Potential Therapeutic Targets

- Androgen receptors, PI3KCA, MEK, ADC

Sung-Bae Kim, MD, PhD

Dept of Oncology, Asan Medical Center

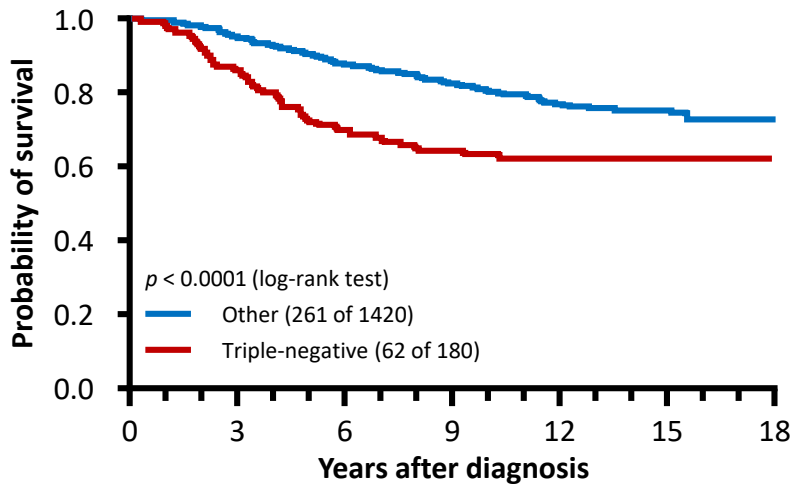
University of Ulsan College of Medicine

Seoul, Korea

Clinical Outlook in TNBC

- TNBC constitutes 10–20% of all BC[1,2]
- Highly heterogeneous
  - Molecular subtype is associated with differences in prognosis[1,2]
  - Different subtypes respond preferentially to different therapies[2,3]
- Median survival for women with mTNBC is <1 year[4]

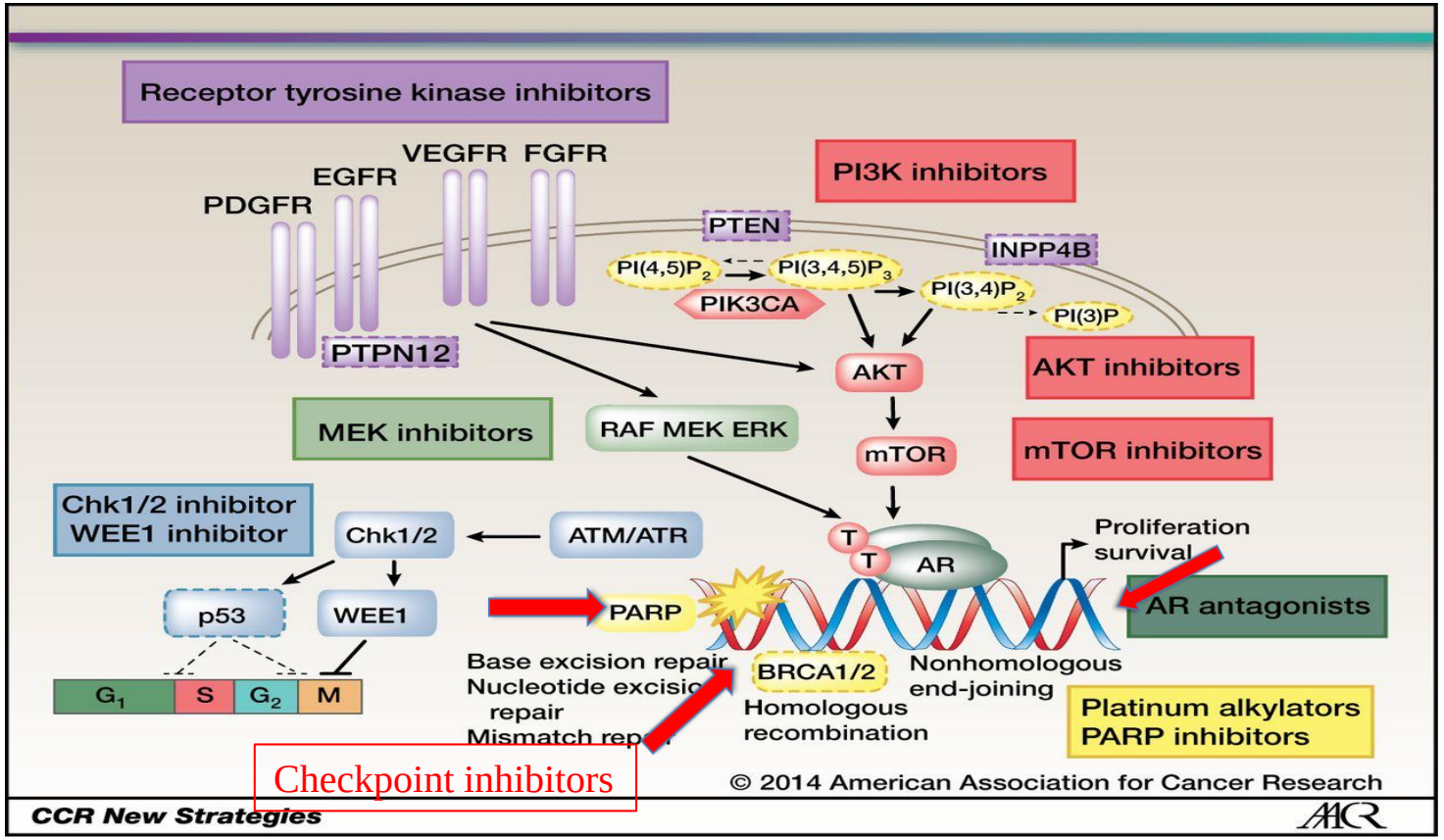
Survival rates for TNBC vs. other breast cancers[4]



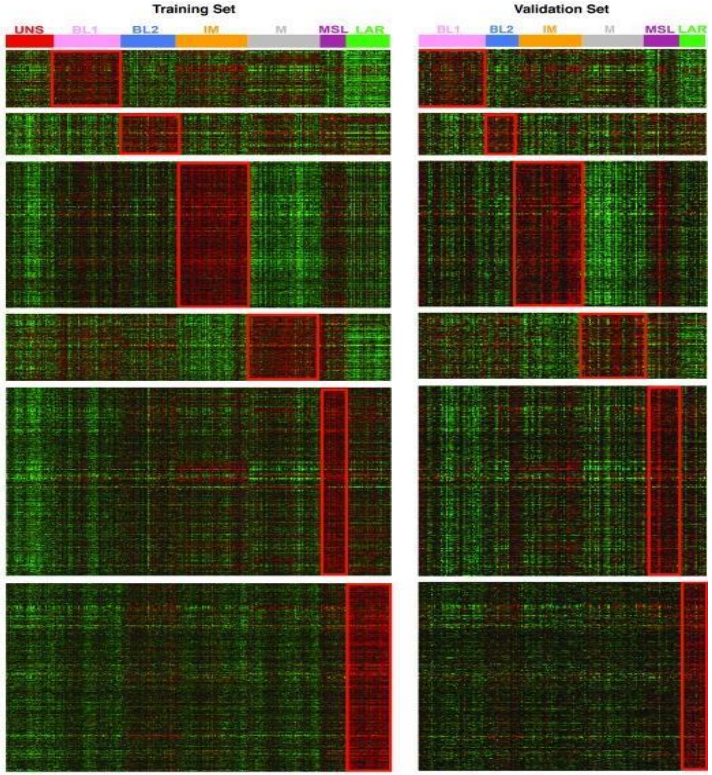
Patients with TNBC have a poorer prognosis than those with other forms of BC[4,5]

1. American Cancer Society, Breast Cancer Facts & Figures 2015-2016; 2. Lehmann BD, et al. J Clin Invest 2011;
3. Abramson VG, et al. Cancer 2014; 4. Dent R, et al. Clin Cancer Res 2007; 5. Pal SK, et al. Breast Cancer Res Treat 2011.

Potential Therapeutic Targets



Classification of TNBC into 6 different subtypes



Basal-like 1 (BL1): Cell-cycle, proliferation and DNA damage response genes

Basal-like 2 (BL2): Growth factor signaling (EGF, MET, Wnt/β-catenin, IGF1R)

Immunomodulatory (IM): Immune cell and cytokine signaling (overlap with medullary breast cancer gene signature)

Mesenchymal (M): Cell motility and differentiation (Wnt, ALK, TGF-β)

Mesenchymal stem-like (MSL): Similar to M, but increased growth factors signaling, low proliferation, enrichment of genes associated with stem cells

Luminal androgen receptor (LAR): Enriched in hormonally-regulated pathways, androgen receptor signaling. Displays luminal expression patterns (molecular apocrine carcinomas)

PARP inhibitors
Platinum compounds

Anti-EGFR MAb

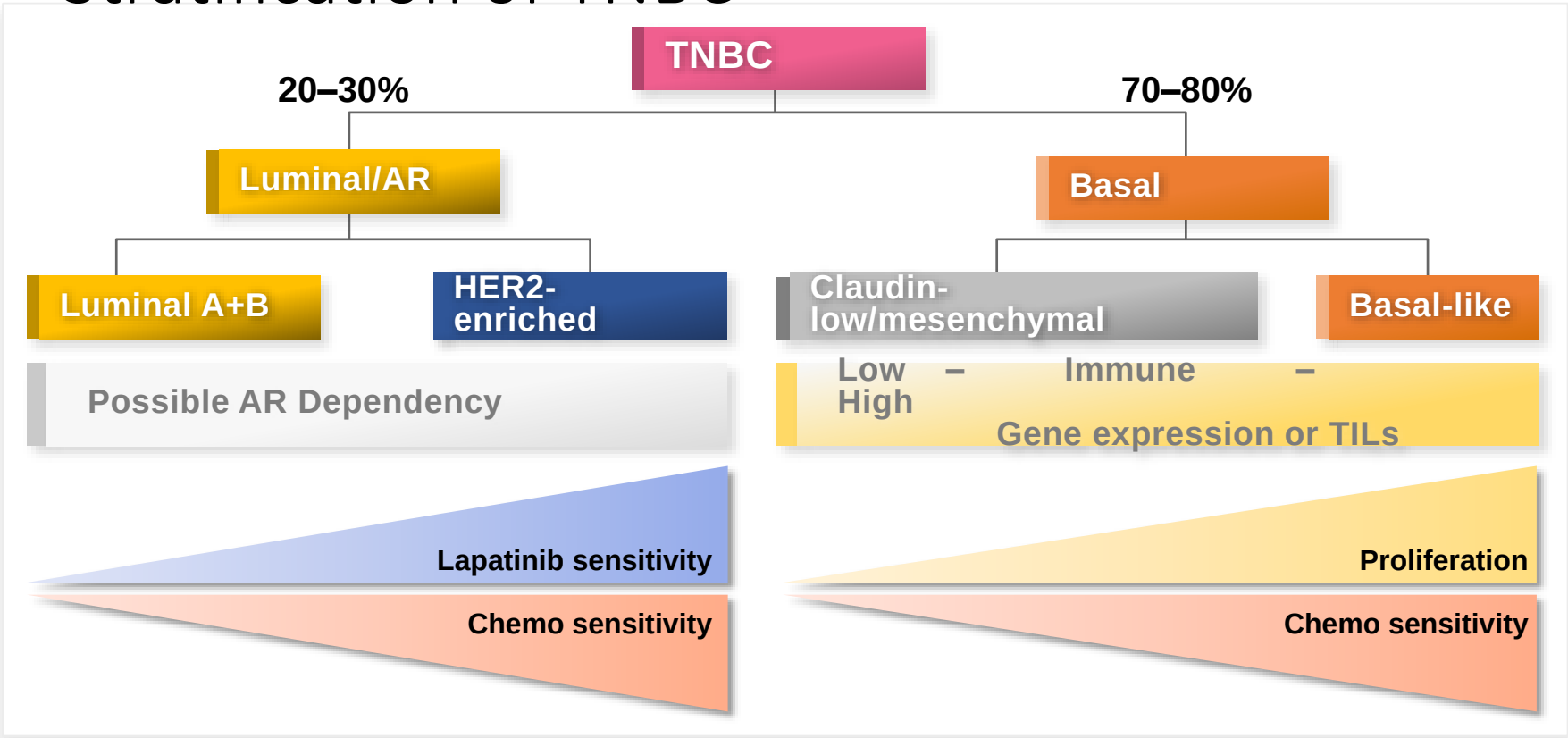
Checkpoint inhibitors
Vaccines

PI3K inhibitors
mTOR inhibitors
c-MET inhibitors
TGF-b inhibitors
NOTCH inhibitors

