Best of ASCO 2019: Update on GI Cancers

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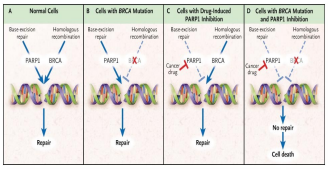
The role of PARP inhibitor maintenance in gBRCA mutated mPDAC

RESULTS OF THE PHASE III POLO TRIAL

Synthetic Lethality and DNA Repair in Pancreatic Cancer



	Phase II trial of olaparib in BRCA mutated cancers (PDAC, N = 23)
Median PFS	4.6 months
ORR	21.7%

Iglehart JD and Silver DP, *NEJM* 2009; 361: 189-191
Kaufman B et al, *JCO* 2015; 33: 244-250

Phase III POLO trial: olaparib as maintenance therapy following platinum-based chemo in gBRCA mutated mPDAC

METHODS

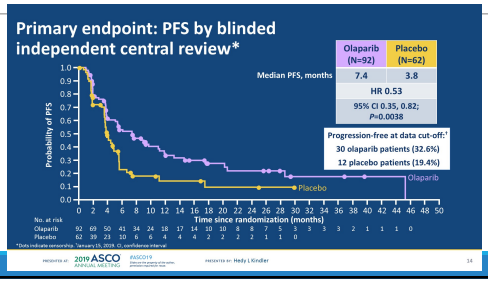
- 3315 patients screened with a 7% detection rate of gBRCA1/2 mutation(247 patients identified) -> 154 randomized
- Received at least 16 weeks of first line platinum based chemo for metastatic disease without progression
- 154 patients randomized 3:2 to maintenance olaparib (300mg BID) or placebo
- Primary endpoint: PFS (starting from time of randomization)

PATIENT CHARACTERISTICS

Patient Characteristics		Olaparib (N = 92)	Placebo (N = 62)
Time from diagnosis to randomization	Median, months (range)	6.9 (3.6 – 38.4)	7.0 (4.1 – 30.2)
Duration of first-line chemotherapy	Median, months (range)	5.0 (2.5 – 35.2)	5.1 (3.4 – 20.4)
First-line chemo	FOLFIRINOX	79 (85.9)	50 (80.6)
Best response on chemo	CR or PR	46 (50)	30 (48.4)

Kindler HL et al, *JCO suppl*; abstract LBA4

Improved PFS with olaparib maintenace



Other Conclusions

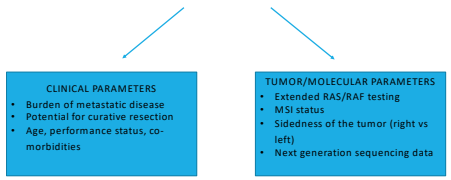
- Interim OS data showed no difference between arms at 46% maturity (18.9 vs 18.1 months, HR 0.91, p = 0.68)
- No difference between the two arms in terms of quality of life assessments
- There was no unexpected toxicity from olaparib compared to AE data from other trials
  - Most common AEs: fatigue, nausea, diarrhea, abdominal pain, anemia, decreased appetite, constipation, vomiting, back pain and arthralgia

Is there a role for 1st line therapy with FOLFOXIRI in mCRC

VISNU-1: FOLFOXIRI + bevacizumab vs FOLFOX + bevacizumab in mCRC deemed high risk by presence of ≥ 3 CTC

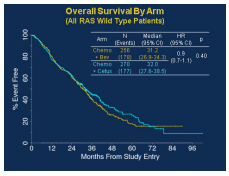
TRIBE-2: FOLFOXIRI plus bevacizumab vs sequential FOLFOX + bevacizumab -> FOLFIRI plus bevacizumab

General Principles of Treating Metastatic Colorectal Cancer Patients



CALGB 80405: Establishing a paradigm for RAS/RAF wild-type mCRC

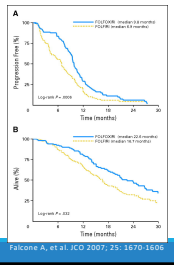
- First line randomized study of mFOLFOX6 vs FOLFIRI combined with either cetuximab or bevacizumab in 1137 patients with untreated RAS wt mCRC
- Global provider preference for FOLFOX over FOLFIRI (73 vs 27%)
- Response rates were 55% in the bevacizumab group and 59% in the cetuximab group (p = 0.13)
- 140 patients underwent curative resection following chemotherapy (mOS for bevaciumab group 62 months, cetixumab 65 months).



