updated toxicity management guidelines implemented (December 2019)

Incidence of ILD over time

	2016 (n=74)	2017 (n=168)	2018 (n=569)	2019 (n=179)	2020 (n=160)
Any Grade ILD, n (%)	18 (24.3)	33 (19.6)	87 (15.3)	28 (15.6)	11 (6.9)
Grade ≥3 ILD, n (%)	2 (2.7)	6 (3.6)	21 (3.7)	8 (4.5)	3 (1.9)
Grade 5 ILD, n (%)	1 (1.4)	5 (3.0)	12 (2.1)	5 (2.8)	2 (1.3)

Patients grouped by year of enrollment, based on a data snapshot from **December 2020**.

- Patients enrolled in 2020 (after implementation of toxicity management guidelines) appear to have had lower rates of all grade (6.9%), grade ≥3 (1.9%) and grade 5 ILD (1.3%) compared with those enrolled in previous years based on a December 2020 snapshot; however, this may be partly due to the shorter treatment duration

NALA Phase III Trial of Neratinib + Capecitabine

Inclusion criteria
- MBC
- Centrally confirmed HER2+ disease
- ≥2 lines of HER2-directed therapy for MBC
- Asymptomatic and stable brain mets permitted

R (1:1)

n=621

Neratinib 240 mg/d + Capecitabine 1500 mg/m² 14/21 d Loperamide (cycle 1)[a] → PD

Lapatinib 1250 mg/d + Capecitabine 2000 mg/m² 14/21 d → PD

Follow-up (survival)

Stratification variables
- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

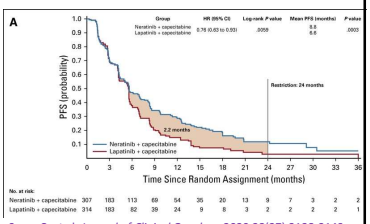
Endpoints
- **Co-primary: PFS (centrally confirmed) and OS**
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

a Loperamide 4 mg with first dose of neratinib, followed by 2 mg Q4H, d1-3, then loperamide 2 mg Q6–8H to end of cycle 1; thereafter as needed.

Saura C, et al. ASCO 2019. Abstract 1002.

NALA Results

- PFS (by restricted means analysis at 24 mos)
  - 8.8 mos (neratinib) vs. 6.6 mos (lapatinib) p=0.003
- Cumulative incidence intervention CNS mets
  - 22.8% (neratinib) vs 29.2% (lapatinib); p=0.043
- Grade 3/4 diarrhea
  - 24% (neratinib) vs. 13% (lapatinib)



Saura C, et al. *Journal of Clinical Oncology* 2020:38(27):3138-3149.

NALA: Efficacy in 101 Patients With Baseline CNS Disease

Efficacy Outcome	Neratinib + Cape (n = 51)	Lapatinib + Cape (n = 50)
Restricted mean PFS*, mos	7.8	5.5
HR (95% CI)	0.66 (0.41-1.05; P = .074)	
Restricted mean OS*, mos	16.4	15.4
HR (95% CI)	0.90 (0.59-1.38; P = .635)	
Time to intervention for CNS disease		
▪ 12-mo cumulative incidence, %	25.5	36.0
▪ P value	.430	
Median CNS PFS, mos	12.4	8.3
HR (95% CI)	0.62 (0.32-1.18; P = .143)	

*Prespecified restriction of 24 mos for PFS and 48 mos for OS. Data cutoff: September 28, 2018.
Median duration of study tx: neratinib, 5.7 mos (range: 0.4-28.6); lapatinib, 3.5 mos (range: 0.5-20.8).

Among 3 patients with LMD: n = 2 in neratinib arm had PD after 5.6 and 9.8 mos with an OS of 17.4 and 19.8 mos, respectively; n = 1 in lapatinib arm had PD after 4.3 mos with an OS of 6.5 mos

Saura. SABCS 2020. Abstr PD13-09.

Phase II HER2CLIMB Trial of Tucatinib + Capecitabine + Trastuzumab: Design

Key Eligibility Criteria
- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- Active brain mets not needing local therapy allowed but not required
- No lapatinib in past 12 mo
- No prior neratinib, afatinib, or investigational HER2 TKI

Randomized 2:1
N = 612

Tucatinib (300 mg orally BID) + capecitabine (1000 mg/m² orally BID days 1-14 Q3W) + trastuzumab (8mg/kg loading → 6mg/kg IV Q3W)

Placebo (orally BID) + capecitabine (1000 mg/m² orally BID days 1-14 Q3W) + trastuzumab (8mg/kg loading → 6mg/kg IV Q3W)

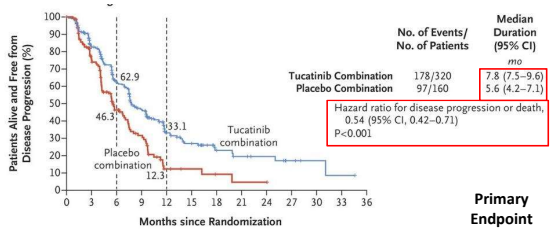
*Stratification Factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region of world (US or Canada or rest of world)

Baseline Characteristics of Note
- 60% HR+
- 48% CNS mets
- 36% de novo MBC
- Median 3 prior lines of therapy in metastatic setting (range 1-14)

Primary endpoint: PFS by BICR

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

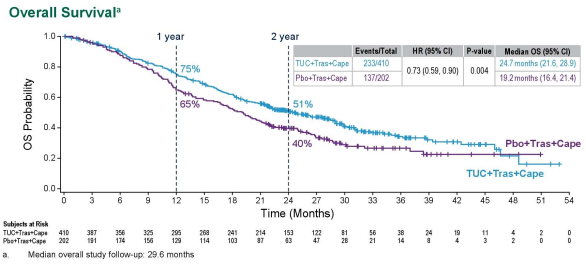
Phase II HER2CLIMB Trial of Tucatinib + Capecitabine + Trastuzumab: PFS



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

Murthy RK, et al. N Engl J Med. 2020;382:597-609. Epub 2019 Dec 11.

HER2CLIMB: Updated Overall Survival

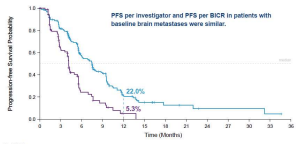


a. Median overall study follow-up: 29.6 months

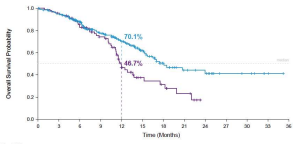
Curigliano G et al. ASCO 2021. Abstract 1043.