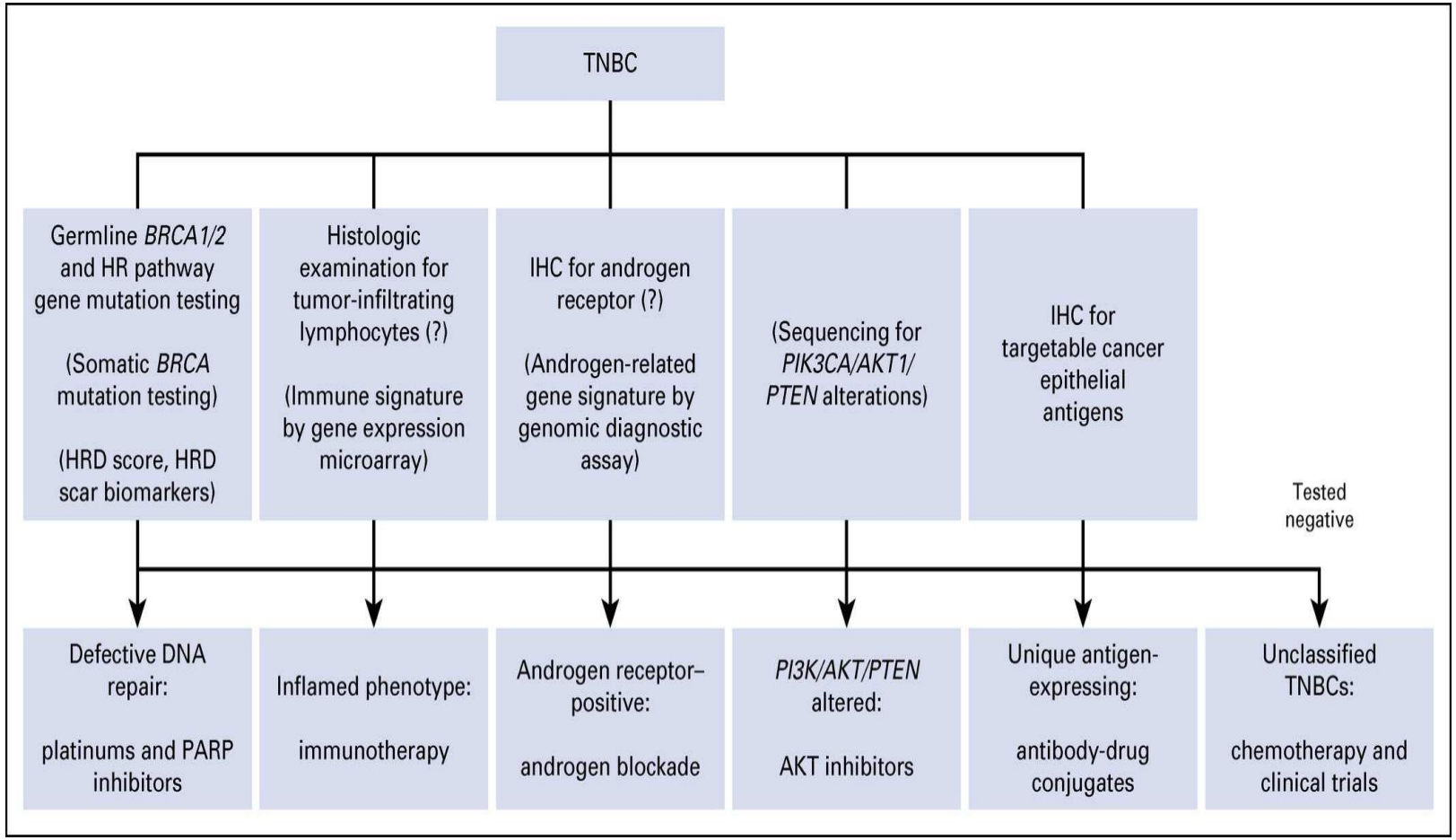
AR antagonists

Lehmann et al, J Clin Invest 2011

Stratification of TNBC

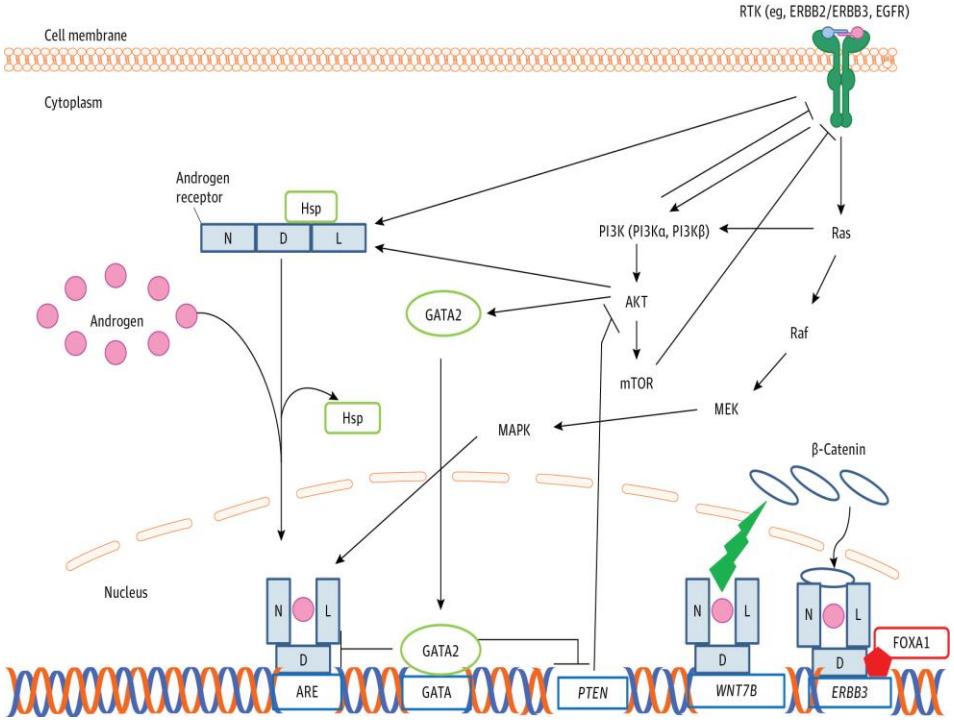


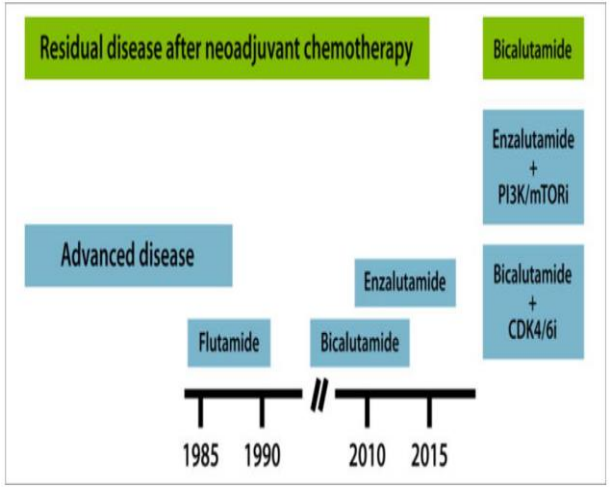
- Adapted from Perou C. SABCS 2016



Jack J. Chan; Tira J.Y. Tan; Rebecca A. Dent
Journal of Oncology Practice **May 11, 2018**

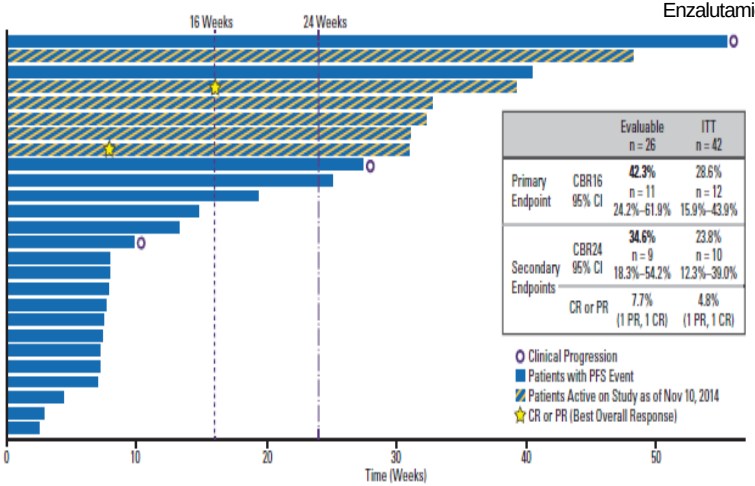
Androgen Receptor





Targeting the Androgen Receptor (AR) in TNBC

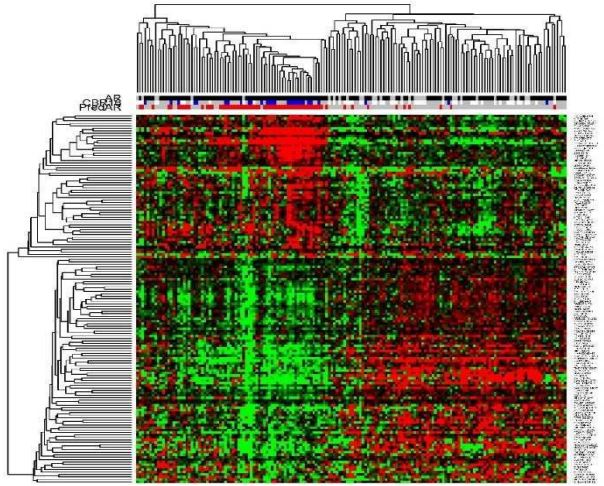
Enzalutamide



	Bicalutamide	Enzalutamide
RR (%)	0	6
CBR6m (%)	19	20

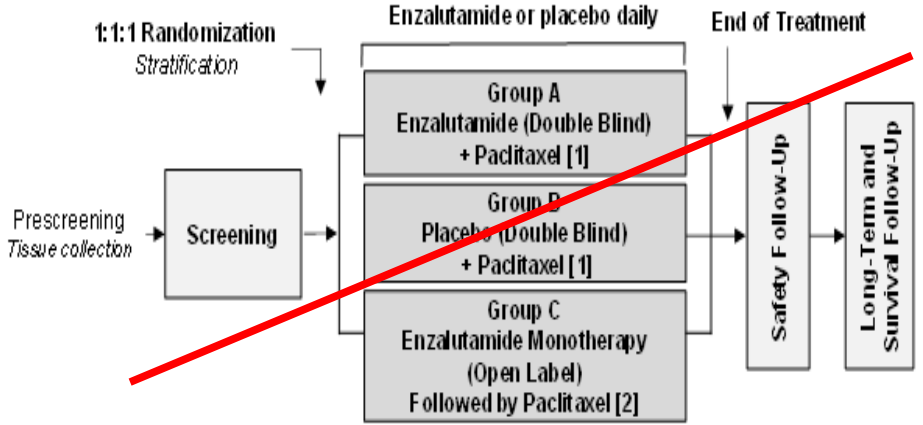
MDV3100-11. Traina T et al, JCO 2018
TBCRC011. Gulpa A et al, CCR 2013

AR-Driven Biology in TNBC
using Gene Expression Profiling Assay



Park er et l, ASCO 2015a

ENDEAR: Phase 3 Randomised, Placebo- Controlled 3-Armed Study



[1] Paclitaxel will be given for at least 16 weekly cycles, then may be discontinued at investigator discretion. Enzalutamide/placebo treatment will continue after paclitaxel discontinuation until disease progression.

[2] Patients will receive enzalutamide until disease progression, then receive paclitaxel and continue assessments until second disease progression.