Venook AP et al. JAMA 317(23): 2392-2401, 2017

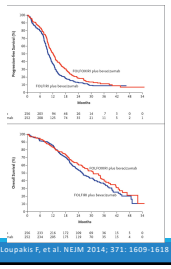
Phase III trials with improved outcomes with FOLFOXIRI compared to FOLFIRI

Phase III GONO (N = 244)



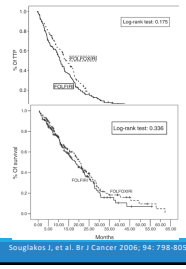
Falcone A, et al. JCO 2007; 25: 1670-1606

TRIBE (N = 508)



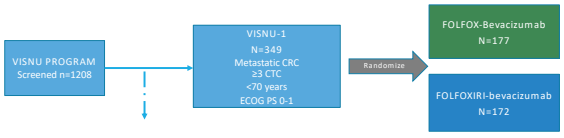
Loupakis F, et al. NEJM 2014; 371: 1609-1618

Phase III HORG (N = 285)



Souglakos J, et al. Br J Cancer 2006; 94: 798-805

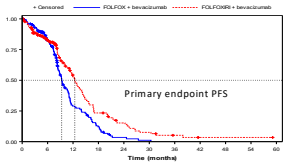
VISNU-1 Design



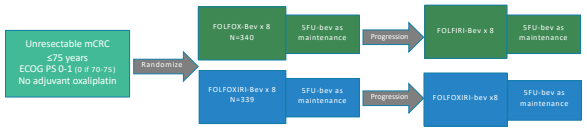
Sastre J et al, JCO 37 (Abstract 3507); ASCO 2019

VISNU-1: Key Results

	FOLFOXIRI-bev N=172	FOLFOX-bev N=177	HR, 95% CI
PFS	12.4m	9.3m	0.64 (.49-.82) P = 0.0004
OS	22.3m	17.6m	0.862 (.66-1.06)
RR	59%	52%	

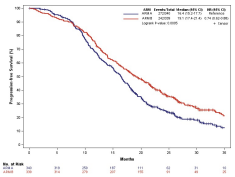


TRIBE-2 Design



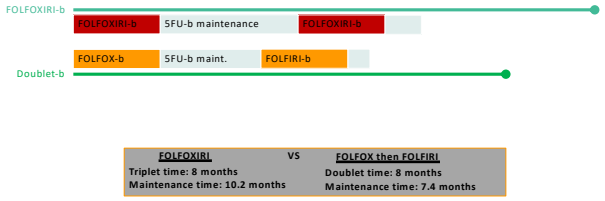
Cremolini C et al. JCO 37, 2019 (Abstract 3508) ASCO 2019

TRIBE2: Key Results



	FOLFOXIRI-bev N=339	Sequential doublet-bev N=340	
PFS2	**19.1m**	**17.5 m**	**HR 0.74 (.62-.88)**
PFS1	12.0m	9.8 m	HR 0.75 (.63-.88)
OS	27.6m	22.6 m	HR 0.81 (.67-.98)
RR	62%	50% (FOLFOX-bev)	
2nd line RR	19%	12%	
2nd line PFS	6.2 m	5.6 m	HR .87 (.73-1.04)

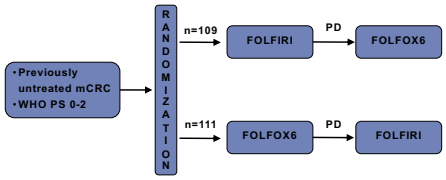
Time on Treatment during TRIBE-2



FOLFOXIRI	VS	FOLFOX then FOLFIRI
Triplet time: 8 months		Doublet time: 8 months
Maintenance time: 10.2 months		Maintenance time: 7.4 months

Slide courtesy of Dr. Hanna Sanoff, ASCO 2019

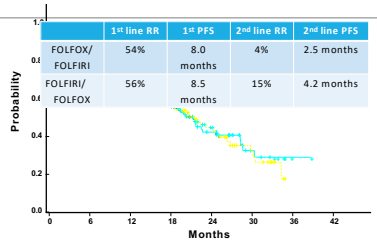
Are we burning a bridge by using all our cytotoxics up front?



Tournigand et al. *J Clin Oncol.* 2004;22:229.

1st line therapy provides majority of benefit with lower 2nd line PFS

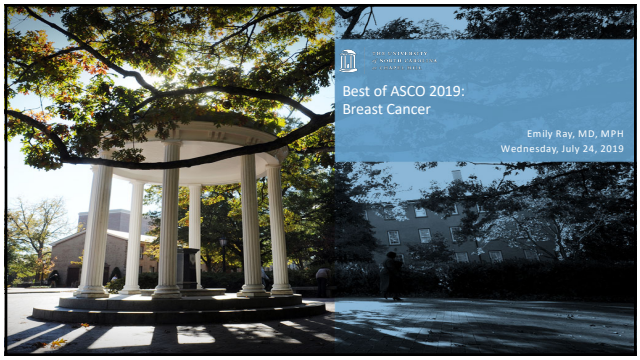
	1st line RR	1st PFS	2nd line RR	2nd line PFS
FOLFOX/ FOLFIRI	54%	8.0 months	4%	2.5 months
FOLFIRI/ FOLFOX	56%	8.5 months	15%	4.2 months