HER2CLIMB: Patients With Brain Metastases

PFS per Investigator Assessment in All Patients with BM



OS in All Patients with Brain Metastases



	Events	HR (95%CI)	P Value	One-year PFS (95% CI)	Median PFS (95% CI)
TUC+Tras+Cape	126/158	0.45 (0.33, 0.62)	<0.001	22.0% (15.0, 29.0)	7.3 months (5.5, 8.6)
Pbo+Tras+Cape	52/83			5.3% (1.1, 14.6)	4.1 months (3.6, 5.4)

Risk of progression or death was reduced by 55% in all patients with brain metastases in the TUC arm

	Events	HR (95%CI)	P Value	One-year OS (95% CI)	Median OS (95% CI)
TUC+Tras+Cape	68/158	0.58 (0.40, 0.85)	0.005	70.7% (62.1, 78.7)	18.1 months (15.5, –)
Pbo+Tras+Cape	46/83			46.7% (33.0, 59.4)	12.0 months (11.2, 15.2)

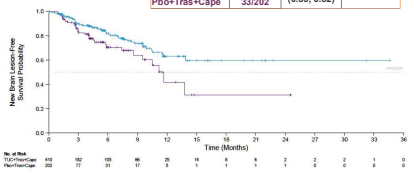
Risk of death was reduced by 42% in all patients with brain metastases in the TUC arm[a]

- Risk of progression or death in patients with brain metastases was reduced by 55% in the total population

Bachelot T, et al. ESMO 2020. Presentation 293P.

HER2CLIMB: Time to New Brain Lesions or Death in All Patients

	Events N=612	HR (95% CI)	P Value
TUC+Tras+Cape	52/410	0.52 (0.33, 0.82)	0.005
Pbo+Tras+Cape	33/202		



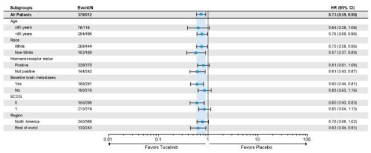
Risk of developing new CNS lesions or death was reduced by 48% in all patients with or without brain metastases in the TUC arm

Median new brain lesion-free survival (95% CI):

Not reached (13.9, -)	11.7 months (9.5, -)

Bachelot T, et al. ESMO 2020. Presentation 293P.

HER2CLIMB: Subgroup Analyses



OS in Prespecified Subgroup Analyses

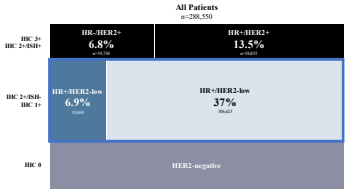
- OS benefit with tucatinib was generally consistent across patient subgroups

OS in an Exploratory Analysis in Patients With and Without Visceral Metastases

	Patients With Visceral Metastases (n = 455)			Patients Without Visceral Metastases (n = 157)		
	HR (95% CI)	P	Median OS (95% CI)	HR (95% CI)	P	Median OS (95% CI)
Tuc + Tras + Cape	0.70 (0.55, 0.89)	.004	21.6 mo (18.1, 25.6)	0.80 (0.48, 1.3)	.36	32.9 mo (27.7, 46.7)
PBO + Tras + Cape			16.9 mo (12.3, 19.4)			26.9 mo (20.5, NE)

Curigliano G et al. ASCO 2021. Abstract 1043.

Ongoing Clinical Trials Have Defined Tumors With HER2-Low Expression as IHC 1+ or IHC 2+ and in-Situ Hybridization (ISH)-Negative



*Source: Decision Resources, inclusive of US, Europe, and Japan (Breast Cancer, Last updated, December 2017; CAncerMPACT (2017))

J101 Ongoing Phase 1 Trial With T-DXd Demonstrated Positive Results in Patients With Heavily Pretreated, Advanced, HER2-Low BC

PATIENTS

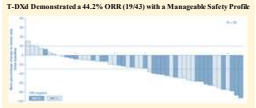
Patients with breast cancer or gastric/GEJ adenocarcinoma

mCRM with EWOC

Two-part dose escalation and dose expansion phase

ANTITUMOR ACTIVITY

T-DXd Demonstrated a 44.2% ORR (19/43) with a Manageable Safety Profile



SAFETY RESULTS

- 99.4% of patients experienced a TEAE regardless of causality
- 22.9% of patients experienced a serious TEAE
- 50.0% of patients experienced grade ≥3 TEAE
- 4 fatal cases of ILD/pneumonitis

N = 51	Confirmed ORR n/N (%)	Confirmed DCR n/N (%)	DOR Median (range), mo	PFS Median (95% CI), mo
HER2-low BC (IHC 2+ / ISH– or IHC 1+)	44.4%	83.3%	11 (4.5, 12.8)	8 (5.6, 13.9)

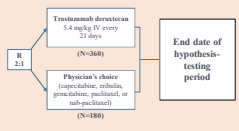
EWOC, escalation with overdose control; GEJ, gastroesophageal junction; IHC, immunohistochemistry; ISH, in situ hybridization; mCRM, modified Continuous Reassessment Method; TEAE, treatment-emergent adverse event.
Modi S et al. J Clin Oncol. 2020;38(17):1887-1896.

DESTINY-Breast04: Multicenter, Int'l, Randomized, Open-Label Phase 3 Study of T-DXd vs Investigators Choice in HER2-Low BC

PATIENTS

- Unresectable and/or metastatic HER2-low BC
- (IHC 2+/ISH- or IHC 1+)

STUDY DESIGN



ENDPOINTS

1º

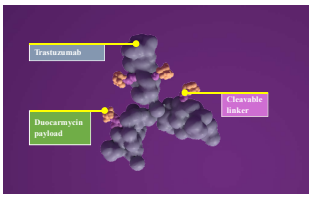
PFS

Select 2º

- OS
- ORR
- Safety

Estimated study completion: January 2023

U.S. National Library of Medicine ClinicalTrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03734029. Accessed November 7, 2020. Last updated: October 20, 2020.



- HER2-targeting ADC[1]
- Duocarmycins are DNA-alkylating agents composed of a DNA-alkylating and a DNA-binding moiety[2]

Trastuzumab Duocarmazine (SYD985)[1,2]

1. Banerji U et al. *Lancet Oncol.* 2016;20(8):1124-1135. 2. Rinnerthaler G et al. *Int J Mol Sci.* 2019;20(5):1115.

37

TULIP: Ph 3 Randomized, Active-Controlled, Superiority Study of SYD985 vs PC in Patients With HER2-Positive Locally Advanced or mBC

PATIENTS

- Female pts with unresectable HER2-positive locally advanced or mBC
- Progression during or after at least 2 HER2-targeting treatment regimens

STUDY DESIGN

HER2-Positive Locally Advanced or mBC
N=345
RANDOMIZED
Experimental: (Vic-)trastuzumab duocarmazine SYD985
Active Comparator: PC
1. Lap+Cap
2. T/Cap
3. T/Vino
4. T/Eri
Comparing Efficacy and Safety

ENDPOINTS

1ᵉ
PFS

Select 2ᵉ
- OS
- ORR
- Investigator-assessed PFS
- PROs for HRQoL

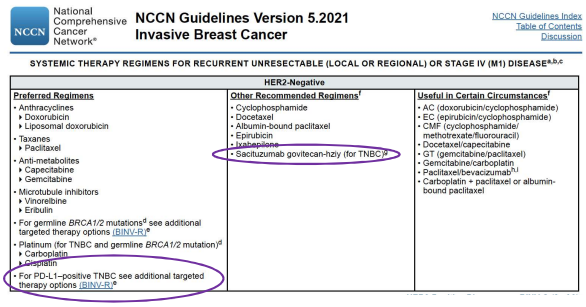
Eri, eribulin; Pc, physician's choice; PROS, patient-reported outcomes; T, trastuzumab; Vino, vinorelbine.
U.S. National Library of Medicine ClinicalTrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03262935. Accessed November 9, 2020. Last updated: October 5, 2020.

