



TNBC: Novel targets and Overview of Ongoing Clinical Trials

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**MD Anderson
Cancer Center**

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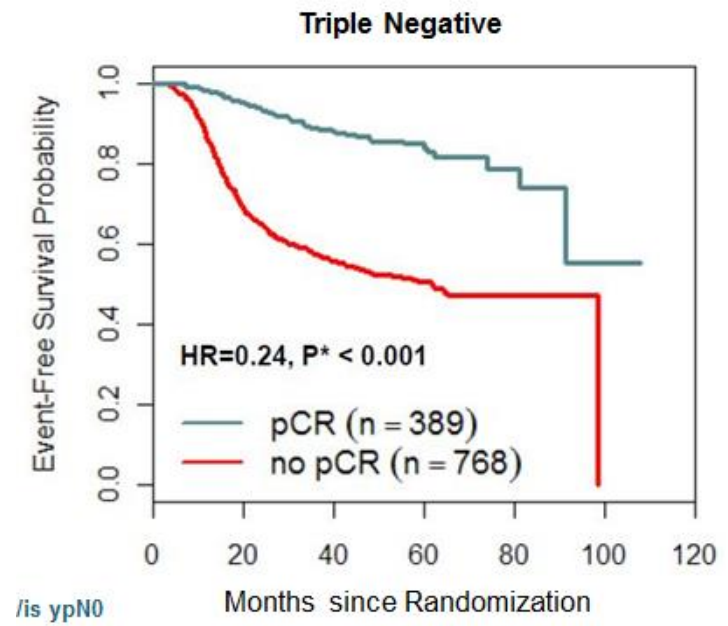
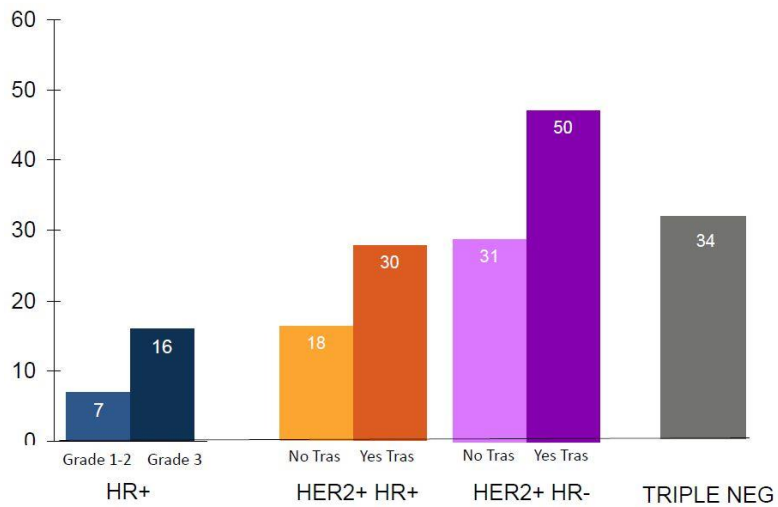
Disclosures

Financial Relationship	Commercial Interest
Grant or research support	Novartis, AstraZeneca, Taiho, Genentech, Calithera, Debiopharma, Bayer, Puma, Aileron, CytoMx, Effector Therapeutics, Zymeworks, PUMA, Curis, Pfizer
Paid consultant	Dialecta, Sumitomo Dainippon Pharma
Membership on advisory committees or review panels, board membership, etc.	Inflection Biosciences, Clearlight Diagnostics, Pieris, Darwin Health, GRAIL
Employee	MD Anderson Cancer Center

Outline

- Heterogeneity of TNBC
- Cell signaling
- DNA damage repair
- Cancer metabolism
- Antibody drug conjugates
- Other novel targets

TNBC and Chemotherapy Response

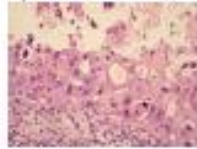


TNBC is a Heterogenous Disease

a Histological subtypes

- Invasive ductal carcinoma (95%)
- Invasive lobular carcinoma (1–2%)
- Metaplastic carcinoma with squamous differentiation (<1%)
- Spindle-cell metaplastic carcinoma (<1%)
- Adenoid cystic carcinoma (<1%)
- Secretory carcinoma (<1%)
- Typical medullary carcinoma (<1%)
- Atypical medullary carcinoma (<1%)
- Apocrine carcinoma (<1%)