Tournigand et al. *J Clin Oncol.* 2004;22:229

Overview of treating mCRC

- While FOLFOXIRI has been shown to improve outcomes compared to both FOLFIRI and FOLFOX, this approach is not appropriate for all patients
  - Both trials excluded patients based on age (no one greater than 75). For frailer patients or those with lower burden of disease, may be more reasonable to start with a doublet
- Importantly, patients having received adjuvant oxaliplatin were excluded from TRIBE2 (only 4% in VISNU1)
- TRIBE2 shows minimal benefit for re-introducing FOLFOXIRI vs restarting a doublet at time of progression



Outline

Neoadjuvant and Adjuvant Therapies

-HER2+ breast cancer (Abstract 500)

-HR+ breast cancer (Abstract 514)

Metastatic Breast Cancer Therapies

-HER2+ breast cancer (Abstract 1000)

-HR+ breast cancer (Late-breaking abstract 1008)

-Triple negative breast cancer (Abstract 1003)

Supportive Therapies (Abstract 6527)

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Neoadjuvant and Adjuvant Therapies

HER2+ breast cancer

KATHERINE trial (N Engl J Med 2019; 380:617-628)

- Established the role of trastuzumab emtansine (T-DM1), an antibody-drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1) in the **adjuvant** setting for patients with **residual invasive breast cancer** following neoadjuvant therapy
- Invasive disease–free survival was significantly higher in the T-DM1 group than in the trastuzumab group (HR 0.50)

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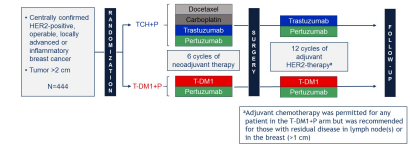
KRISTINE Study Design



*Adjuvant chemotherapy was permitted for any patient in the T-DM1+P arm but was recommended for those with residual disease in lymph node(s) or in the breast (>1 cm)

Stratification factors: local HR status, geographic location, and clinical stage at presentation

Primary endpoint: pCR by local assessment (ypT0/is, ypN0)

Secondary endpoints: EFS, IDFS, OS, safety, PRO

EFS, event-free survival; HR, hormone receptor; IDFS, invasive disease-free survival; OS, overall survival; pCR, pathological complete response; PRO, patient-reported outcomes.

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J Clin Oncol 37, 2019 (suppl; abstr 500)

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Primary Results

- Neoadjuvant TCH+P resulted in a superior pCR rate compared with T-DM1+P
  - 56% vs 44%, *P*=0.0155[1]
  - pCR rates were higher with TCH+P in tumors with IHC2+ HER2 staining (21% vs 7%), or IHC3+ HER2 staining (61% vs 50%)[2]
- During neoadjuvant treatment, T-DM1+P had a more favorable safety profile than TCH+P[1]
  - Lower incidence of grade ≥3 adverse events (13% vs 64%)
  - Lower incidence of serious adverse events (5% vs 29%)
  - Lower incidence of adverse events leading to treatment discontinuation (3% vs 8%)

1. Hurvitz et al. *Lancet Oncol* 2018;19:115; 2. de Haas et al. Presented at SABCS 2016; P6-07-09.

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EFS Events

Event, n (%)	T-DM1+P (n=223)	TCH+P (n=221)
Total number of EFS events	31 (13.9)	13 (5.9)
Locoregional progression before surgery	15 (6.7)[a]	0
Invasive disease recurrence after surgery	11 (4.9)	11 (5.0)
Non-invasive recurrence (DCIS) after surgery	3 (1.3)	0
Death without prior EFS event	2 (0.9)	2 (0.9)

[a]No surgery date was recorded for these patients; therefore they were not included in the IDFS analysis. All of these patients, however, were included in the OS analysis.

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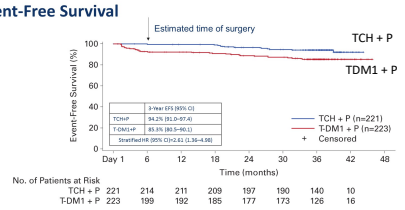
Event-Free Survival



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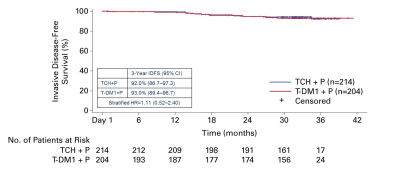
Invasive Disease-Free Survival



J Clin Oncol 37, 2019 (suppl; abstr 500)