Byondis Announces Positive Topline Results of Pivotal Phase III TULIP® Study in Patients With HER2-Positive Unresectable Locally Advanced or Metastatic Breast Cancer

- **08 June 2021**
- ***Study Meets Primary Endpoint**, Confirming the ADC [Vic-]Trastuzumab Duocarmazine (SYD985) is Superior to Physician's Choice in Delaying Disease Progression*
- Byondis B.V. today announced positive topline results from the Phase III TULIP® study, a multi-center, open-label, randomized clinical trial. The trial compared the efficacy and safety of the company's antibody-drug conjugate (ADC) [vic-]trastuzumab duocarmazine (SYD985) to physician's choice treatment in patients with pretreated HER2-positive unresectable locally advanced or metastatic breast cancer (MBC).
- The Phase III TULIP study *"SYD985 vs. Physician's Choice in Participants With HER2-positive Locally Advanced or Metastatic Breast Cancer"* **met its primary endpoint of progression-free survival (PFS),** demonstrating a statistically significant improvement over physician's choice. PFS is defined as the time from the date of randomization to the date of first documented disease progression or death due to any cause, whichever occurred earlier. The study also demonstrated preliminary supportive overall survival (OS) results.
- "There is considerable unmet medical need in patients with HER2-positive metastatic breast cancer and [vic-]trastuzumab duocarmazine represents a promising potential clinical advance," said Byondis Chief Medical Officer Jan Schellens, M.D., Ph.D. "We are excited by the topline results of TULIP and indebted to all patients who participated in the clinical studies."

Summary

- Gold standard of care 1st line: THP
  - Endocrine therapy plus HER2-targeted therapy if HR+, but as would still do induction chemo in most
- 2nd line: T-DM1 (Tucatinib may be reasonable in some?)
- New 3rd line options
  - T-DXD
  - Tucatinib/capecitabine/trastuzumab
  - Neratinib/capecitabine (benefit after tucatinib??)
  - Margetuximab plus chemo (only for FcGRIIIA F-carriers?)



National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2021
Invasive Breast Cancer

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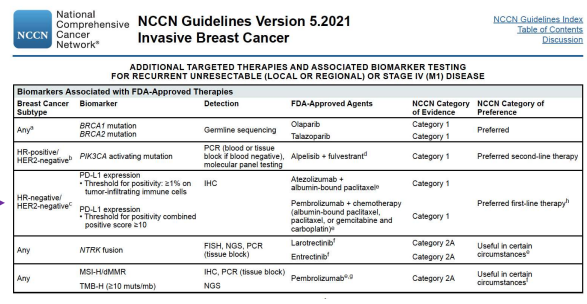
SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a,b,c]

HER2-Negative

Preferred Regimens	Other Recommended Regimens[f]	Useful in Certain Circumstances[f]
• Anthracyclines ▸ Doxorubicin ▸ Liposomal doxorubicin • Taxanes ▸ Paclitaxel • Anti-metabolites ▸ Capecitabine ▸ Gemcitabine • Microtubule inhibitors ▸ Vinorelbine ▸ Eribulin • For germline *BRCA1/2* mutations[d] see additional targeted therapy options (BINV-R)[e] • Platinum (for TNBC and germline *BRCA1/2* mutation)[d] ▸ Carboplatin ▸ Cisplatin • For PD-L1–positive TNBC see additional targeted therapy options (BINV-R)[e]	• Cyclophosphamide • Docetaxel • Albumin-bound paclitaxel • Epirubicin • Ixabepilone • Sacituzumab govitecan-hziy (for TNBC)[g]	• AC (doxorubicin/cyclophosphamide) • EC (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/methotrexate/fluorouracil) • Docetaxel/capecitabine • GT (gemcitabine/paclitaxel) • Gemcitabine/carboplatin • Paclitaxel/bevacizumab[h,i] • Carboplatin + paclitaxel or albumin-bound paclitaxel



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ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
Any[b]	*BRCA1* mutation *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib	Category 1 Category 1	Preferred
HR-positive/ HER2-negative[b]	*PIK3CA* activating mutation	PCR (blood or tissue block if blood negative), molecular panel testing	Alpelisib + fulvestrant[d]	Category 1	Preferred second-line therapy
HR-negative/ HER2-negative[c]	PD-L1 expression • Threshold for positivity: ≥1% on tumor-infiltrating immune cells	IHC	Atezolizumab + albumin-bound paclitaxel[e]	Category 1	Preferred first-line therapy[h]
	PD-L1 expression • Threshold for positivity combined positive score ≥10		Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[e]	Category 1	
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[f] Entrectinib[f]	Category 2A Category 2A	Useful in certain circumstances[c]
Any	MSI-H/dMMR TMB-H (≥10 muts/mb)	IHC, PCR (tissue block) NGS	Pembrolizumab[e,g]	Category 2A	Useful in certain circumstances[i]

Immunotherapy: First-Line Rx for mTNBC

	IMPASSION 131	IMPASSION 130	KEYNOTE 355
N (PD-L1+)	943 (292, 45%) ≥1%	902 (369, 41%) ≥1%	847 (332, 38%) CPS≥10
Randomization and Treatment	2:1 Paclitaxel 90 mg/m2 Atezolizumab	1:1 nab-Paclitaxel 100 mg/m2 Atezolizumab	2:1 Pac/nab/gem+carbo Pembrolizumab
de novo	28-30%	~37% (no chemo)	30%
Prior taxane	51-53%	51%	45%
PFS in PD-L1+	5.7 → 6 mo HR 0.82 P=0.2	5 → 7.5mo HR 0.62 P<0.0001	5.6 → 9.7mo HR0.65 P=0.0012
OS benefit	No	YES	early

Mills et al, ESMO 2020; Schmid et al, Lancet Oncol 2020 and Emens et al, ESMO 2020; Cortes et al, Lancet 2020