Metaplastic carcinoma with squamous differentiation



Spindle-cell metaplastic carcinoma



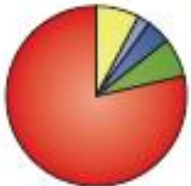
Adenoid cystic carcinoma



Secretory carcinoma



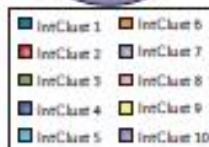
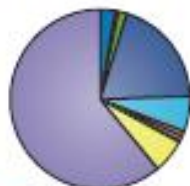
b Intrinsic PAM50 subtypes



c Molecular subtypes defined by Lehmann et al.

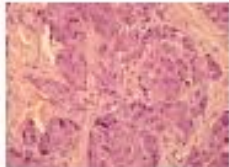


d Integrative clusters

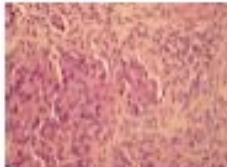


e Heterogeneity of tumour-infiltrating lymphocytes

Low



Intermediate

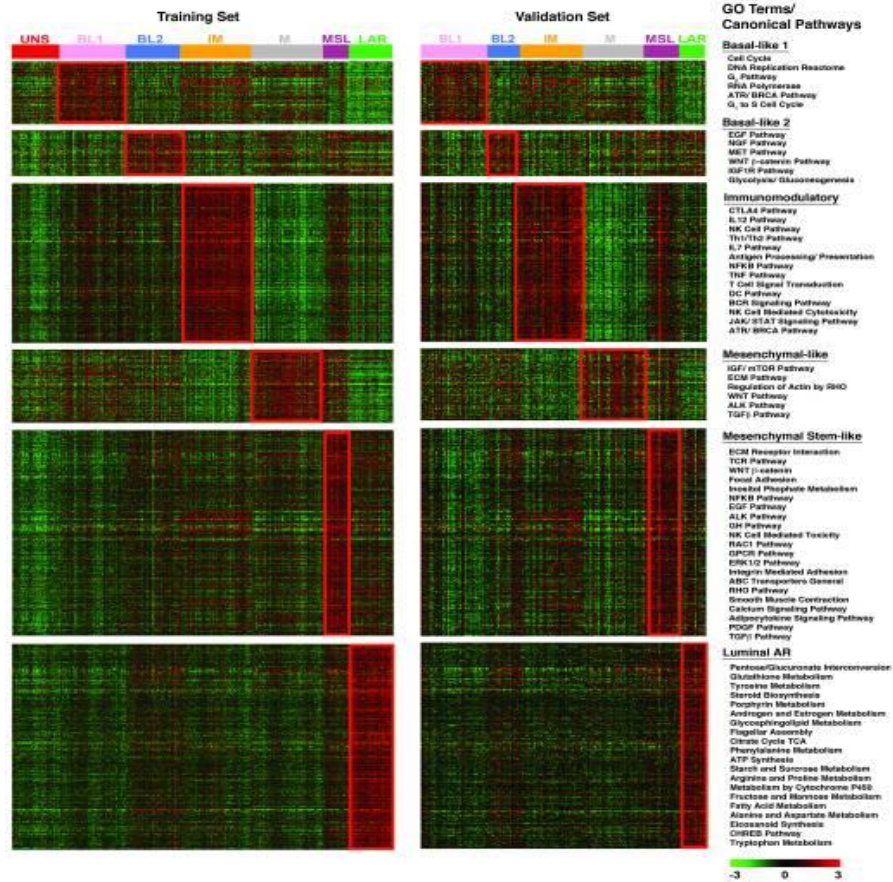


High



- “Triple negative” are heterogenous basket of tumors that lack ER, PR, HER2
- Differing histologic subtypes
- Heterogenous gene expression profiles by PAM50 but predominantly basal) And Lehman classification
- Heterogeneity of tumor infiltrating cells

TNBC is a Heterogenous Disease



Basal-like 1:

Basal-like 2:

Immunomodulatory

Mesenchymal-like

Mesenchymal Stem-Like

Luminal AR

Can Gene Expression Subtypes be Used for Therapy Selection?