This trial was cancelled in May 2017
Numerous other ongoing Enzalutamide and other ARantagonist trials
NEEDbetter biomarker definition (prognostic vs predictive, IHC vs other)

ABC4 Guidelines: Androgen Receptor Targeting

Guideline Statement	LoE/ GoR	Consensus Rate
The AR is a potential target in advanced TNBC. There are, however, no standardized methods to assay AR. Limited data suggest a low level of efficacy for AR antagonist agents such as bicalutamide and enzalutamide. At this time, these agents should not be used in routine clinical practice. More definitive trials are needed, and research efforts must continue to optimise and standardise the determination of AR.	II/D	85%

Cardoso F et al, Ann Oncol 2018

PIK3CA/AKT/mTOR pathway

PIK3CA/AKT/mTOR signaling is frequently activated in TNBC through activating mutations in *PIK3CA or AKT1* and alterations in PTEN

Deficient PTEN is common in TNBC

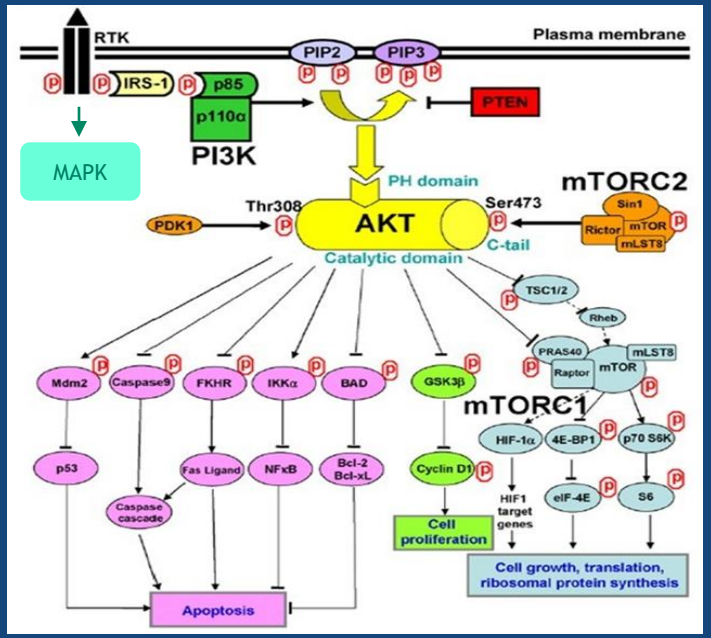
Ipatasertib and Capivasertib : selective small molecule AKT inhibitors

IPAT enzyme potency

Enzyme	IC 50 (nM)
Akt1	5
Akt2	18
Akt3	8
PKA	3100 (x620)

Breast cancer and PI3K/AKT pathway

The PI3K/AKT pathway is one of the most frequently altered pathways in breast cancer and is key for survival and growth of tumors



AKT can be activated by:

- Loss of function of negative regulators:
  - **PTEN**
  - INPP4B
  - PHLPP
  - PP2A
- Gain of function of positive regulators:
  - **PI3K**
  - **AKT**
  - Receptor tyrosine kinases (**HER2**)
- Therapy-induced survival response:
  - Chemotherapy
  - Hormone therapy

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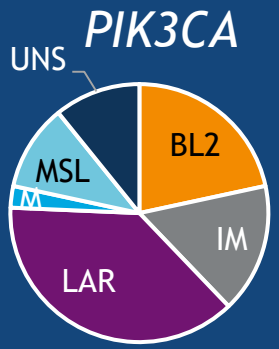
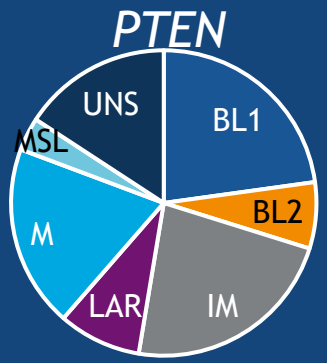
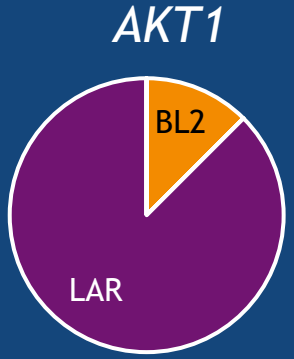
Yap TA, et al. Curr Opin Pharmacol 2008; Manning BD and Toker A. Cell 2017







TNBC is a heterogeneous disease with frequent activation of the PI3K/AKT pathway not limited to the LAR subtype

BL = basal-like; IM = immunomodulatory; LAR = luminal androgen receptor; M = mesenchymal; MSL = mesenchymal stem-like; UNS = unspecified

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Data from Pereira et al. Nat Commun 2016

LOTUS (NCT02162719) randomized phase II trial

- Measurable locally advanced/metastatic TNBC[a] not amenable to curative resection
- No prior systemic therapy for advanced/metastatic disease
- ECOG performance status 0/1
- Archival or newly obtained tumor tissue for central PTEN assessment
- Chemotherapy-free interval ≥6 months

(n=124)

R
1:1

PAC 80 mg/m^2 days 1, 8, & 15 +
IPAT 400 mg qd days 1–21 q28d

PAC 80 mg/m^2 days 1, 8, & 15
+ PBO days 1–21 q28d

Treatment until disease progression, intolerable toxicity,[b] or withdrawal of consent

Stratification factors
- (Neo)adjuvant chemotherapy
- Chemotherapy-free interval
- Tumor PTEN status

Endpoints
- Co-primary: PFS in ITT and PTEN-low populations
- Secondary: ORR, DoR, OS (ITT, PTEN-low, and PI3K/AKT pathway-activated populations), safety

[a]Defined as <1% tumor cell expression of estrogen and progesterone receptors and negative HER2 status (FISH/CISH HER2:CEP17 ratio <2.0, or locally assessed IHC 0 or 1+ [or 2+ but negative by FISH/CISH]). [b]Patients discontinuing PAC or IPAT/PBO due to toxicity could continue on single-agent treatment. Protocol did not specify primary prophylactic antidiarrheal use

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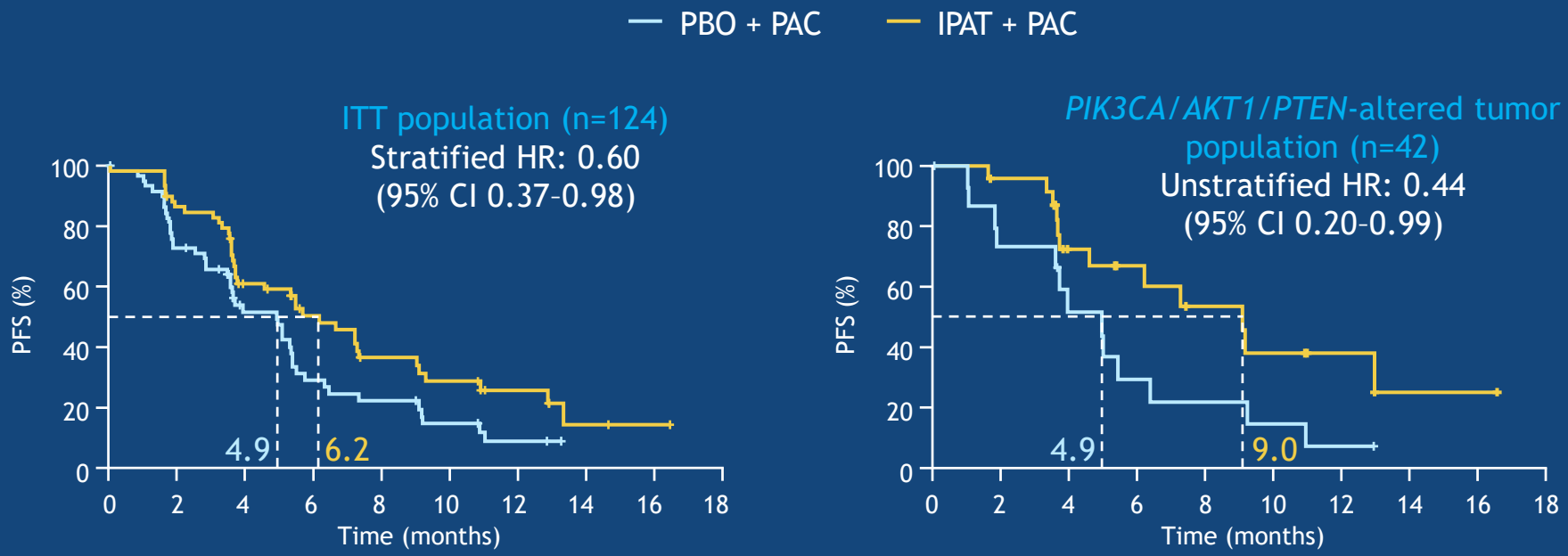
DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; FISH/CISH = fluorescence/chromogenic in situ hybridization; IHC = immunohistochemistry; ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PAC = paclitaxel; PBO = placebo; PFS = progression-free survival; q28d = every 28 days; qd = once daily; R = randomization

Primary analysis: IPAT effect on PFS enhanced in *PIK3CA/AKT1/PTEN*-altered subgroup (Foundation Medicine)



CI = confidence interval; HR = hazard ratio

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Kim et al. Lancet Oncol 2017

Primary analysis: Summary of additional efficacy endpoints

Endpoint	ITT population		PTEN-low population (by IHC)		*PIK3CA/AKT/PTEN*-altered tumor population (by NGS)	
	PBO + PAC (n=62)	IPAT + PAC (n=62)	PBO + PAC (n=23)	IPAT + PAC (n=25)	PBO + PAC (n=16)	IPAT + PAC (n=26)
ORR, % (95% CI)	32 (21-45)	40 (29-54)	26 (12-47)	48 (30-68)	44 (20-70)	50 (30-70)
Median DoR, months (95% CI)	7.4 (3.9-9.2)	7.9 (5.6-NE)	7.5 (7.3-NE)	6.5 (4.4-NE)	6.1 (3.8-7.6)	11.2 (5.6-NE)
Clinical benefit rate, % (95% CI)[a]	37 (25-50)	48 (36-61)	30 (13-53)	56 (35-76)	44 (20-70)	54 (33-72)

[a]Defined as either an objective response, or a best overall response of complete or partial response or stable disease together with PFS of ≥24 weeks
NE = not estimable; NGS = next-generation sequencing

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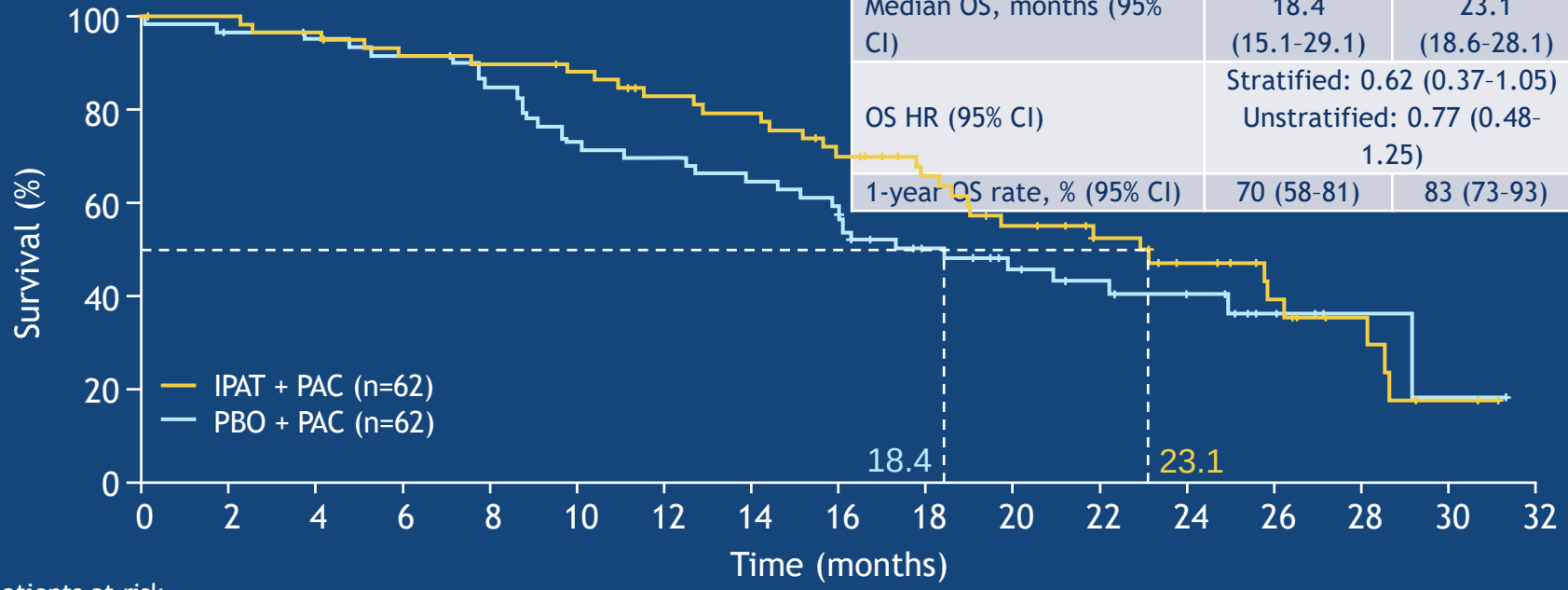
Kim et al. Lancet Oncol 2017. Roche data on file 2018