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Take-Home Points

Higher risk of EFS event in T-DM1+P arm (HR 2.61, 95% CI 1.36-4.98)
- Driven by presurgical locoregional progression which was associated with lower HER2 expression and greater HER2 heterogeneity

Similar risk of IDFS event between arms (HR 1.11, 95% CI 0.52-2.40)
- Is systemic chemotherapy unnecessary for some patients?
- Area of needed investigation before can be implemented in practice

Patients attaining pCR had ~97% 3-year IDFS

AEs and PROs favor T-DM1

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Clinical Application

Would not routinely use T-DM1+P in the neoadjuvant setting

Could consider using for patients unable to tolerate chemotherapy or unwilling to take chemotherapy

Unclear if we can use chemotherapy-sparing neoadjuvant regimens in some patients – further investigation required

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Neoadjuvant and Adjuvant Therapies

HR+ breast cancer – Duration of Endocrine Tx

The **Clinical Treatment Score at 5 years (CTS5)** is a prognostic tool using clinicopathological data to estimate **distant recurrence (DR) risk after 5 years of endocrine therapy** for postmenopausal women with estrogen receptor positive (ER+) breast cancer.

It was developed and validated in the ATAC and BIG 1-98 trials.

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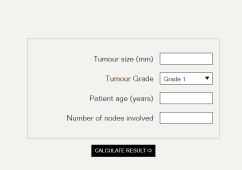
J Clin Oncol 37, 2019 (suppl; abstr 514)

HR+ breast cancer – Duration of ET



https://www.cts5-calculator.com/

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J Clin Oncol 37, 2019 (suppl; abstr 514)

HR+ breast cancer – Duration of ET

Methods: The validity of CTS5 was tested in a retrospective cohort of unselected, non-trial patients diagnosed with early ER+ breast cancer at the Royal Marsden Hospital from 2000-2007 who were alive and distant recurrence-free at 5 years.

Primary endpoint: Time to late distance recurrence (5-10 years).

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HR+ breast cancer – Duration of ET

		HR for late distant recurrence (95% CI)	P-value
Postmenopausal (N=1662, DR=107)	CTSS (continuous)	1.95 (1.59-2.39)	<0.0001
	CTSS low	Reference	
	CTSS intermediate	2.28 (1.32-3.93)	0.003
	CTSS high	3.81 (2.27-6.41)	<0.0001
Premenopausal (N=776, DR=51)	CTSS (continuous)	1.72 (1.23-2.40)	0.001
	CTSS low	Reference	
	CTSS intermediate	1.69 (0.84-3.51)	0.16
	CTSS high	2.63 (1.29-5.34	0.008

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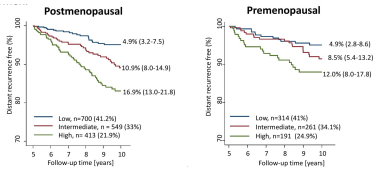
HR+ breast cancer – Duration of ET



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HR+ breast cancer – Duration of ET

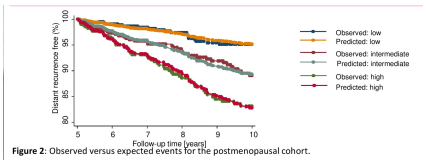

Figure 2: Observed versus expected events for the postmenopausal cohort.

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Take-Home Points

CTS5 is validated in an unselected, non-trial cohort, including pre-menopausal patients

Calibration was less accurate in pre-menopausal patients compared to post-menopausal

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Clinical Application

These findings highlight the prognostic value of the CTS5 calculator, not the predictive value (i.e. likelihood of benefit of further endocrine therapy)

- Therefore, this tool should be used to identify patients whose risk of distant recurrence after 5 years of ET is so low that extended ET could not possibly be beneficial

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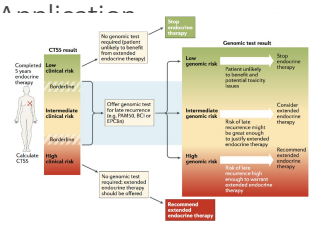
Clinical Application



Proposed extended endocrine therapy algorithm, adapted from Richman and Dowsett, NCRO, 2018.

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J Clin Oncol 37, 2019 (suppl; abstr 514)

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- Triple negative breast cancer (Abstract 1003)

Supportive Therapies (Abstract 6527)

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Metastatic Breast Cancer – HER2+

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Persistent Unmet Need in HER2+ MBC After Anti-HER2 Therapy

- Current standard of care for HER2-positive MBC
  - First-line: trastuzumab and pertuzumab with chemotherapy[1-3]
  - Second-line: T-DM1[4,5]
- After the above therapies, there is no recognized standard of care
  - Subsequent therapies are poorly defined, including sequential chemotherapy with trastuzumab and/or lapatinib[6,7]
  - Continued anti-HER2 therapy after progression is generally preferred, in combination with chemotherapy[8-11]

HER2=human epidermal growth factor receptor 2; MBC=metastatic breast cancer; T-DM1=ado-trastuzumab emtansine.

1. Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119. 2. Swain SM, et al. *Lancet Oncol*. 2013;14(6):461-471. 3. Swain SM, et al. *N Engl J Med*. 2015;372(8):724-734. 4. Verma S, et al. *N Engl J Med*. 2012;367(19):1783-1791. 5. Dieras V, et al. *Lancet Oncol*. 2017;18(6):732-742. 6. Giordano SH, et al. *J Clin Oncol*. 2018;36(26):2736-2740. 7. Cardoso F, et al. *Ann Oncol*. 2018;29(6):1634-1657. 8. von Minckwitz G, et al. *J Clin Oncol*. 2009;27(12):1999-2006. 9. von Minckwitz G, et al. *Eur J Cancer*. 2011;47(15):2273-2281. 10. Geyer CE, et al. *N Engl J Med*. 2006;355(26):2733-2743. 11. Cameron D, et al. *Oncologist*. 2010;15(9):924-934.

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J Clin Oncol 37, 2019 (suppl; abstr 1000)

Presented By Hope Rugo at 2019 ASCO Annual Meeting

SOPHIA Primary PFS Analysis: A Phase 3 Study of Margetuximab + Chemotherapy vs Trastuzumab + Chemotherapy in Patients With HER2+ Metastatic Breast Cancer After Prior Anti-HER2 Therapies

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Abstract #1000 PRESENTED AT 2019 ASCO ANNUAL MEETING #ASCO19

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J Clin Oncol 37, 2019 (suppl; abstr 1000)
Presented By Hope Rugo at 2019 ASCO Annual Meeting

Margetuximab: Fc-engineered to Activate Immune Responses

Trastuzumab

Fab:
- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival

Fc:
- Wild-type immunoglobulin G1 (IgG1) immune effector domains
- Binds and activates immune cells

Margetuximab[1,2]

Fab:
- Same specificity and affinity
- Similarly disrupts signaling

Fc engineering:
- ↑ Affinity for activating FcγRIIIA (**CD16A**)
- ↓ Affinity for inhibitory FcγRIIB (**CD32B**)

Margetuximab Binding to FcγR Variants:

Receptor Type	Receptor	Allelic Variant	Relative Fc Binding	Affinity Fold-Change
Activating	CD16A	158F	Lower	6.6x ↑
		158V	Higher	4.7x ↑
	CD32A	131R	Lower	6.1x ↓
		131H	Higher	↔
Inhibitory	CD32B	232T	Equivalent	8.4x ↓

1. Nordstrom JL, et al. Breast Cancer Res. 2011;13(6):R123. 2. Stevenhagen JB, et al. Cancer Res. 2007;67(18):8882-8890.

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Study CP-MGAH22-04 (SOPHIA) Design[1,2]

HER2+ advanced breast cancer
- ≥2 prior anti-HER2 therapies, including pertuzumab
- 1-3 prior treatment lines in metastatic setting
- Prior brain metastasis ok if treated and stable

Investigator's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)

1:1 Randomization (N=536)

Arm 1
Margetuximab (15 mg/kg Q3W) + **chemotherapy** in 3-week cycles

Arm 2
Trastuzumab (8 mg/kg loading → 6 mg/kg Q3W) + **chemotherapy** in 3-week cycles

Sequential Primary Endpoints	• **PFS** (by CBA; n=257; HR=0.67; α=0.05; power=90%) • **OS** (n=385; HR=0.75; α=0.05; power=80%)
Secondary Endpoints	• PFS (investigator assessed) • Objective response rate (by CBA)
Tertiary/Exploratory Endpoints	• Clinical benefit rate (CBR), duration of response (DoR) • Safety profile, antidrug antibody • Effect of CD16A, CD32A, and CD32B on margetuximab efficacy

Stratification:
- Chemotherapy choice
- Prior therapies (≤2 *vs* >2)
- Metastatic sites (≤2 *vs* >2)

HR=hazard ratio; CBA=central blinded analysis.

1. Rugo HS, et al. J Clin Oncol. 2019;37(suppl 15):TPS630. 2. Clinicaltrials.gov. NCT02492711. www.clinicaltrials.gov/ct2/show/NCT02492711. Accessed April 8, 2019.

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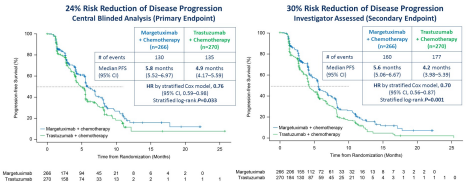
PFS Analysis in ITT Population



• PFS analysis was triggered by last randomization on October 10, 2018, after 265 PFS events occurred

ITT population; N=536, CI=confidence interval.