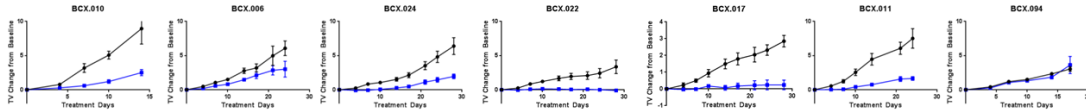
TNBC subtype	Proportion of TNBC (%) ^a	Gene expression profile	Emerging therapies
BL1	35	Cell cycle genes DNA damage repair genes	PARP inhibitors CDK inhibitors Taxanes
BL2	22	Growth factor signalling (EGF, IGF1, MET, Wnt/ β -catenin pathways) Growth factor receptors (EGFR, IGF1R, MET, EPHA2) Glycolysis and gluconeogenesis	mTOR inhibitors Growth factor inhibitors
LAR	16	Luminal gene expression Androgen receptor gene	Anti-androgens HDAC inhibitors Hsp90 inhibitors Src inhibitors PI3K inhibitors
M	25	EMT Cell motility and differentiation Regulation of cancer stem cells Growth factor signalling	Drugs targeting pathways involved in EMT (TGF- β , MET, Wnt/ β -catenin)

A

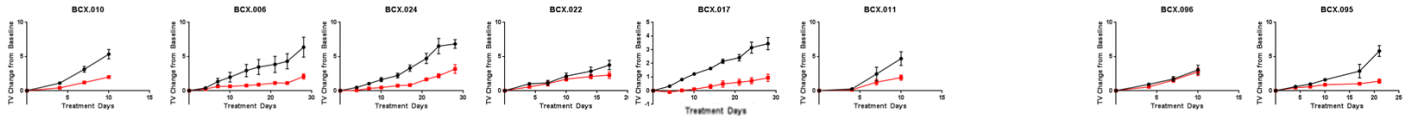
	PIK3CA	AKT	PTEN	4E-BP1 pS65	4E-BP1 pT37/T46	Akt pS473	Akt pT308	PRA540 pT246	mTOR	S6 pS235/236	S6 pS240/244	PI3K Score	MAPK pT202/Y204	MEK1 pS217/S221	MEK/Erk Total
BCX.087				1.02	1.23	6.6	4.6	1.2	1.1	1.3	1.4	18.4	1.0	0.9	1.9
BCX.010				1.02	1.25	3.8	3.0	0.5	0.9	1.7	1.5	13.9	0.9	0.9	1.8
BCX.006				1.01	1.2	3.0	1.7	1.5	1.0	1.9	1.6	12.9	1.3	1.0	2.3
BCX.070				0.93	0.96	4.2	1.7	1.0	0.8	1.3	1.3	12.4	1.3	1.0	2.3
BCX.024				0.78	0.74	3.0	2.3	1.0	1.0	1.2	1.2	11.2	1.1	0.9	2.0
BCX.009				1.03	1.68	0.8	0.7	1.8	1.3	0.8	0.9	8.8	1.0	0.9	1.9
BCX.100				0.64	0.85	2.5	1.6	0.3	0.9	1.1	1.0	8.8	0.9	0.8	1.7
BCX.022				0.91	0.95	1.5	1.0	0.8	0.9	1.2	1.1	8.4	1.1	1.0	2.0
BCX.017				0.81	0.99	0.7	0.6	1.6	0.8	0.9	1.0	7.7	1.6	1.0	2.6
BCX.051				1.12	1.45	0.7	0.7	0.8	0.9	1.0	1.1	7.7	1.1	0.9	2.0
BCX.055				0.89	1.07	1.5	1.2	0.9	0.9	0.7	0.7	7.7	0.9	0.9	1.8
BCX.011				0.99	1.05	0.5	0.6	1.0	1.1	0.9	0.9	7.1	0.9	0.9	1.8
BCX.096				0.91	0.95	0.5	0.6	1.0	1.3	0.8	0.8	6.6	1.1	1.0	2.1
BCX.060				0.91	0.84	0.7	0.7	0.7	1.0	0.7	0.9	6.5	1.2	1.0	2.3
BCX.066				0.92	0.75	0.5	0.7	1.0	1.3	0.8	0.9	6.5	1.0	1.0	2.0
BCX.102				0.96	0.74	0.6	0.7	1.2	1.1	0.6	0.5	6.5	1.2	1.0	2.2
BCX.095				1.01	0.94	0.6	0.9	0.5	1.0	0.6	0.7	6.1	1.2	1.2	2.4
BCX.080				0.9	0.58	0.6	0.7	0.8	1.1	0.8	0.7	6.0	1.2	1.0	2.2
BCX.094				0.92	0.75	0.4	0.6	0.8	1.2	0.7	0.7	5.9	1.1	1.1	2.2
BCX.042				0.78	0.83	0.7	0.7	0.4	1.2	0.4	0.5	5.2	1.1	1.0	2.1