OS in the ITT population

	PBO + PAC (n=62)	IPAT + PAC (n=62)
OS events, n (%)	35 (56)	33 (53)
Median OS, months (95% CI)	18.4 (15.1-29.1)	23.1 (18.6-28.1)
OS HR (95% CI)	Stratified: 0.62 (0.37-1.05) Unstratified: 0.77 (0.48-1.25)	
1-year OS rate, % (95% CI)	70 (58-81)	83 (73-93)



No. of patients at risk

IPAT + PAC	62	60	58	54	53	51	46	44	37	31	25	20	15	10	6	2
PBO + PAC	62	59	57	55	50	43	41	38	32	24	19	16	13	6	2	1

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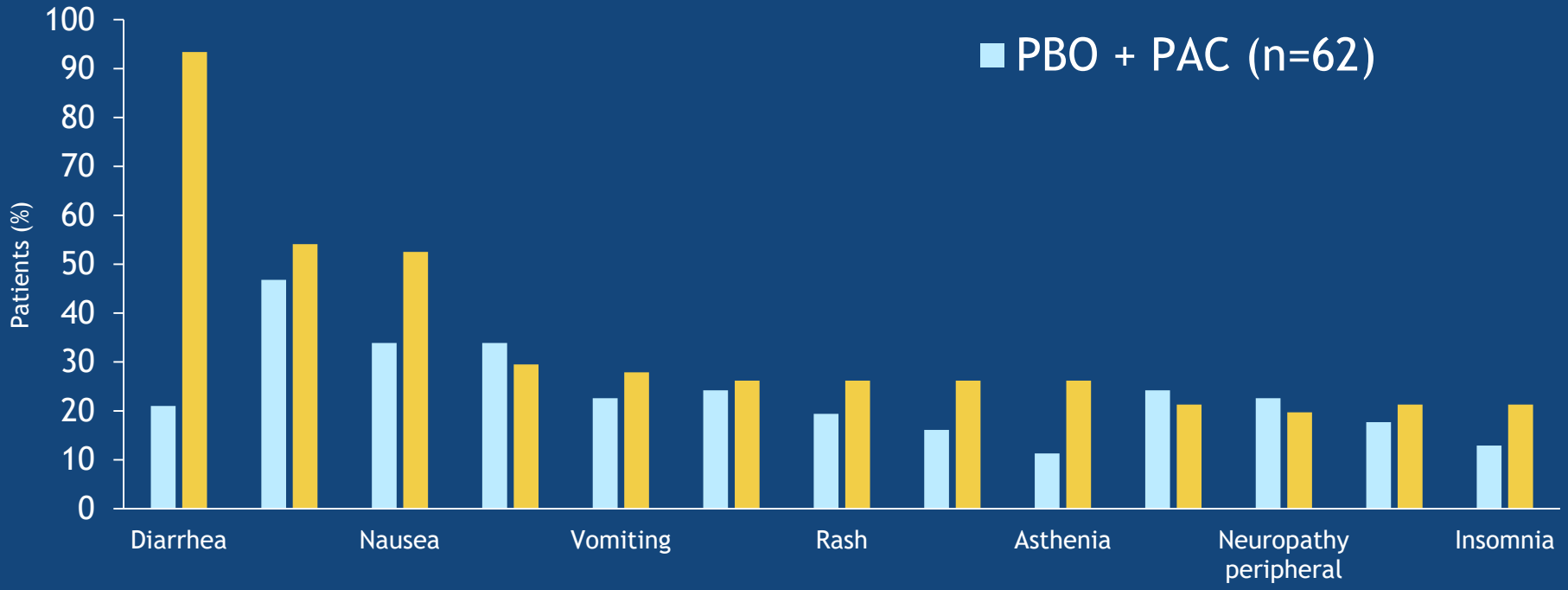
Updated safety: Most common[a] adverse events (all grades)



[a]Adverse events occurring in >20% of patients in either treatment arm

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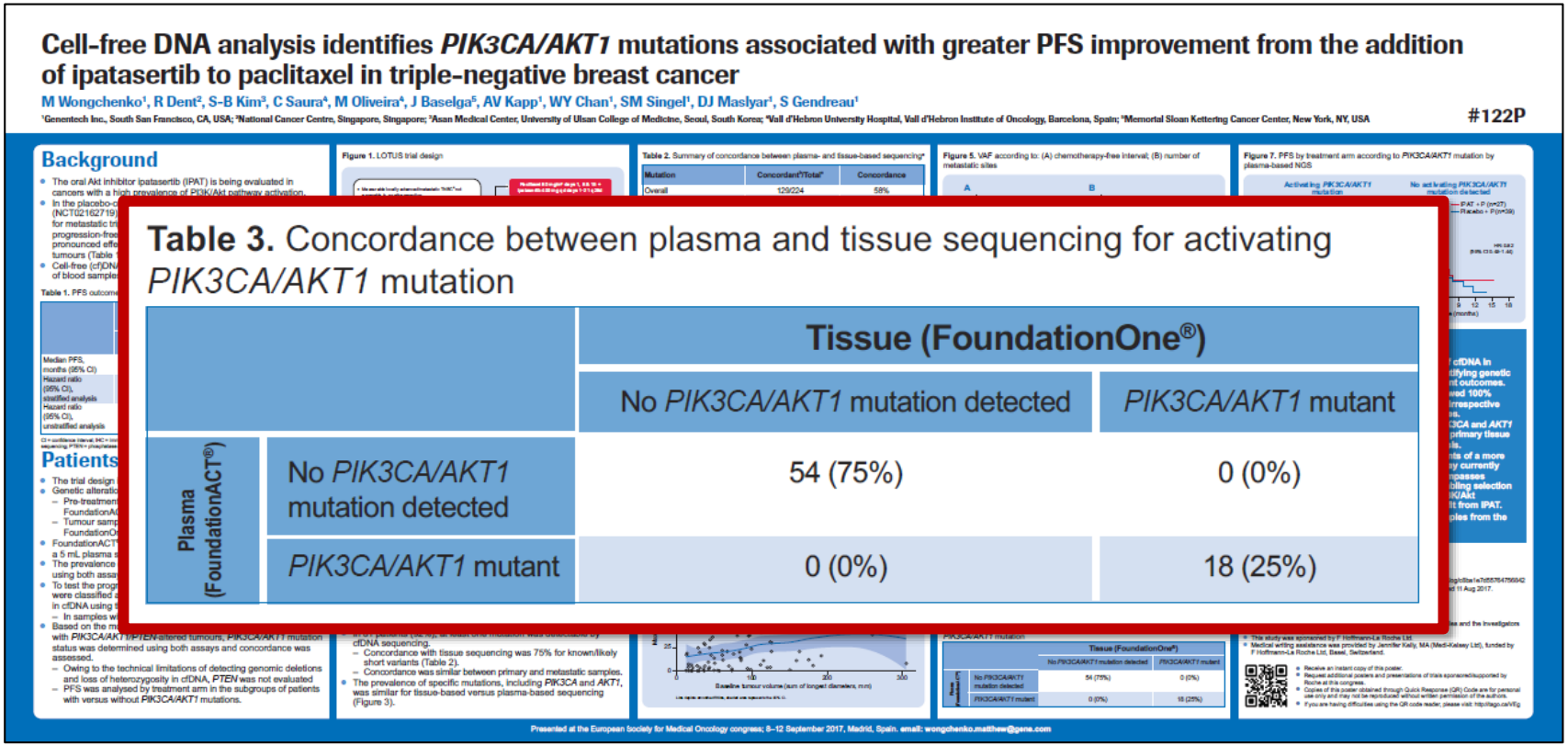
LOTUS: biomarkers



Cell-free DNA analysis identifies *PIK3CA/AKT1* mutations associated with greater PFS improvement from the addition of ipatasertib to paclitaxel in triple-negative breast cancer

M Wongchenko[1], R Dent[2], S-B Kim[3], C Saura[4], M Oliveira[4], J Baselga[5], AV Kapp[1], WY Chan[1], SM Singel[1], DJ Maslyar[1], S Gendreau[1]

[1]Genentech Inc., South San Francisco, CA, USA; [2]National Cancer Centre, Singapore, Singapore; [3]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [4]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA

#122P

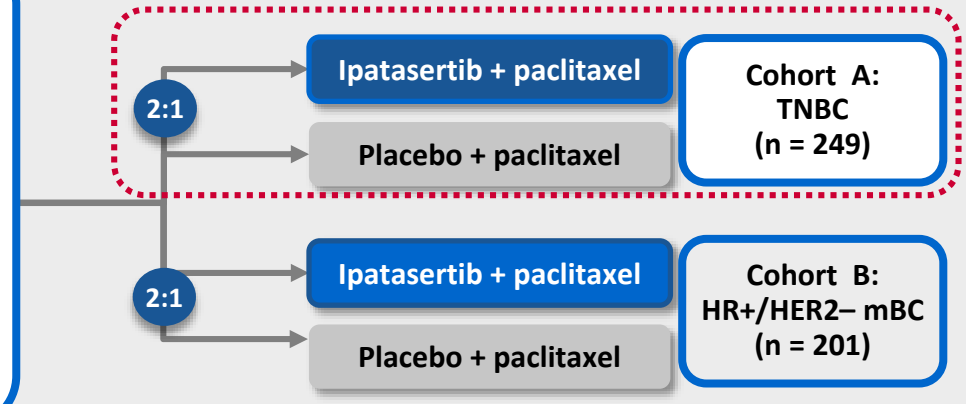
Table 3. Concordance between plasma and tissue sequencing for activating *PIK3CA/AKT1* mutation

		Tissue (FoundationOne®)	
		No *PIK3CA/AKT1* mutation detected	*PIK3CA/AKT1* mutant
Plasma (FoundationACT®)	No *PIK3CA/AKT1* mutation detected	54 (75%)	0 (0%)
	PIK3CA/AKT1 mutant	0 (0%)	18 (25%)

- Wongchenko M, *et al*. ESMO 2017. Kim et alLancet Oncology 2017

Phase III study of paclitaxel ± ipatasertib in first-line mBC: IPATunity130

- PI3K/Akt pathway-activated, locally adv or mTNBC or HR+/HER2– mBC
- ***PIK3CA/AKT1/PTEN*-altered tumour**
- Relapsed ≥12 months after last dose of chemo for eBC
- No prior chemo for locally adv or mBC



FOUNDATION MEDICINE®

IPATunity130 will study patients with PIK3CA/AKT1/PTEN-altered tumours, assessed using FoundationONE® on tumour tissue

PAKT randomized phase II trial

Trial Sponsor: Queen Mary University of London

- Metastatic breast cancer
- Triple-negative disease:
  - ER/PR <1%
  - HER2 IHC0-2 and/or ISH negative
- Measurable or evaluable disease
- No prior treatment for MBC
- No taxane treatment <12 months