Safety of IO in Metastatic TNBC

Organ-specific Immune-related Adverse Events in metastatic TNBC trials (n>1000 patients)

irAE		All grades (%)	Grade 3-4 (%)	Grade 5 (%)
Dermatologic	Pruritis, Rash	18	0.5	0
Endocrine	Hypothyroidism	12	0	0
	Hyperthyroidism	5	0.1	0
Gastro-intestinal	Hepatitis; elevated transaminases	10	3	0.2
	Colitis, diarrhea	2.5	0.45	0
Hematologic	Prespecified autoimmune anemia, lymphopenia, thrombocytopenia and clotting abnormalities	4	1	0.2
Respiratory	Pneumonitis	3	0.5	0.1
Other (<1%)	Adrenal insufficiency, type 1 diabetes, ocular, myositis, neurological/myositis, nephritis/elevated creatinine	<1	<0.5	0

irAE incidence in mTNBC (any grade)

- Single agent: 18.5%
- Higher in combination trials:
  - 57% atezolizumab+nab-pac
  - 42% nab-pac monotherapy

Management guidelines ASCO/NCCN
(Brahmer et al, J Clin Oncol 2018; SITC guidelines)

D'Abreo and Adams. Nat Rev Clin Oncol 2019

What is the Evidence: IO in Advanced TNBC

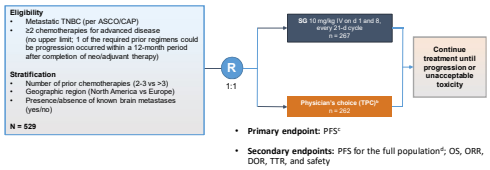
- Combining immune checkpoint inhibitors with chemotherapy
  - Improved PFS in two randomized phase III trials and continued OS benefit with atezolizumab
  - Benefit is limited to the population of patients whose tumors test positive for PD-L1
  - U.S. FDA has given accelerated approval for atezolizumab as well as pembrolizumab in PD-L1+ mTNBC.
- PD-L1
  - An imperfect biomarker although the best to date
  - Enrichment in PD-L1 positivity associated with efficacy (SP142 ≥1% correlates with CPS ≥10)
  - Different platforms require further evaluation in prospective trials
  - Use the right PD-L1 test for the chosen checkpoint inhibitor

What is the Evidence: IO in Advanced TNBC (2)

- Chemotherapy partner
  - Uncertainty without resolution; difference in unknown biomarkers
  - Best partners appear to be nab-paclitaxel, or gemcitabine and carboplatin in early relapsers; do not use paclitaxel with atezolizumab
- Toxicity
  - Provider education is critical for early diagnosis and appropriate management
- IMpassion 132
  - Gem/Carbo or capecitabine with atezolizumab or placebo in early relapsers
- Effective therapies for PD-L1- mTNBC: immunotherapy meets only a fraction of the need
  - Despite progress for PD-L1+ mTNBC, median OS still only about two years

ASCENT (Phase 3): Sacituzumab Govitecan (SG) in Pretreated mTNBC Study Design[1,2a]

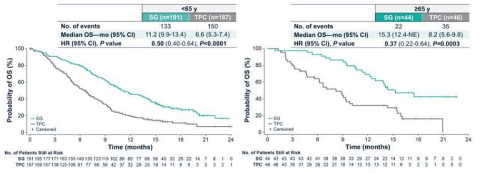
ASCENT (NCT02574455) was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation. Here, we report the primary results from ASCENT, including PFS and OS.



- **Primary endpoint:** PFS[c]
- **Secondary endpoints:** PFS for the full population[d]; OS, ORR, DOR, TTR, and safety

[a] Data cutoff date: March 11, 2020. [b] TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. [c] PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST v1.1 criteria in patients without brain metastases. [d] The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastases.
Bardia A et al. ESMO 2020. LBA17. https://clinicaltrials.gov/ct2/show/NCT02574455.

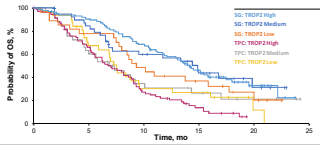
Phase 3 ASCENT Survival Outcomes: OS



- In patients aged ≥65 years, improvement in median OS with SG vs TPC treatment was comparable with that of the overall population (12.1 vs 6.7 months)[1]

1. Kalinsky K et al. ASCO 2021. Abstract 1011.

ASCENT Subgroup Analysis: OS by TROP2 Expression[1]

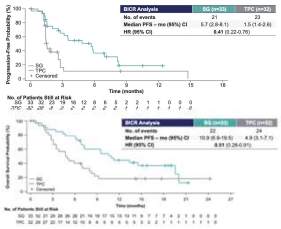


	TROP2 High | H-Score: 200-300		TROP2 Medium | H-Score: 100-200		TROP2 Low | H-Score: <100	
	SG (n = 85)	TPC (n = 72)	SG (n = 39)	TPC (n = 35)	SG (n = 27)	TPC (n = 32)
Median OS, mo (95% CI)	14.2 (11.3-17.5)	6.9 (5.3-8.9)	14.9 (6.9-NE)	6.9 (4.6-10.1)	9.3 (7.5-17.8)	7.6 (5.0-9.6)

1. Hurvitz S et al. SABCS 2020. Abstract GS3-06.

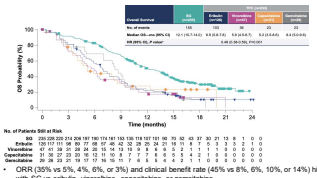
Phase 3 ASCENT Recurrence Subgroup Analysis: Survival Outcomes [1]

- 65 patients with metastatic TNBC without brain metastases
- Recurrence ≤1 year after (neo)adjuvant chemotherapy
- Patients received only 1 line of therapy in the metastatic setting
- Received SG vs TPC as 2L therapy
- Median OS: SG 10.9 mo vs TPC 4.9 mo



1. Carey LA et al. ASCO 2021. Abstract 1080.

Phase 3 ASCENT TPC Subgroup Analysis: Survival Outcomes [1]



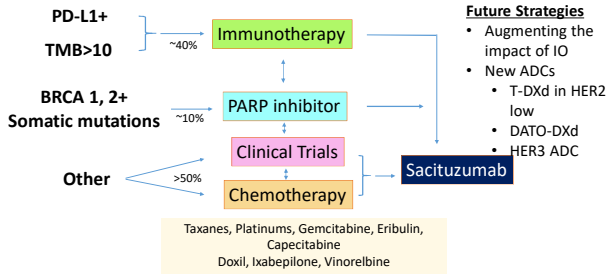
- ORR (35% vs 5%, 4%, 6%, or 3%) and clinical benefit rate (45% vs 8%, 6%, 10%, or 14%) higher with SG vs eribulin, vinorelbine, capecitabine, or gemcitabine
- 10 patients in the SG arm had a CR vs 2 in the TPC arm (eribulin)
- Median DOR was 6.3 mo for SG and ranged from 2.8-3.6 mo for TPC agents