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PFS Subgroup Analyses

	Median PFS (95% CI), Months: Margetuximab + Chemotherapy	Trastuzumab + Chemotherapy	HR by Unstratified Cox Model	95% CI	Unstratified Log-Rank *P* Value
All patients, n=536	5.8 (5.52–6.97)	4.9 (4.17–5.59)	0.78	(0.61–0.99)	0.044
Capecitabine, n=543	8.3 (5.55–11.50)	5.5 (4.17–8.28)	0.77	(0.47–1.26)	0.302
Eribulin, n=336	6.0 (3.81–8.05)	4.2 (3.38–5.55)	0.66	(0.42–1.05)	0.080
Gemcitabine, n=66	5.6 (4.07–11.01)	3.5 (1.45–7.16)	0.58	(0.29–1.18)	0.128
Vinorelbine, n=191	5.6 (4.26–6.97)	5.1 (3.42–6.67)	0.90	(0.60–1.35)	0.606
>2 metastatic sites, n=256	6.3 (5.42, 8.08)	4.2 (3.38, 5.55)	0.63	(0.44–0.89)	0.009
≤2 metastatic sites, n=282	5.7 (4.47, 6.97)	5.5 (4.24, 5.85)	0.94	(0.67–1.31)	0.702
Hormone Receptor+, n=390	5.8 (4.80, 7.23)	4.2 (2.83, 5.55)	0.58	(0.39–0.86)	0.007
Hormone Receptor-, n=334	5.7 (5.52, 8.18)	5.5 (4.24, 7.03)	0.88	(0.64–1.19)	0.393
HER2 IHC 3+, n=293	6.9 (5.55, 8.31)	5.6 (3.98, 5.85)	0.64	(0.46–0.90)	0.011
HER2 ISH amplified, n=245	5.9 (4.01, 8.60)	4.6 (4.07, 5.55)	1.01	(0.71–1.42)	0.972
Age >60 years, n=170	8.9 (5.52, 10.51)	5.6 (4.14, 5.85)	0.58	(0.36–0.92)	0.020
Age ≤60 years, n=366	5.6 (4.24, 6.97)	4.6 (4.01, 5.59)	0.87	(0.66–1.16)	0.337
Prior (neo)adjuvant Tx: yes, n=303	6.3 (5.59–6.93)	5.4 (4.01–5.59)	0.67	(0.48–0.93)	0.014
Prior (neo)adjuvant Tx: no, n=233	5.6 (3.71–6.97)	4.9 (4.07–7.16)	0.99	(0.68–1.42)	0.935

0.0 0.5 1.0 1.5 2.0

Margetuximab Better | Trastuzumab Better

Hormone receptor positive=ER+ and/or PgR+; hormone receptor negative=ER- and PgR-; IHC=immunohistochemistry; ISH=in situ hybridization; Tx=treatment.

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Planned* Exploratory PFS Analyses by FcγR Genotypes (CBA)

Margetuximab benefit appears to be increased in low-affinity CD16A-158F allele carriers

		Median PFS (95% CI), Months: Margetuximab + Chemotherapy	Trastuzumab + Chemotherapy	HR by Unstratified Cox Model	95% CI	Unstratified Log-Rank *P* Value
	All patients	5.8 (5.52–6.97)	4.9 (4.17–5.59)	0.78	(0.61–0.99)	0.044
Activating function	CD16A/F carrier (FV or FF), n=457	6.9 (5.55–8.15)	5.1 (4.14–5.59)	0.68	(0.52–0.90)	0.005
	CD16A/FF, n=192	8.2 (5.52–10.51)	5.6 (4.50–8.31)	0.69	(0.46–1.05)	0.080
	CD16A/FV, n=245	6.3 (5.52–7.23)	4.3 (4.01–5.59)	0.71	(0.50–1.01)	0.055
	CD16A/VV, n=69	4.8 (2.46–5.65)	5.4 (2.86–11.04)	1.78	(0.87–3.62)	0.110
	CD32A/RR, n=122	5.7 (4.00–10.55)	3.5 (2.76–4.21)	0.69	(0.41–1.17)	0.166
	CD32A/RH, n=247	6.9 (5.55–8.15)	5.6 (4.17–6.67)	0.74	(0.52–1.06)	0.102
	CD32A/HH, n=137	5.6 (3.29–8.28)	4.1 (2.79–5.59)	0.80	(0.49–1.30)	0.365
Inhibitory function	CD32B/I+, n=380	5.8 (5.55–7.66)	3.5 (4.17–5.65)	0.85	(0.64–1.13)	0.265
	CD32B/I-, n=117	6.0 (4.14–NA)	3.5 (2.79–7.16)	0.63	(0.36–1.10)	0.098

0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0

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*Non-alpha allocating, exploratory analysis.
†CD32B/TT not included on forest plot because n=9 is too small (5 on margetuximab, 4 on trastuzumab) to make analysis meaningful.