R (1:1)

n=70 → Paclitaxel + Capivasertib

n=70 → Paclitaxel + Placebo

Stratification factors:
- Number of metastatic sites (<3, ≥3)
- DFI (end of (neo)adjuvant chemotherapy ≤12 months ago, end of (neo)adjuvant) chemotherapy >12 months or no prior chemotherapy)

Treatment:
- **Paclitaxel, 90 mg/m^2, IV, days 1, 8, & 15, q4 weeks**
- **Capivasertib/Placebo, 400mg orally BD, days 2-5, 9-12, 16-19**
- Paclitaxel for ≥6 cycles, Capivasertib/Placebo until PD
- If paclitaxel stopped prior to PD, Capivasertib/Placebo to be continued until PD
- Tumour assessments every 8 weeks

Primary endpoint:
- Investigator-assessed PFS (ITT)

Secondary endpoints:
- PFS in patients with/without *PIK3CA/AKT1/PTEN* alterations
- Overall Survival
- Response rates (ORR)
- Clinical benefit rate (CBR)
- Duration of response
- Safety
- Health-related quality of life

ER = Estrogen Receptor; PR = Progesterone Receptor; IHC = Immunohistochemistry; ISH = In situ Hybridisation; PFS = Progression-free survival

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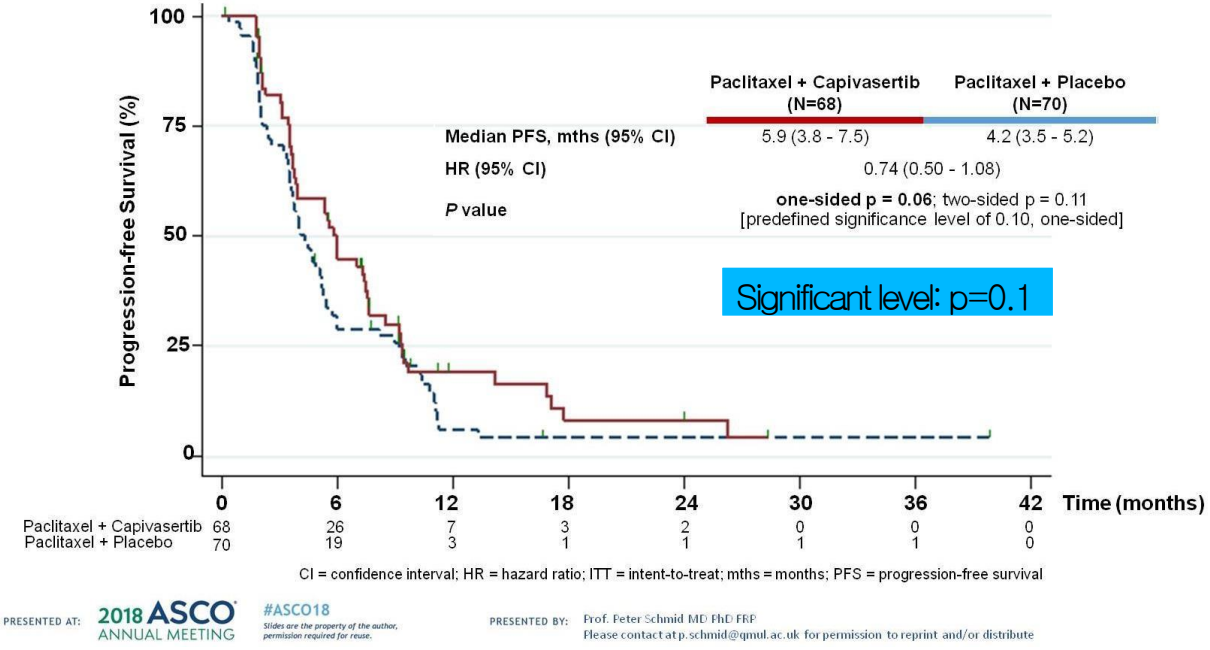
PAKT randomized phase II trial

PFS in ITT population



CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; mths = months; PFS = progression-free survival

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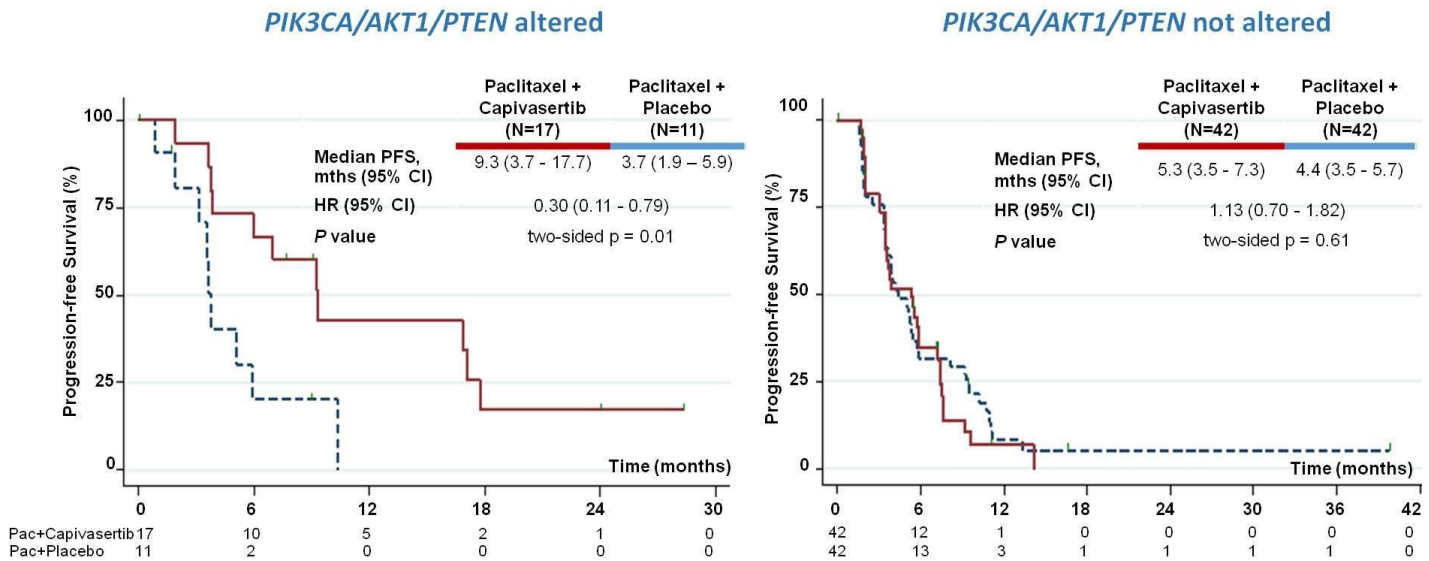
PAKT randomized phase II trial

PFS by tumour *PIK3CA/AKT1/PTEN* status



CI = confidence interval; HR = hazard ratio; mths = months; PFS = progression-free survival

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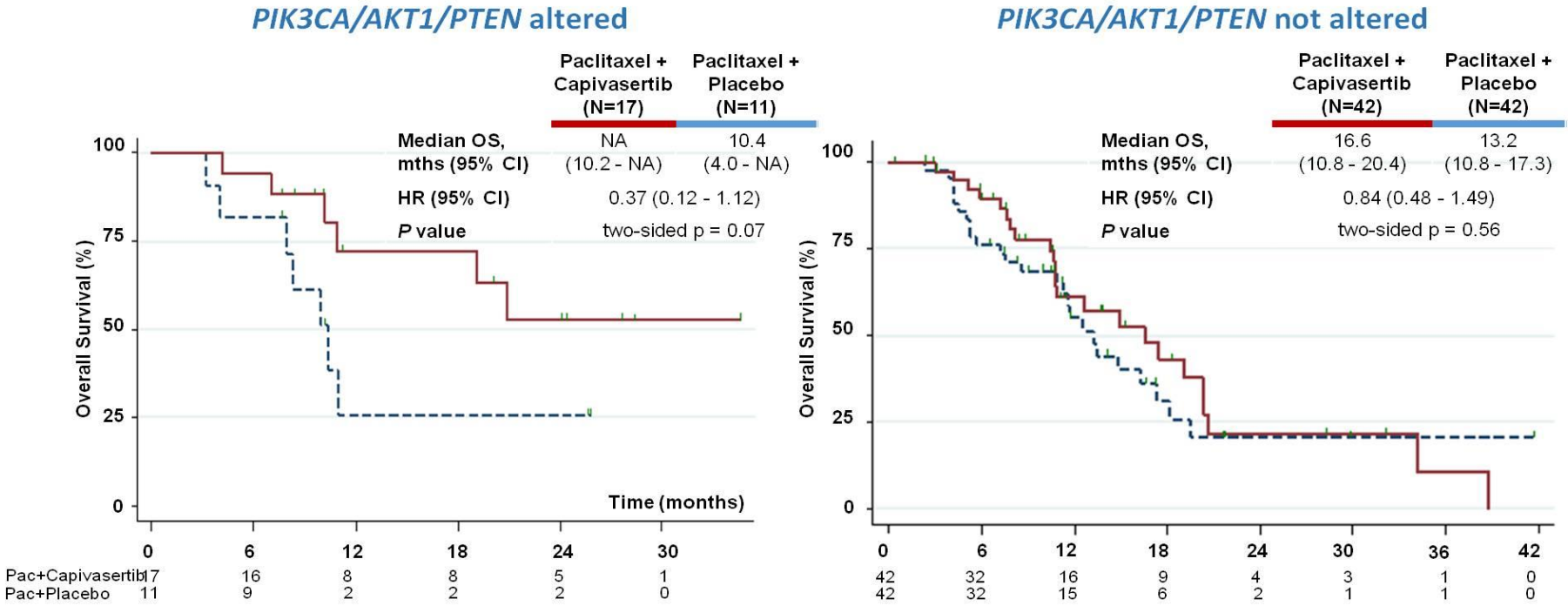
OS enhanced in *PIK3CA/AKT1*/PTEN-altered group



CI = confidence interval; HR = hazard ratio; mths = months; OS = overall survival

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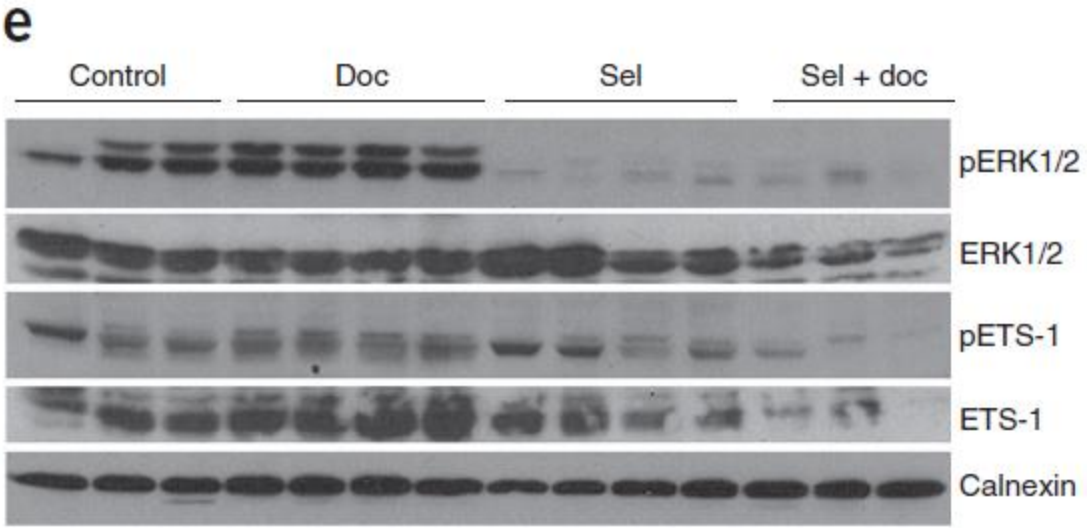
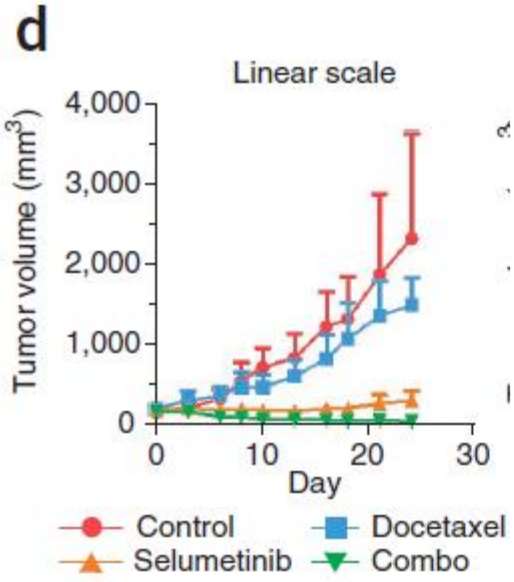
Chemo-resistance → RAS/ERK pathway in TNBC