SG improved OS compared with each TPC agent

ORR 35% with SG and 3% to 6% with TPC agents

1. O'Shaughnessy J et al. ASCO 2021. Abstract 1077.

Metastatic TNBC: Algorithm for Treatment 2021

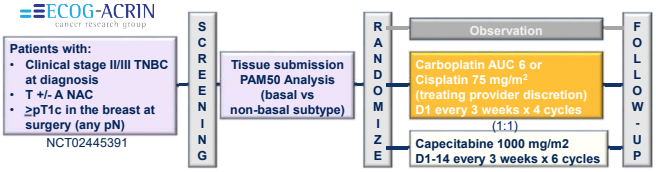


Early -Stage Disease

Northwestern Medicine

EA1131

Hypothesis: iDFS with Platinum > iDFS Capecitabine in Basal Subtype TNBC



Stratification Factors:
- Clinical stage at diagnosis (II or III)
- Tumor diameter at surgery (1-3 or >3 cm)
- Planned platinum (carboplatin or cisplatin)
- Anthracycline use (yes or no)
- RT at any time (yes or no)

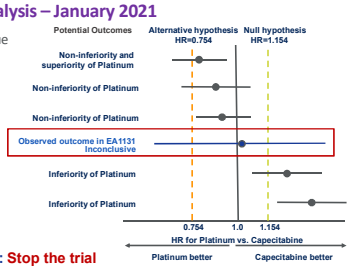
Radiotherapy:
- Prior to or after treatment (treating provider discretion)
- Required for BCS and post-mastectomy if T >5 cm and/or N3

Northwestern Medicine

Ingrid A. Mayer, MD, MSCI
(ingrid.mayer@vumc.org)

5th Interim Analysis – January 2021

- At each interim analysis, trial would be stopped due to futility if:
- Lower boundary of the two-sided 95%RCI for platinum/capecitabine > 0.754
- Conditional power < 10%



5th Interim Analysis Results

- HR for platinum/ capecitabine: 1.09 (95%RCI: 0.62, 1.90)
- Conditional power: **6%**

DSMC Recommendation (March 25, 2021): Stop the trial

- Unlikely that the trial would be able to show non-inferiority or superiority of the platinum arm
- Grade 3 and 4 toxicities were more common with platinum agents

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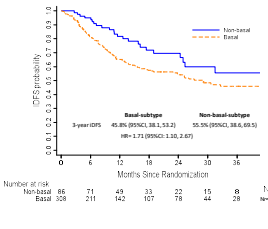
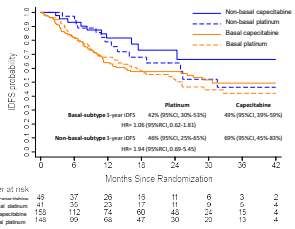
Ingrid A. Mayer, MD, MSCI (ingrid.mayer@vumc.org)

3-year iDFS by Intrinsic Subtype and Treatment

iDFS by Intrinsic Subtype



iDFS by Treatment and Intrinsic Subtype



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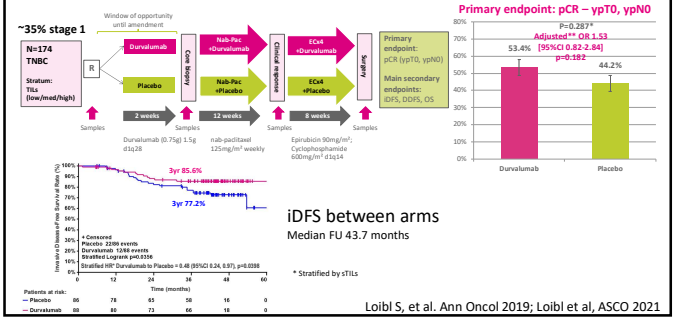
Ingrid A. Mayer, MD, MSCI (ingrid.mayer@vumc.org)

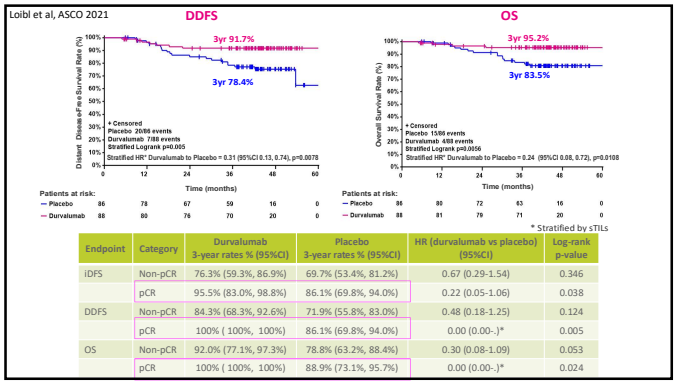
GeparNUEVO: Phase II Durvalumab Neoadjuvant Trial



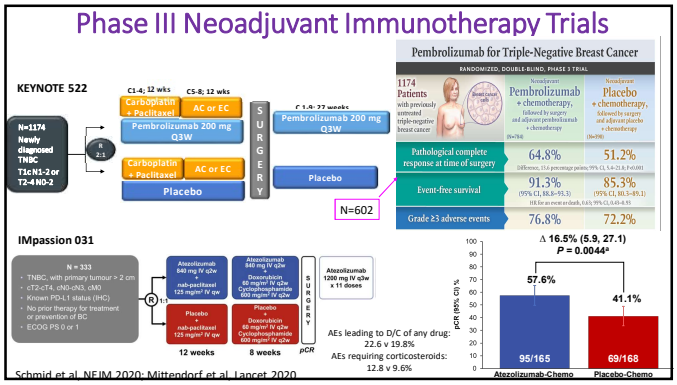
iDFS between arms
Median FU 43.7 months

* Stratified by sTILs

Loibl S, et al. Ann Oncol 2019; Loibl et al, ASCO 2021



Endpoint	Category	Durvalumab 3-year rates % (95%CI)	Placebo 3-year rates % (95%CI)	HR (durvalumab vs placebo) (95%CI)	Log-rank p-value
iDFS	Non-pCR	76.3% (59.3%, 86.9%)	69.7% (53.4%, 81.2%)	0.67 (0.29-1.54)	0.346
	pCR	95.5% (83.0%, 98.8%)	86.1% (69.8%, 94.0%)	0.22 (0.05-1.06)	0.038
DDFS	Non-pCR	84.3% (68.3%, 92.6%)	71.9% (55.8%, 83.0%)	0.48 (0.18-1.25)	0.124
	pCR	100% (100%, 100%)	86.1% (69.8%, 94.0%)	0.00 (0.00-.)*	0.005
OS	Non-pCR	92.0% (77.1%, 97.3%)	78.8% (63.2%, 88.4%)	0.30 (0.08-1.09)	0.053
	pCR	100% (100%, 100%)	88.9% (73.1%, 95.7%)	0.00 (0.00-.)*	0.024