B

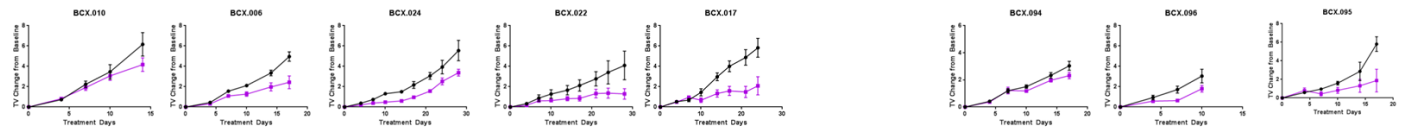
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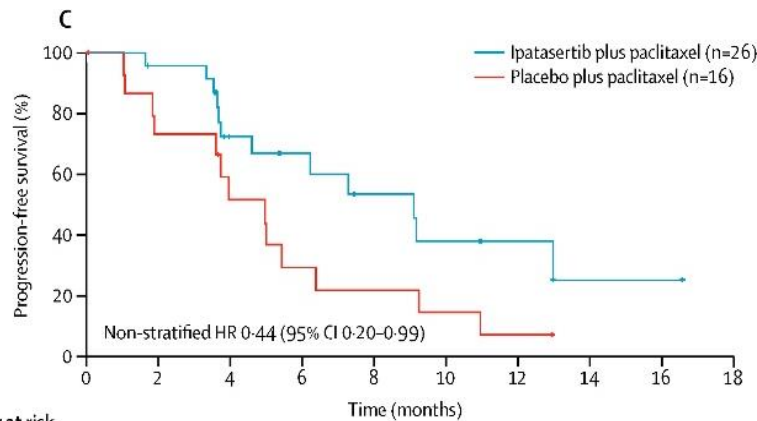
TAK228



Trametinib



Akt1 as a Therapeutic Target in Combination with Chemo



	0	2	4	6	8	10	12	14	16	18
Ipatasertib plus paclitaxel	26	22 (3)	13 (7)	10 (9)	7 (10)	5 (10)	3 (12)	1 (13)	1 (13)	0 (14)
Placebo plus paclitaxel	16	11 (1)	7 (2)	4 (2)	3 (2)	2 (2)	1 (2)	0 (3)		

Randomized Phase 2 trial
(LOTUS) ipatasertib
Ipatasertib +paclitaxel vs
ipatertib