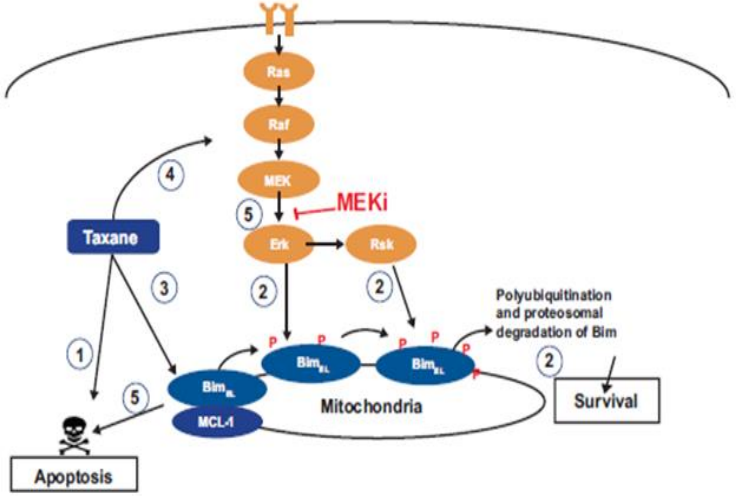


Balko JM et al, Nature Med 2012

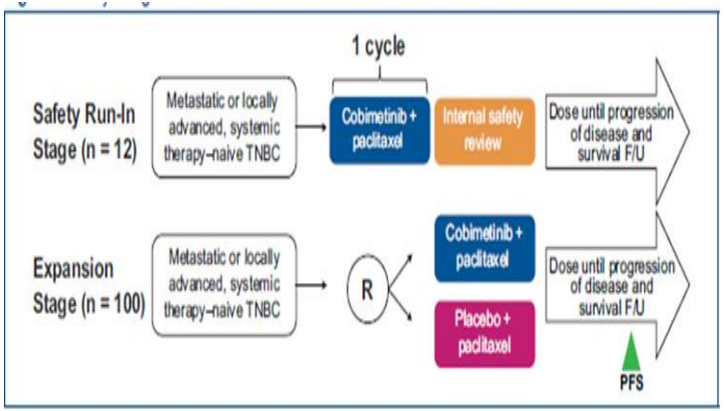
A Multistage, Phase 2 Study Evaluating the Safety and Efficacy of Cobimetinib in Combination With Paclitaxel as First-Line Treatment for Patients With Metastatic Triple-Negative Breast Cancer (NCT02322814)

Sung-Bae Kim,[1] David Miles,[2] Joon Rhee,[3] Yibing Yan,[3] Jessie Hsu,[3] Adam Brufsky[4]

[1]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Mount Vernon Cancer Centre, London, UK; [3]Genentech, Inc., South San Francisco, CA, USA; [4]University of Pittsburgh, Pittsburgh, PA, USA



1. Taxanes block cell cycle progression by centrosomal and spindle impairment, which leads to apoptosis
2. MAPK pathway can promote cell survival by phosphorylating and degrading pro-apoptotic BH3-only proteins such as Bim
3. Taxanes up-regulate levels of BH3-only protein Bim (pro-apoptotic)
4. Taxanes up-regulate the MAPK pathway (antiapoptotic)
5. Inhibition of MEK prevents Erk/Rsk phosphorylation of Bim, forcing cells toward apoptosis



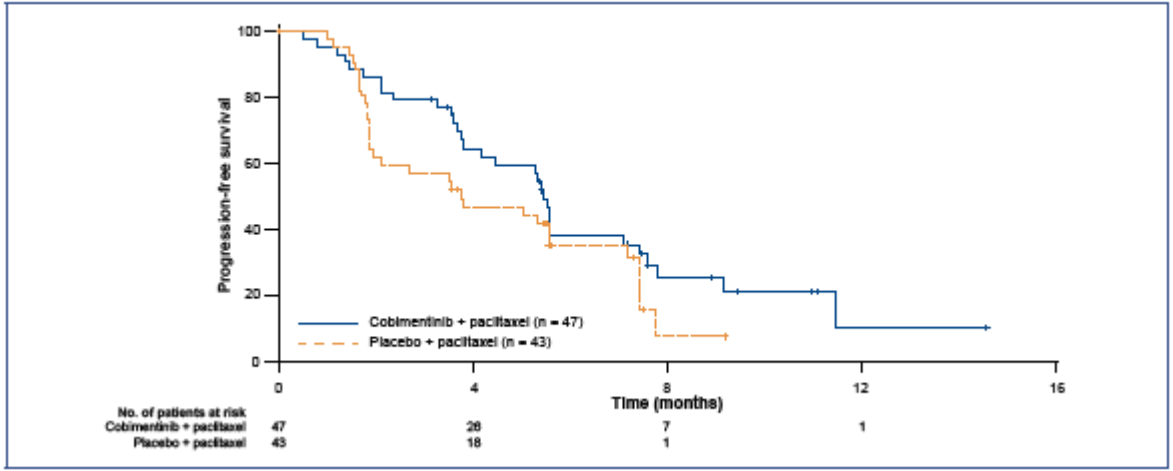
Primary end point: PFS

Kim SB et al. 2015 SABCS

Table 1. Patient demographics and disease characteristics at baseline (ITT population)

	Cobimetinib + paclitaxel (n = 47)	Placebo + paclitaxel (n = 43)
Median age (range), years	55.0 (34–73)	53.0 (31–80)
Disease stage, n (%)		
Locally advanced	5	3
Metastatic	42	40
Race, n (%)		
White	32 (68.1)	34 (79.1)
Asian	11 (23.4)	9 (20.9)
Other/Unknown	4 (8.5)	0
Prior neoadjuvant/adjuvant taxane therapy, n (%)	27 (57.4)	28 (65.1)
Disease-free interval from last dose of chemotherapy, n (%)		
≤12 months		
>12 months/no prior chemotherapy		

Figure 3. Progression-free survival (ITT population)



Brufsky et al. SABCS 2017

Figure 5. Best confirmed tumor response (ITT population)

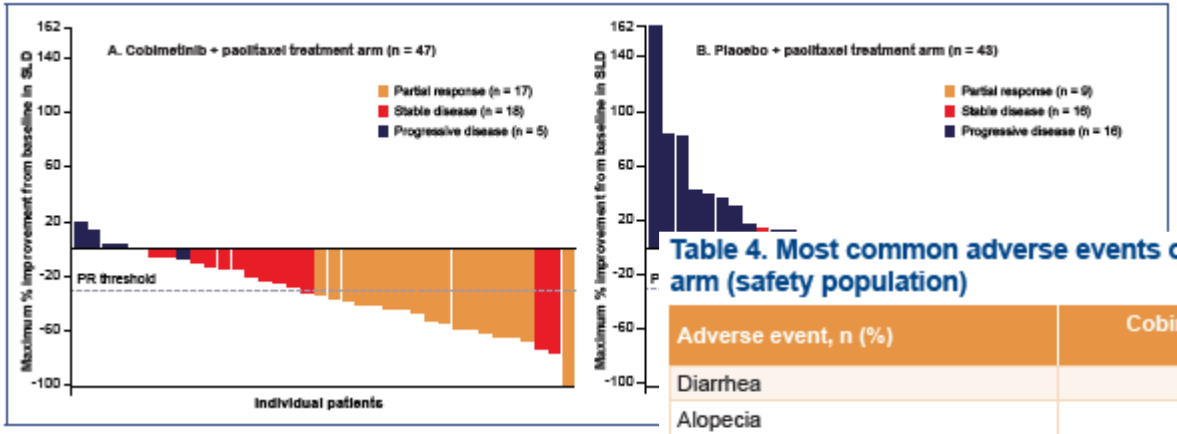
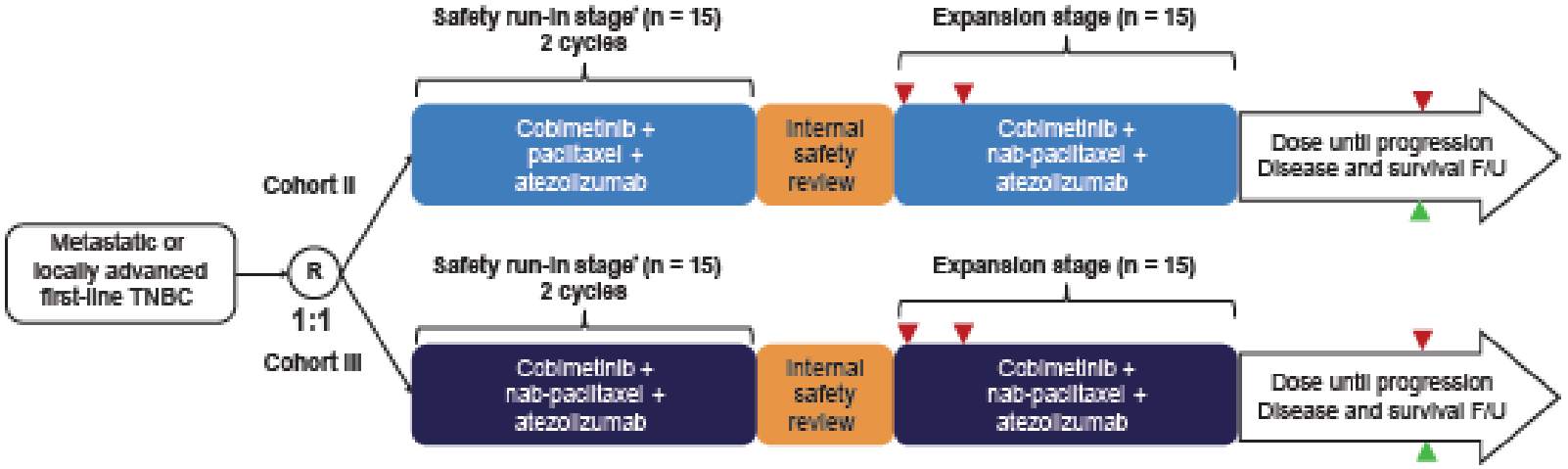


Table 4. Most common adverse events occurring in ≥20% of patients in either treatment arm (safety population)

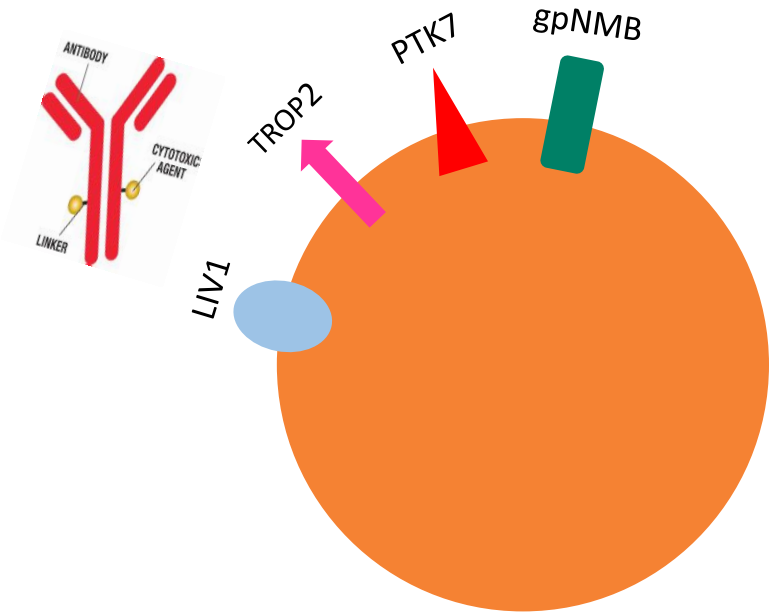
Adverse event, n (%)	Cobimetinib + paclitaxel (n = 47)	Placebo + paclitaxel (n = 43)
Diarrhea	36 (76.6)	12 (27.9)
Alopecia	21 (44.7)	19 (44.2)
Nausea	21 (44.7)	16 (37.2)
Rash	20 (42.6)	5 (11.6)
Fatigue	13 (27.7)	13 (30.2)
Pyrexia	13 (27.7)	7 (16.3)
Asthenia	12 (25.5)	11 (25.6)
Stomatitis	12 (25.5)	6 (14.0)
Anemia	11 (23.4)	6 (14.0)
Pruritus	10 (21.3)	1 (2.3)
Decreased appetite	9 (19.1)	9 (20.9)
Neutropenia	8 (17.0)	13 (30.2)
Peripheral sensory neuropathy	8 (17.0)	9 (20.9)
Cough	7 (14.9)	11 (25.6)
Headache	7 (14.9)	9 (20.9)