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AEs Regardless of Causality

	Margetuximab + Chemotherapy (n=264)		Trastuzumab + Chemotherapy (n=265)	
Most common AEs, n (%)	**All Grade***	**Grade ≥3†**	**All Grade***	**Grade ≥3†**
Fatigue	103 (39.0)	12 (4.5)	92 (34.7)	7 (2.6)
Nausea	81 (30.7)	3 (1.1)	84 (31.7)	1 (0.4)
Neutropenia	73 (27.7)	51 (19.3)	51 (19.2)	30 (11.3)
Diarrhea	59 (22.3)	6 (2.3)	62 (23.4)	5 (1.9)
Anemia	48 (18.2)	12 (4.5)	55 (20.8)	17 (6.4)
Neutrophil count decreased	32 (12.1)	22 (8.3)	35 (13.2)	25 (9.4)
Febrile neutropenia	8 (3.0)	8 (3.0)	12 (4.5)	12 (4.5)
AEs of special interest, n (%)	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**
Infusion-related reaction (IRR)[‡]	**34 (12.9)**	**4 (1.5)**	**10 (3.8)**	**0**
Left ventricular dysfunction	6 (2.3)	3 (1.1)	7 (2.6)	1 (0.4)
Discontinuation due to IRRs, n (%)	3 (1.1)	2 (0.8)	0	0

Safety Population: N=529.
*Incidence ≥20% in either treatment group.
†Incidence ≥3% in either treatment group.
‡All patients received prior trastuzumab. In pivotal trials of trastuzumab, IRRs occurred in 21% to 40% of patients (US package insert).

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Take-Home Points

In combination with chemotherapy in pretreated HER2+ MBC, margetuximab improves PFS over trastuzumab with comparable safety.

Overall survival data in the ITT population showed a non-significant 1.7-month difference favoring the margetuximab arm, which grew to 6.7 months in the CD16A FV/FF allele group (94% of patients)

A second interim analysis for overall survival is expected later this year.

Clinical Application

Margetuximab with chemotherapy could be considered in the 3rd line for patients with HER2+ MBC

- Clear PFS benefit
- OS benefit yet to be established, stay tuned
- Need further investigation regarding patient selection according to genotype

Metastatic Breast Cancer – HR+

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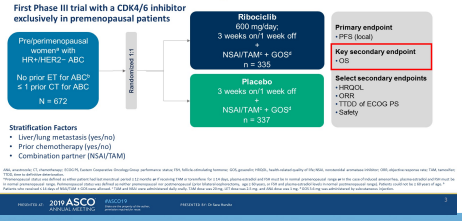
MONALEESA-7 Study Design

First Phase III trial with a CDK4/6 inhibitor exclusively in premenopausal patients



Stratification Factors
- Liver/lung metastasis (yes/no)
- Prior chemotherapy (yes/no)
- Combination partner (NSAI/TAM)

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Unmet Needs in Premenopausal Patients With Advanced Breast Cancer

- Young women with breast cancer tend to have poorer prognoses and more aggressive cancer compared with older women, yet premenopausal patients are underrepresented in clinical trials[1-3]
- Ribociclib, a CDK4/6 inhibitor, plus ET with ovarian suppression demonstrated a significantly longer PFS vs ET alone as initial ET in premenopausal patients with HR+/HER2– ABC in the MONALEESA-7 trial[4] (23.8 vs 13 mos, HR 0.55)
- **To date, there have been no reports of a statistically significant improvement in OS with the addition of a CDK4/6 inhibitor to ET**

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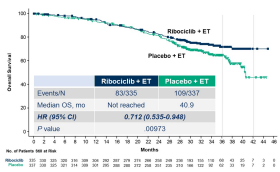
Overall Survival



	Ribociclib + ET	Placebo + ET
Events/N	83/335	109/337
Median OS, mo	Not reached	40.9
HR (95% CI)	*0.712 (0.535-0.948)*	
P value	.00973	

- ≈ 29% relative reduction in risk of death
- The *P* value of .00973 crossed the prespecified boundary to claim superior efficacy

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	71.9%	64.9%
42 months	*70.2%*	*46.0%*

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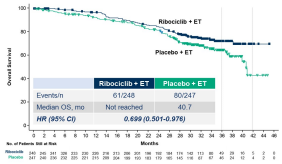
Overall Survival in the NSAI Subgroup