KN 522 FDA ODAC Analysis

Data presented at the FDA ODAC meeting February 9, 2021

	Pembro + Chemo		Placebo + Chemo		P value
	n/N	%(95% CI)	n/N	%(95% CI)	
Primary analysis at IA1 (n=602)					
Patients with pCR	260/401	64.0 (60.2, 67.6)	103/201	51.2 (44.1, 58.3)	
Stratified delta[b], %(95% CI)		13.6 (5.4, 21.8)			0.00055
Supportive analysis at IA2[a] (n=1002)					
Patients with pCR	428/669	64.0 (60.2, 67.6)	182/333	54.7 (49.1, 60.1)	
Stratified delta[b], %(95% CI)		9.2 (2.8, 15.6)			0.00221[c]
Descriptive analysis at IA3[d] (N=1174)					
Patients with pCR	494/784	63.0 (59.5, 66.4)	217/390	55.6 (50.6, 60.6)	
Stratified delta[b], %(95% CI)		7.5 (1.6, 13.4)			

[a] IA2 data cut-off data: April 24, 2019.
[b] Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors.
[c] Pre-calculated P value boundary for significance of 0.0028.
[d] IA3 Data cutoff date: March 23, 2020.

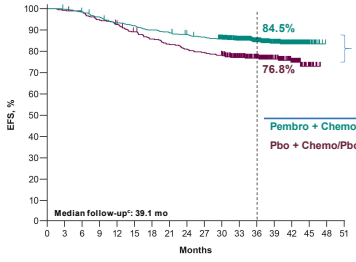
ESMO VIRTUAL PLENARY

KEYNOTE-522: Phase 3 Study of Neoadjuvant Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab versus Placebo for Early-Stage Triple-Negative Breast Cancer

Peter Schmid[1], Javier Cortes[2], Rebecca Dent[3], Lajos Pusztai[4], Heather McArthur[5], Sherko Kümmel[6], Jonas Bergh[7], Carsten Denkert[8], Yeon Hee Park[9], Rina Hui[10], Nadia Harbeck[11], Masato Takahashi[12], Michael Untch[13], Peter A. Fasching[14], Fatima Cardoso[15], Yu Ding[16], Konstantinos Tryfonidis[17], Gursel Aktan[17], Vassiliki Karantza[17], Joyce O'Shaughnessy[18]

1. Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University London, London, UK; 2. International Breast Cancer Center, Quirón Group, Madrid and Barcelona, Spain and Vall d'Hebron Institute of Oncology, Barcelona, Spain; 3. National Cancer Center Singapore, Duke–National University of Singapore Medical School, Singapore; 4. Yale School of Medicine, Yale Cancer Center, New Haven, CT, USA; 5. Breast Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; 6. Breast Unit, Kliniken Essen-Mitte, Essen, Germany; 7. Department of Oncology-Pathology, Karolinska Institutet and Breast Cancer Centre, Cancer theme, Karolinska University Hospital, Solna, Sweden; 8. Institute of Pathology, Philipps-University Marburg and University Hospital Marburg (UKGM), Marburg, Germany; 9. Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 10. Westmead Breast Cancer Institute, Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; 11. Breast Center, LMU University Hospital, Munich, Germany; 12. Department of Breast Surgery, Hokkaido Cancer Center, Sapporo, Japan; 13. Breast Cancer Center, Helios Klinikum Berlin-Buch, Berlin, Germany; 14. University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany; 15. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; 16. Biostatistics, Merck & Co., Inc., Kenilworth, NJ, USA; 17. Merck Research Laboratories, Merck & Co., Inc., Kenilworth, NJ, USA; 18. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA

Statistically Significant and Clinically Meaningful EFS at IA4



	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

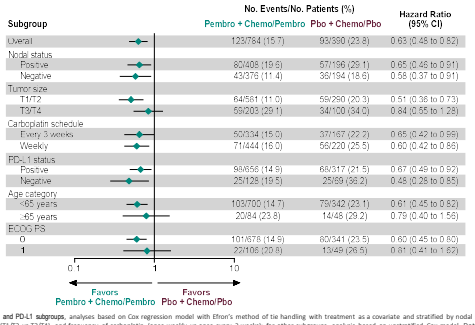
8.1% difference in EFS events
5.4% difference in distant recurrence

No. at Risk

Pembro + Chemo/Pembro	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Pbo + Chemo/Pbo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

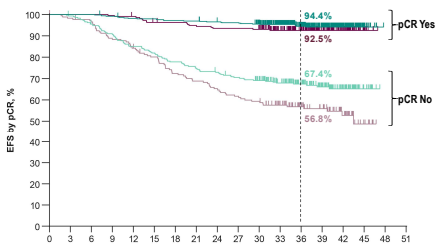
[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00517 reached at this analysis.
[c]Defined as the time from randomization to the data cutoff date of March 23, 2021.

EFS in Patient Subgroups



For overall population and PD-L1 subgroups, analyses based on Cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4), and frequency of carboplatin (once weekly vs once every 3 weeks); for other subgroups, analysis based on unstratified Cox model. Data cutoff date: March

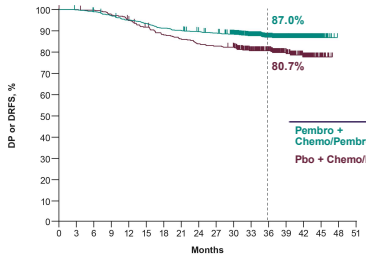
EFS by pCR (ypT0/Tis ypN0)



No. at Risk																
Pembro + Chemo/Pembro Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Pbo + Chemo/Pbo Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembro + Chemo/Pembro Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Pbo + Chemo/Pbo Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

Data cutoff date: March 23, 2021.

Distant Progression- or Distant Recurrence-Free Survival



	Events	HR (95% CI)
Pembro + Chemo/Pembro	12.8%	0.61[a] (0.46-0.82)
Pbo + Chemo/Pbo	20.3%	

No. at Risk																
Pembro + Chemo/Pembro	784	782	773	758	741	728	711	702	692	685	663	561	439	308	167	29	0	0
Pbo + Chemo/Pbo	390	389	387	379	367	352	337	330	321	317	312	259	202	143	84	17	0	0

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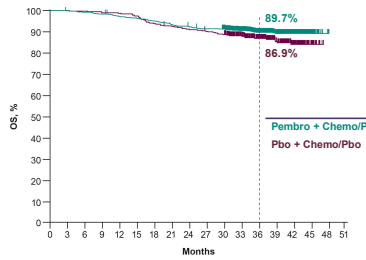
[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff date: March 23, 2021.