Advanced/metastatic
previously untreated TNBC

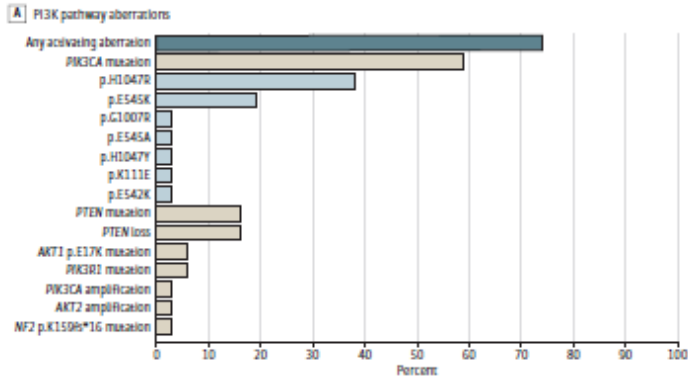
In PIK3CA/AKT1/PTEN-
altered pts

PFS of 9.0 months vs 4.9
months (HR 0.44; p=0.041)

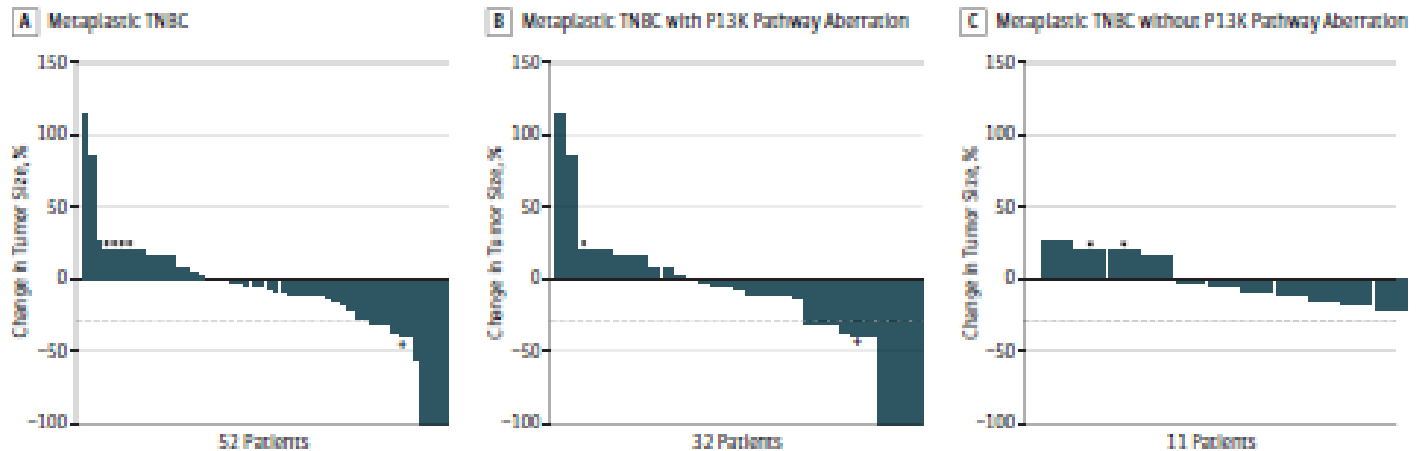
Kim et al Lancet Onc, 2017

PI3K Pathway Alterations in Metaplastic Breast Cancer

Figure 2. Spectrum of Mutations in Patients With Metaplastic Breast Cancer

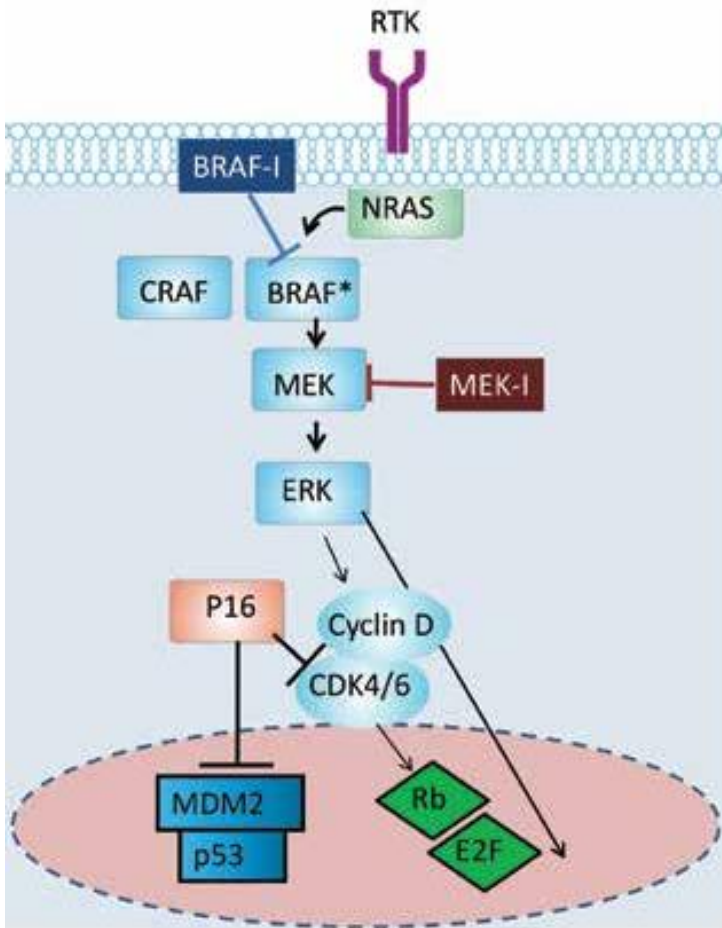


- 52 patients with metaplastic breast cancer treated with liposomal doxorubicin, bevacixumab and temsirolimus
- 43 with tissue available for testing
 - 32 (74%) had PI3K pathway alterations
- ORR
 - 31% in pts with and
 - 0% in pts without PI3K pathway alterations