Brufsky et al. SABCS 2017

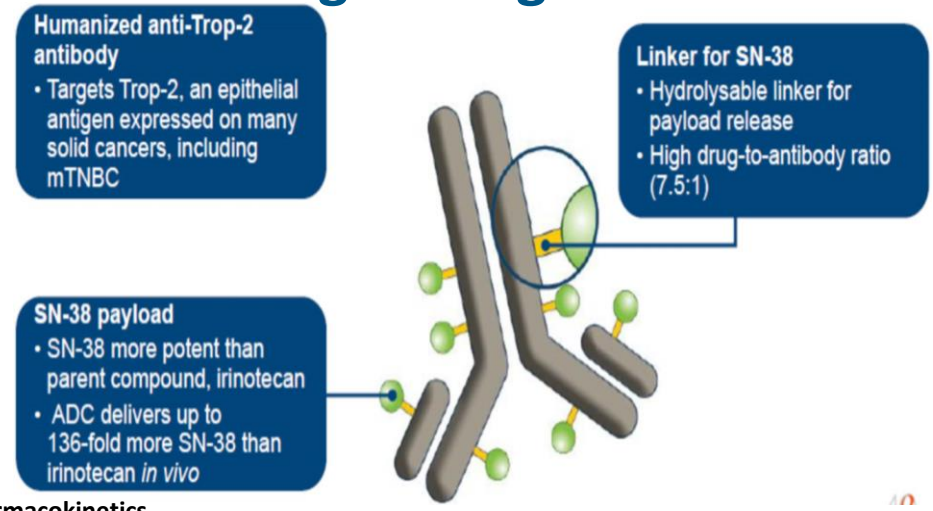
Cohort 2/3, COLET trial with addition of atezolizumab to MEK inhibitor plus taxane therapy



Cell Surface Markers: Targets for Antibody–Drug Conjugates



Sacituzumab Govitecan: FDA Breakthrough Designation



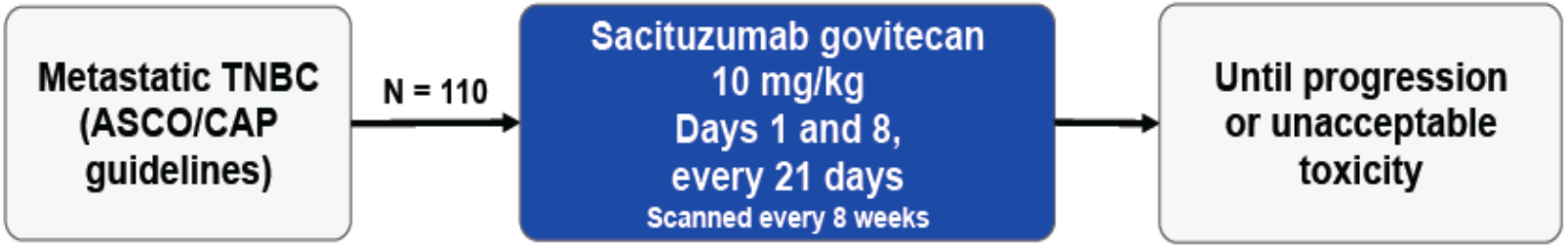
Pharmacokinetics

- **Clearance kinetics in 8 pts**
- **Terminal half-life: IMMU-132 = 15.3 ± 2.7 h; IgG itself = 86.5 ± 40.5 h**
- **Free SN-38 (unbound): AUC = 3% of total SN-38 (e.g., IgG bound)**

Antibody–Drug Conjugates in mTNBC

	Glembatumumab vedotin	Ladiratuzumab vedotin	Sacituzumab govitecan
“Real” Name	CDX-011	SNG-LIV1A	IMMU-132
Target	gpNMB (40%)	LIV-1 (71%) Trop-2 (88%)	
Cytotoxic	MMAE	MMAE	SN-38
Activity	ORR 28%	ORR 37%	ORR 30%
Trial to Know	METRIC	ASCENT	

Phase II: Sacituzumab in metastatic TNBC



Key Eligibility Criteria

- Adults, ≥18 years of age
- ECOG 0-1
- ≥2 prior therapies in metastatic setting or >1 therapy if progressed within 12 months of (neo)adjuvant therapy
- Prior taxane therapy
- Measurable disease

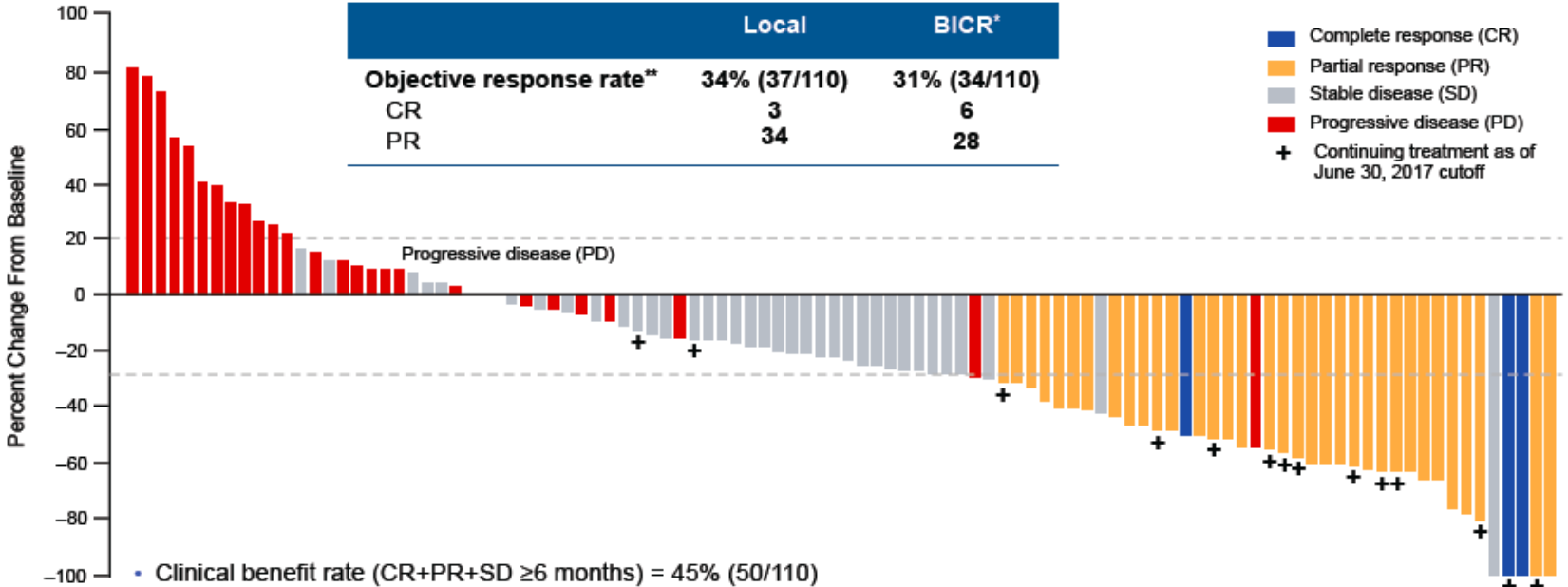
Evaluations

- Response evaluation by investigators
- Blinded independent central review of all CRs, PRs, and ≥20% tumor reductions
- Other evaluations: safety, immunogenicity, Trop-2 expression

Bardia et al, SABCS 2017

Tumor Response to Treatment

	Local	BICR*
Objective response rate**	**34% (37/110)**	**31% (34/110)**
CR	**3**	**6**
PR	**34**	**28**



- Clinical benefit rate (CR+PR+SD ≥6 months) = 45% (50/110)
- 74% (75/102) of patients with at least one CT response assessment had reduction of target lesions (sum of diameters)***
- 102 patients had ≥1 scheduled CT response assessment. 8 patients withdrew prior to assessment (4 PD, 4 MRI brain metastases)

*Patients with at least 20% tumor reduction (n = 56) were reviewed; **Confirmed objective response rate per RECIST; ***Waterfall is based on local assessment; BICR = Blinded Independent Adjudicated Central Review.

Immunomedics

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Sacituzumab: Adverse Events

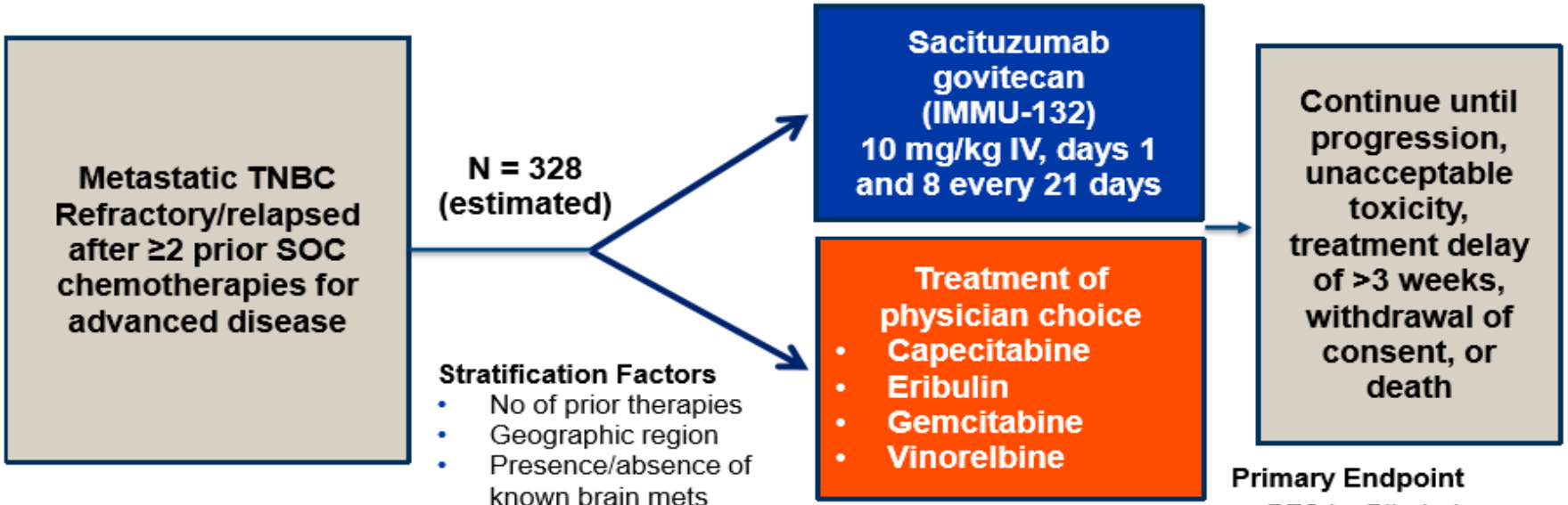
Adverse Events	All grades	Grade 3 or 4
Neutropenia Febrile neutropenia	63% 8%	41% 7%
Anemia	52%	10%
Nausea	63%	5%
Diarrhea	56%	8%
Vomiting	46%	5%
Fatigue	50%	7%
Alopecia	36%	NA
Decreased appetite	30%	0%
Hyperglycemia	23%	4%