Overall Survival



	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	10.2%	0.72[a] (0.51-1.02)	0.03214[b]
Pbo + Chemo/Pbo	14.1%		

No. at Risk																
Pembro + Chemo/Pembro	784	782	777	770	759	752	742	729	720	712	701	586	461	323	178	30	0	0
Pbo + Chemo/Pbo	390	390	389	386	385	380	366	360	354	350	343	286	223	157	89	17	0	0

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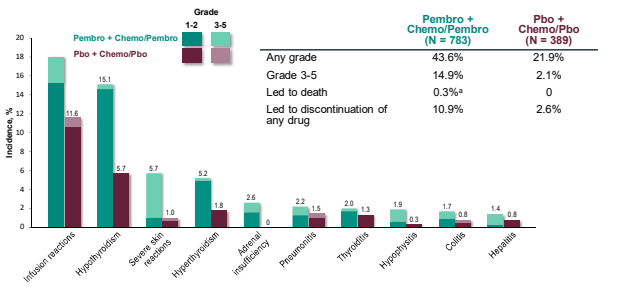
[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00086 not reached at this analysis. Data cutoff date: March 23, 2021.

Immune-Mediated AEs and Infusion Reactions in Combined Phases

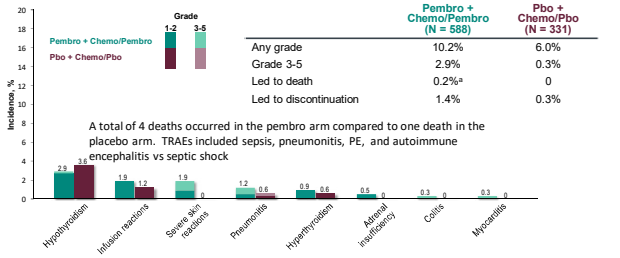


	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	10.9%	2.6%

Immune-Mediated AEs and Infusion Reactions with Incidence ≥10 Patients

[a]1 patient from pneumonitis and 1 patient from autoimmune encephalitis. Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in

Immune-Mediated AEs and Infusion Reactions in Adjuvant Phase



	Pembro + Chemo/Pembro (N = 588)	Pbo + Chemo/Pbo (N = 331)
Any grade	10.2%	6.0%
Grade 3-5	2.9%	0.3%
Led to death	0.2%[a]	0
Led to discontinuation	1.4%	0.3%

A total of 4 deaths occurred in the pembro arm compared to one death in the placebo arm. TRAEs included sepsis, pneumonitis, PE, and autoimmune encephalitis vs septic shock

Immune-Mediated AEs and Infusion Reactions with Incidence ≥2 Patients

[a]1 patient from autoimmune encephalitis. Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed.
Data cutoff date: March 23, 2021.

U.S. FOOD & DRUG ADMINISTRATION

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FDA approves pembrolizumab for high-risk early-stage triple-negative breast cancer

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Oncology (Cancer) /

On July 26, 2021, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck) for high-risk, early-stage, triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

Content current as of: 07/27/2021

Regulated Product(s)

Drugs

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A New SOC for Early TNBC! Now the Questions.....

Variable	I-SPY	KEYNOTE-522	IMPASSION 031	NeoTRIP	GeparNUEVO
Total patients	69/180	1174 (602)	333	280	174
Type of CPi	PD1 Pembro	PD1 Pambro	PD-L1 Atezo	PD-L1 Atezo	PD-L1 Durva
Stage	Stage II/III	Stage II/III	Stage II/III	Included N3 disease	35% stage I
Anthracycline pre-op	yes	yes	yes	no	yes
Included carboplatin	no	yes	No (nab-pac)	Yes (nab-pac) 2 wks on, 1 wk off x 8	no
Improved pCR	yes	yes	yes	no	yes
Improved EFS	NR: pCR>nonpCR	Yes 76.8 vs 84.5%	NR	NR	yes

- Results from GeparNUEVO raise question of optimal duration of IO therapy for early TNBC
  - With pCR - Is neoadjuvant sufficient or is one year needed?
- Optimal chemotherapy backbone? Carboplatin/anthracycline?
- Selection of those who benefit – stage? TILS? – balancing cost and toxicity in high-risk disease

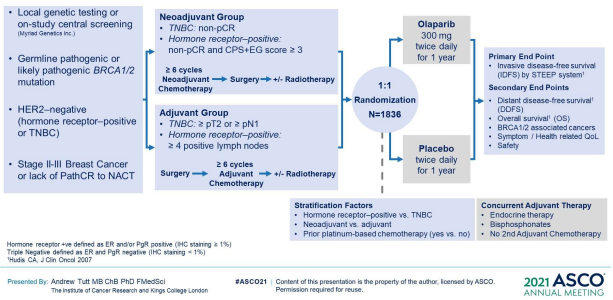
Nanda et al, JAMA Onc 2020; Schmid et al, NEJM 2020 & ESMO 2021; Mittendorf, Lancet 2020; Gianni et al, SABCS 2019; Loibl et al, Ann Oncol 2019

Ongoing Phase III Trials with IO in TNBC

Neoadjuvant/adjuvant	Adjuvant

• Atezolizumab
  • NSABP B59/GeparDouze (n=1520)
  • Pac/carbo → AC/EC
  • EFS NeoTRIPaPDL1 (n=272)
  • EFS Impassion 031 (n=333)
• Pembrolizumab
  • EFS Keynote 522 (n=1174)
  • NeoPACT (n=100)
  • Docetaxel/carbo/pembro x 6
	• Atezolizumab
	  • Impassion 30 (n=2300)
	  • Pac → AC/EC
	• Avelumab
	  • A-Brave (n=335)
	  • Adjuvant and post NAC high risk: avelumab alone
	• Pembrolizumab
	  • SWOG S1418/NRG BR006 (n=1000)
	  • Post NAC: Pembro vs Obs x 1 yr

OlympiA: Trial schema



8

OlympiA: Patient characteristics

	Olaparib (N = 921)	Placebo (N = 915)
Age, years, median (interquartile range)	**42** (36–49)	**43** (36–50)
BRCA gene affected in germline		
BRCA1	657 (**71.3%**)	670 (**73.2%**)
BRCA2	261 (**28.3%**)	239 (**26.1%**)
BRCA1 and *BRCA2*	2 (0.2%)	5 (0.5%)
BRCA testing available		
Local and central BRCA result*	550 (**59.7%**)	540 (**59.0%**)
Local testing only	130 (14.1%)	141 (15.4%)
Central Myriad testing only	240 (26.0%)	234 (25.6%)
No local or central Myriad testing available	1 (0.1%)	0 (0.0%)
Primary breast cancer surgery		
Mastectomy	698 (**75.8%**)	673 (**73.6%**)
Conservative surgery only	223 (24.2%)	240 (26.2%)
Missing	0 (0.0%)	2 (0.2%)