	Ribociclib + ET	Placebo + ET
Events/n	61/248	80/247
Median OS, mo	Not reached	40.7
HR (95% CI)	*0.699 (0.501-0.976)*	

- ≈ 30% relative reduction in risk of death

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	72.2%	64.6%
42 months	69.7%	43.0%

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Take-Home Points

Ribociclib plus ET has favorable PFS and OS compared to ET alone in pre-menopausal patients with HR+ metastatic breast cancer

No other CDK 4/6 inhibitor has a proven OS benefit

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Clinical Application

CDK 4/6 inhibitor plus ET is the clear choice for first-line treatment of HR+, HER2-negative advanced breast cancer

- Different agents have been used interchangeably with choice of agent often driven by affordability to patient, dosing, side effect profile
- Ribociclib may become the preferred agent as the only CDK 4/6 inhibitor with proven overall survival benefit

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Metastatic Breast Cancer – TNBC

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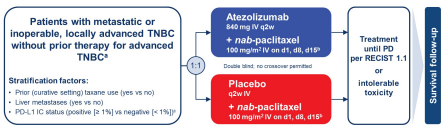
IMpassion130 Study Design



- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

[a] Prior chemotherapy in the curative setting allowed if treatment-free interval ≥ 12 months. [b] 28-day cycle. [c] Centrally evaluated per VENTANA SP142 IHC assay. [d] Efficacy endpoints assessed by investigators per RECIST 1.1; NCT02425891.

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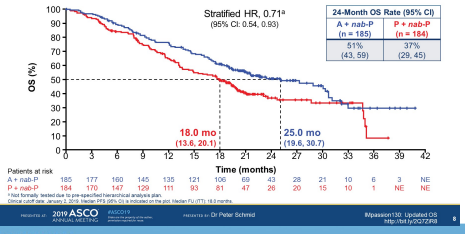
OS in PD-L1+ Population



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Take-Home Points

IMpassion130 is the first and only phase 3 study to show the clinically meaningful benefit of immunotherapy in metastatic TNBC

PD-L1 status predicts clinical benefit of atezolizumab plus nab-paclitaxel

No new safety signals in updated analysis

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Clinical Application

Atezolizumab + nab-paclitaxel is FDA approved and recommended for the treatment of patients with PD-L1+ metastatic TNBC

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Outline

Neoadjuvant and Adjuvant Therapies

- HER2+ breast cancer (Abstract 500)
- HR+ breast cancer (Abstract 514)

Metastatic Breast Cancer Therapies

- HER2+ breast cancer (Abstracts 1000)
- HR+ breast cancer (Late-breaking abstract 1008)
- Triple negative breast cancer (Abstract 1003)

Supportive Therapies (Abstract 6527)

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6527 Growth Factor Use and Rate of Neutropenic Complications in Breast Cancer Patients Treated with Dose-dense Paclitaxel: A 5-year Experience from a Safety Net Hospital

Racha Halawi[1], Larry Brown[2], Kavi Patel[1], Elihan Tobias[1], Samira Syed[1], Nisha Unni[1], Hsiao Ching Li[1], Navid Sadeghi[1]
(1) University of Texas Southwestern Medical Center, Dallas, TX; (2) Parkland Health & Hospital System, Dallas, TX

Parkland

- Dose-dense paclitaxel
  - Less neuropathy than weekly paclitaxel (Chan JK, et al. N Engl J Med. 2016 Feb 25;374(8):738-48.)
  - Shorter duration of treatment than weekly paclitaxel
    - 8 weeks vs 12 weeks
  - Per NCCN guidelines, requires growth factor support with each cycle

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(1) University of Texas Southwestern Medical Center, Dallas, TX; (2) Parkland Health & Hospital System, Dallas, TX

Parkland

Hypothesis: Growth factor support is not necessary with dd-paclitaxel

Methods: Retrospective chart review of 265 patients receiving dd-paclitaxel for breast cancer (1010 cycles of chemotherapy, 783 without GCSF, 227 cycles with GCSF, dependent on provider standard practice)

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Results:

- No episodes of neutropenic fever in all 1010 cycles of dd-paclitaxel
- Similar rates of grade 3/4 neutropenia in both groups (10% without GCSF vs 9% with GCSF)
- Estimated number needed to treat to prevent 1 episode of grade 3/4 neutropenia: 167

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Take-Home Points

Dose-dense paclitaxel confers about a 10% risk of grade 3/4 neutropenia but very low risk of febrile neutropenia

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Clinical Application

Omission of GCSF following dose-dense paclitaxel seems reasonable in patients who otherwise do not have patient-specific risk factors for myelosuppression

- Age > 65
- Persistent neutropenia
- Bone marrow involvement by tumor
- Recent surgery / open wounds
- Liver dysfunction (Bilirubin > 2)
- Renal dysfunction (Cr clearance < 50)

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