Basho et al,
JAMA Oncology, 2017

Targeting MAPK signaling

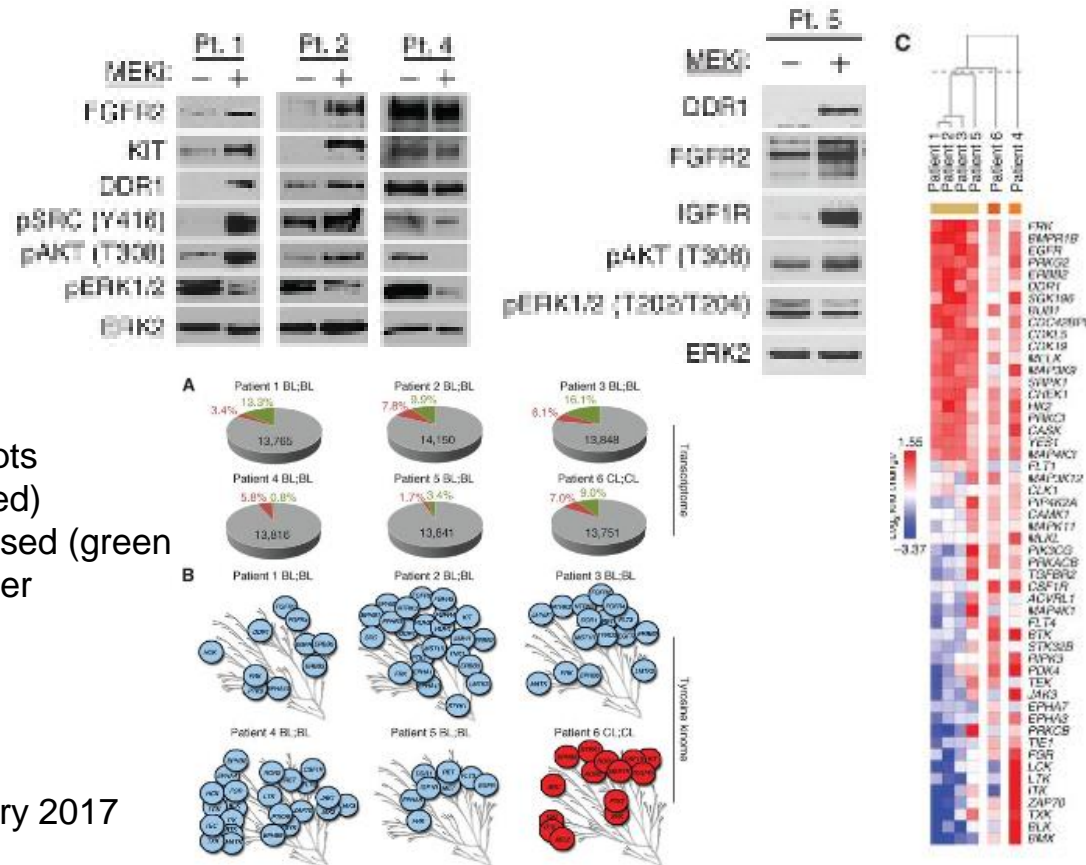


Robert et al Skin Cancer Foundation

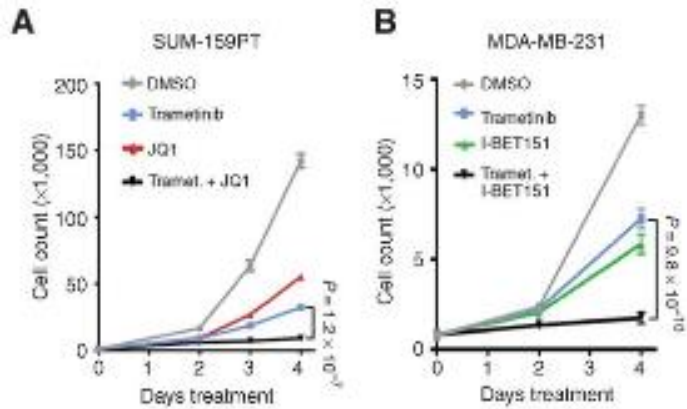
- Increasingly targeting the dysregulated BRAF–MEK–ERK pathway in cancer
- Resistance through multiple mechanisms, often involving nongenomic adaptive bypass mechanisms
- To study adaptive responses:
 - 6 patients with operable TNBC
 - 7 days of preoperative trametinib
- RNASeq on pre-treatment bx and surgical sample

Zawistowski et al
Cancer Discovery 2017

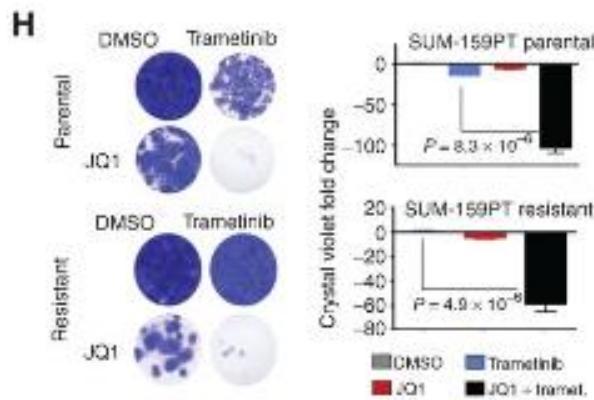
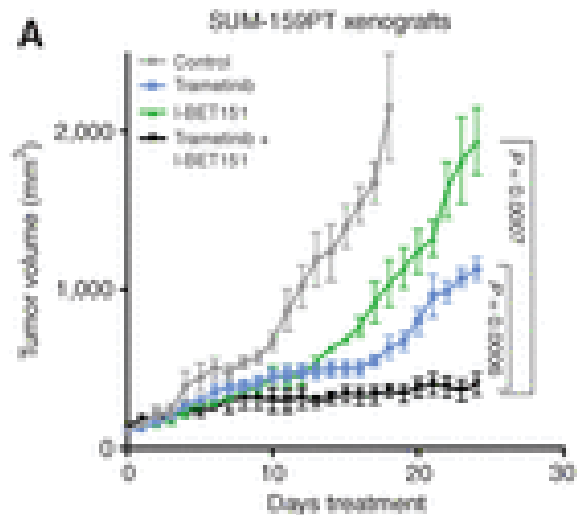
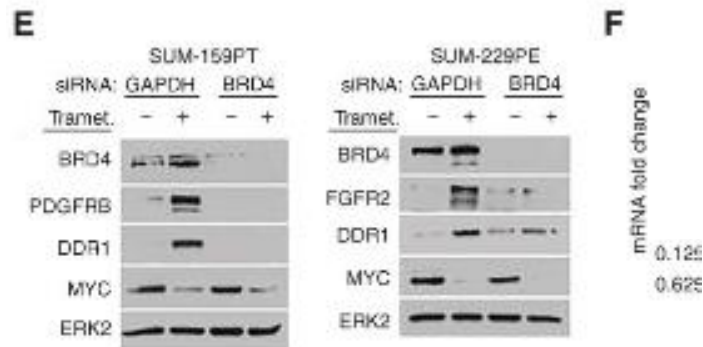
Response to MEK inhibition in TNBC patient Tumors from a Window-of-opportunity Trial