Bardia et al, SABCS 2017

Phase I/II Study: Efficacy

Cancer	ORR	Median DOR	Reference
Urothelial (Bladder)	30.6% (11/36)	7.5 mo.	ASCO GU Symposium, 2017
NSCLC	19% (9/47)	6.0 mo.	Heist et al., J Clin Oncol, 2017
SCLC	14% (7/50)	5.7 mo.	Gray et al., Clin Cancer Res, 2017
TNBC	30% (21/69)	8.9 mo.	Bardia et al., J Clin Oncol, 2017

ASCENT:
Phase III Study of Sacituzumab vs TPC



Primary Endpoint

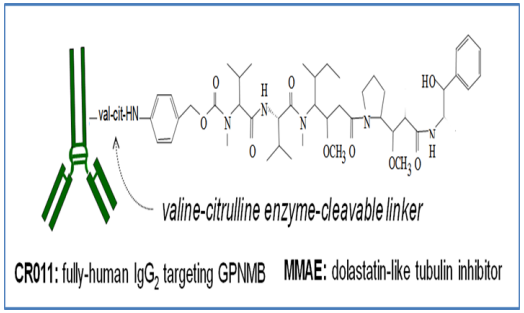
- PFS by Blinded Independent Central Read

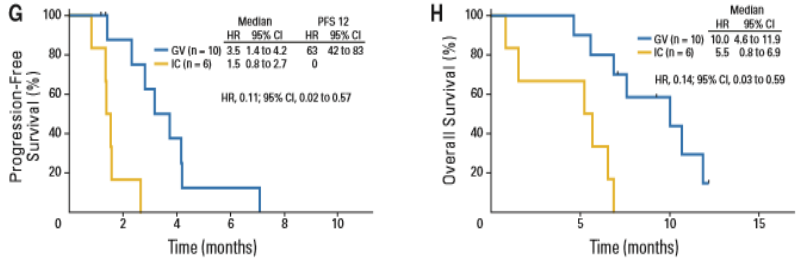
Secondary Endpoint

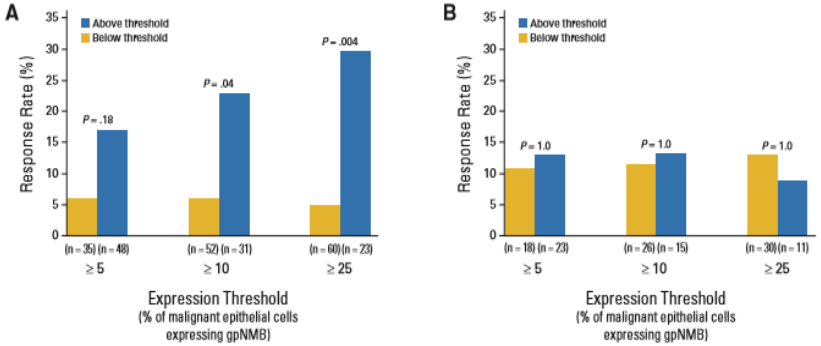
- Overall Survival

- Clinical trials number: NCT02574455
- Presented at: New Agents and Strategies; December 7, 2017; 5:00-7:00 PM, Hall 1 (abstract# 733)

Glembatumumab vedotin in GPNMB+ TNBC







- GPNMB, osteoactivin, is a Type I transmembrane protein
- Overexpression of GPNMB promotes invasion and metastases
- Glembatumumab vedotin (CDX-011) is a GPNM-ADC
- Early studies suggested CDX-011 ORR 18% vs. 0% in TNBC

Glembatumumab Vedotin: Accelerated Approval Registration Study Design in gpNMB Over-expressing TNBC (METRIC)

metric
A Clinical Trial of CDX-011 in Metastatic Triple-Negative Breast Cancer

	METRIC Study Parameters	
Randomization	2:1	
N	Approximately 300	
Control	Capecitabine (Xeloda)	
Patient Population	Anthracycline- and taxane-resistant; gpNMB over-expressing TNBC	
Primary Endpoints: With a trial size of apx. 300 patients, able to submit for approval with positive results for either endpoint		
	ORR Option	PFS Option
Primary endpoint	Objective response	Progression-free survival
Secondary endpoints	Duration of response and PFS	ORR and duration of response
Capecitabine arm	15% ORR	4.0 months PFS

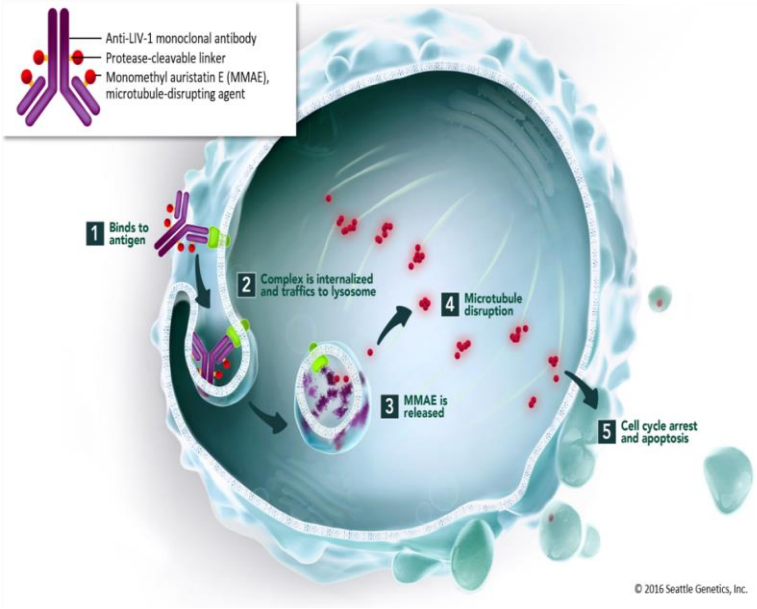
Median PFS 2.9 mo vs. 2.8 mo (HR 0.95; p=0.76)
No advantage seen for CDX-011 in ORR, DoR or OS

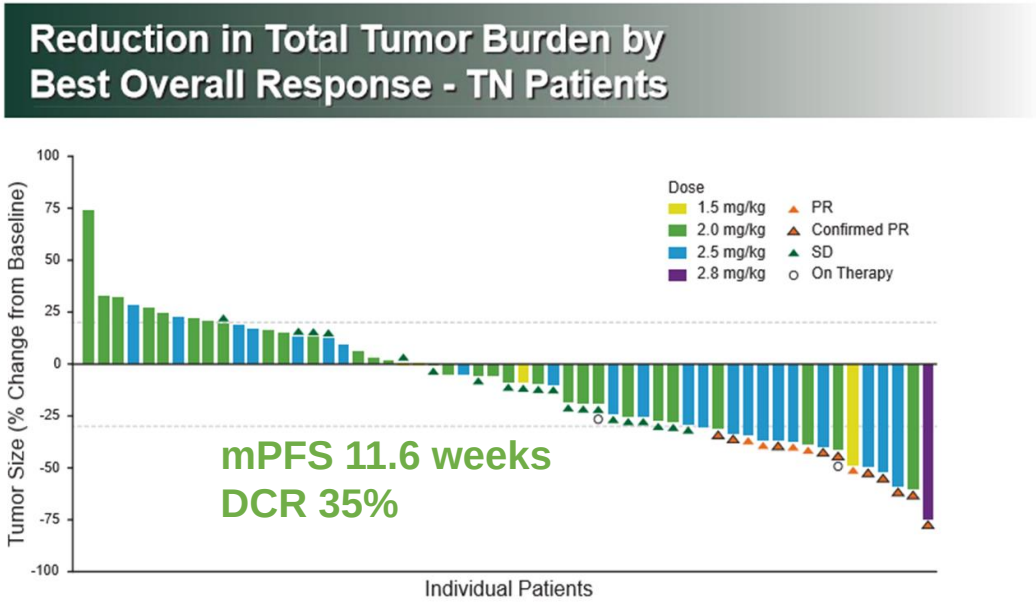
Celldex press release April 2018

Ladiratuzumab Vedotin: Function

Primary Mechanism of Action:

- Selectively binds to the LIV-1 extracellular domain.
- Payload: MMAE is released through proteolytic cleavage of the linker.
- MMAE disrupts microtubule networks in the cell



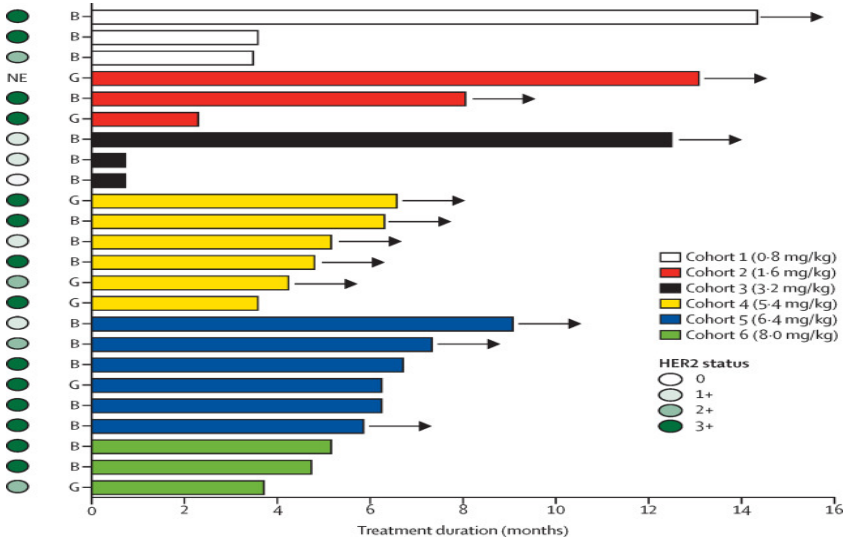


Modi S et al. SABCS 2017

Other Antibody Drug Conjugates in Development for TNBC

- **DS-8201A (Trastuzumab deruxtecan)**
  - **Anti-HER2 ADC**
  - **Promising activity in HER2- low**

- PF-06647263
  - Target: EFNA4
- DLYE5953A
  - Target: Ly6E
  - Ph 1 in breast cancer



Surface Antigen	Antibody-Drug Conjugate	Status of Drug Development: Status	Trial Acronym	Trial No.
Trop-2	Sacituzumab govitecan (IMMU-132)	Phase I/II trial reported[51]		NCT01631552
		Phase III trial recruiting; FDA breakthrough therapy and fast-track designation	ASCENT	NCT02574455
Glycoprotein nonmetastatic B (gpNMB)	Glembatumumab vedotin (CDX-011)	Phase I/II trial reported[51a]		NCT00704158
		Phase II trial reported[52]	EMERGE	NCT01156753
		Phase IIb trial active, not recruiting	METRIC	NCT01997333
LIV-1	Ladiratuzumab vedotin (SGN-LIV1A)	Interim results of phase I trial reported		NCT01969643
		Phase Ib/2 trial in combination with pembrolizumab planned		NCT03310957
Mesothelin	Anetumab ravtansine (BAY94-9343)	Phase I trial (MTD) reported		NCT01439152
		Phase Ib multi-indication trial including TNBC recruiting		NCT03102320
Carbonic anhydrase 6 (CA6)	SAR566658	Phase I trial (MTD) reported		NCT01156870
		Phase II trial recruiting		NCT02984683
Protein tyrosine kinase 7 (PTK7)	PF-06647020	Interim results of phase I trial reported		NCT02222922
		Phase I trial in combination with gedatolisib planned		NCT03243331

Abbreviations: FDA, US Food and Drug Administration; MTD, maximum tolerated dose; TNBC, triple-negative breast cancer.

Jack J. Chan; Tira J.Y. Tan; Rebecca A. Dent
Journal of Oncology Practice **May 11, 2018**

Conclusions

- Increasing understanding of the heterogeneity of TNBC.
- Multiple targets are available.
- Recent AKT inhibitor trials have shown intriguing results.
- Defining **biomarkers of response and resistance** to targeted agents is key to better choose and tailor patient's treatment.