*Local/Central discordant results: Olaparib 12 (2.2%), Placebo 10 (1.9%), Total 22 (2.0%)

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OlympiA: Patient characteristics

	Olaparib (N = 921)	Placebo (N = 915)
Hormone receptor status*		
Hormone receptor ≥ 1% / HER2-†	168 (**18.2%**)	157 (**17.2%**)
Triple Negative Breast Cancer‡	751 (**81.5%**)	758 (**82.8%**)
Menopausal status (female only)		
Premenopausal	572/919 (62.2%)	553/911 (60.7%)
Postmenopausal	347/919 (37.8%)	358/911 (39.3%)
Prior chemotherapy		
Adjuvant (ACT)	461 (**50.1%**)	455 (**49.7%**)
Neoadjuvant (NACT)	460 (**49.9%**)	460 (**50.3%**)
Anthracycline and taxane regimen	871 (**94.6%**)	849 (**92.8%**)
Neo(adjuvant) platinum-based therapy	247 (**26.8%**)	239 (**26.1%**)
Concurrent endocrine therapy (HR–positive only)	146/168 (86.9%)	142/157 (90.4%)

*Defined by local test results
†Following a protocol amended in 2015, the first patient with hormone receptor–positive disease was enrolled in December 2015
‡Two patients are excluded from the summary of the triple–negative breast cancer subset because they do not have confirmed HER2–negative status

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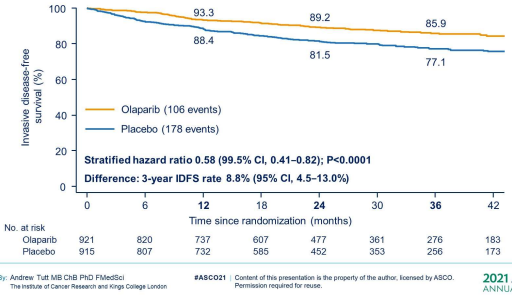
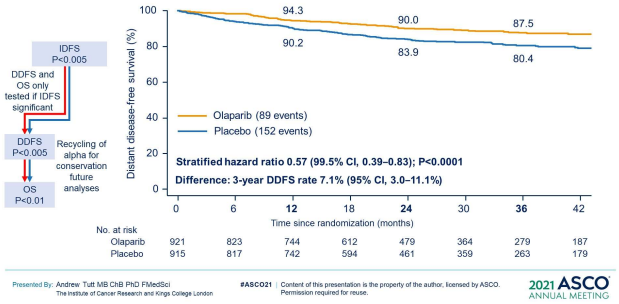
OlympiA: Invasive disease-free survival (ITT)



No. at risk

Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173

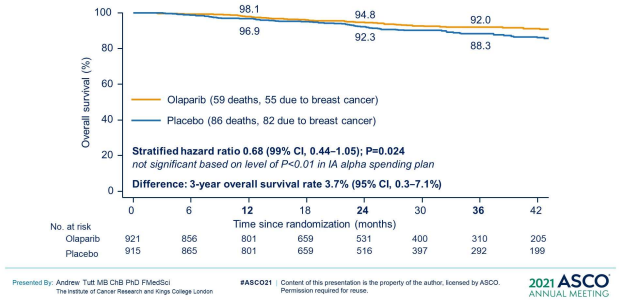
OlympiA: Distant disease-free survival



Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

2021 ASCO ANNUAL MEETING

OlympiA: Overall survival



Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

2021 ASCO ANNUAL MEETING

NCCN Guidelines Now Recommend Olaparib as a Category 1 and Preferred Treatment Regimen in Patients With Early TNBC

PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a,b,c,d,e,f]

HER2-Negative[d,h]	
Preferred Regimens: • Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks[i] • Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel[i] • TC (docetaxel and cyclophosphamide)	
• If triple-negative breast cancer (TNBC) and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy:[j] ▸ Capecitabine; or ▸ Olaparib, if high risk[k] and germline *BRCA1/2* mutations	
Useful in Certain Circumstances: • Dose-dense AC (doxorubicin/cyclophosphamide) • AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B) • CMF (cyclophosphamide/methotrexate/fluorouracil) • AC followed by weekly paclitaxel[i]	**Other Recommended Regimens:** • AC followed by docetaxel every 3 weeks[i] • EC (epirubicin/cyclophosphamide) • TAC (docetaxel/doxorubicin/cyclophosphamide) • Select patients with TNBC in the preoperative setting only:[i] ▸ Weekly paclitaxel + carboplatin[l] ▸ Docetaxel + carboplatin[l]

[a]The regimens listed in the table for HER2-negative disease are all category 1 (except where indicated) when used in the adjuvant setting.
[k]Consider addition of adjuvant olaparib for 1 y after adjuvant chemotherapy for those with germline *BRCA1/2* mutations and either 1) TNBC and ≥pT2 or ≥ pN1 disease (category 1); or 2) HR-positive, HER2-negative h4 positive lymph nodes. For those with germline *BRCA1/2* mutations and HR-positive, HER2-negative disease who received neoadjuvant chemotherapy, consider adjuvant olaparib for 1 y if residual disease and a clinical stage, pathologic stage, estrogen receptor status, and tumor grade (CPS+EG) score ≥3. (The patients in OlympiA trial did not receive capecitabine, thus there is no data on sequencing or to guide selection of one over the other.)
[l]Not-risk group includes those with no cCR and CPS+EG score of ≥3. The CPS+EG scoring system estimates probability of relapse based on clinical and pathological stage (CPS) and estrogen receptor status and histologic grade (EG).

Olaparib Recommended in ASCO guidelines as Adjuvant Therapy in *gBRCA*m High-Risk Early Breast Cancer

2021 Updated Recommendation: The updated recommendation for June of 2021 is -- For patients with early-stage, human epidermal growth factor receptor 2 (HER2)–negative breast cancer with high risk of recurrence and germline ***BRCA1*** or ***BRCA2*** pathogenic or likely pathogenic variants, one year of adjuvant olaparib should be offered after completion of (neo)adjuvant chemotherapy and local treatment, including radiation. For those who had surgery first, adjuvant olaparib is recommended for patients with TNBC and tumor size > 2 cm. or any involved axillary nodes. For those with hormone receptor-positive disease, adjuvant olaparib is recommended for those with at least four involved axillary lymph nodes. For patients who had neoadjuvant chemotherapy, adjuvant olaparib is recommended for patients with TNBC and any residual cancer; for patients with hormone receptor-positive disease, adjuvant olaparib is recommended for patients with residual disease and an estrogen receptor status and tumor grade (CSP+EG) score ≥ 3.

ASCO Guideline. Accessed June 29, 2020. https://www.asco.org/research-guidelines/quality-guidelines/guidelines/breast-cancer#!/143725.

Thank You

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