Zawistowski
Cancer Discovery 2017



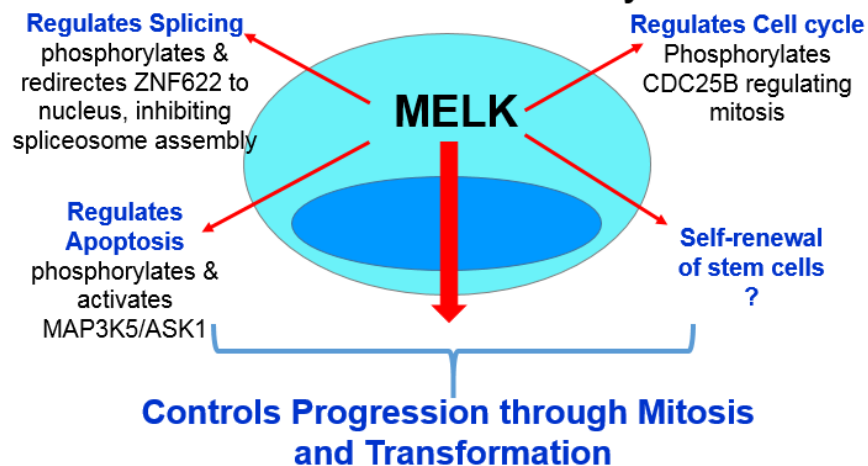
MEK inhibition and
BET bromodomain
inhibition are synergistic
in vivo



Zawistowski
Cancer Discovery 2017

MEK/BET combos in planning stage...

Maternal Embryonic Leucine Zipper Kinase

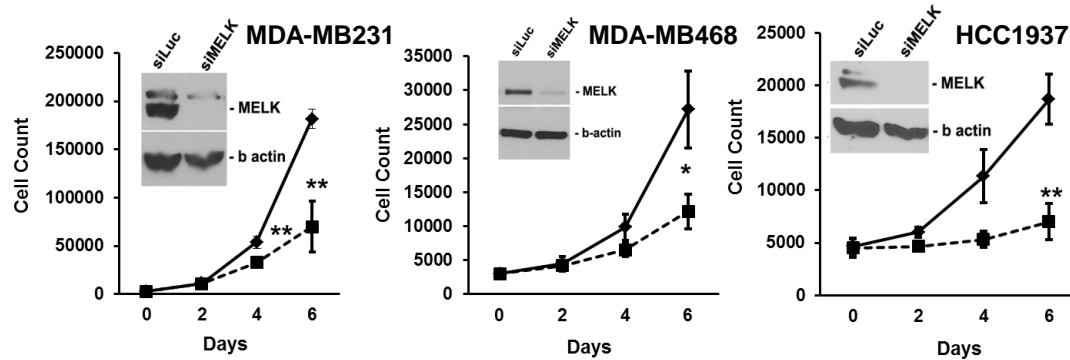


- MELK identified in a kinase screen in ER-positive vs. ER-negative BC (highly expressed in TNBC)
- Associated with poor prognosis
- Associated with resistance to radiation, and inhibition of MELK enhances radio-sensitivity
- MELK is 1 of the 70 MammaPrint genes used to predict risk of breast cancer recurrence
- MELK is 1 of 21 proliferation-related genes in PAM50 used to sub-type breast cancers and predict risk of breast cancer recurrence

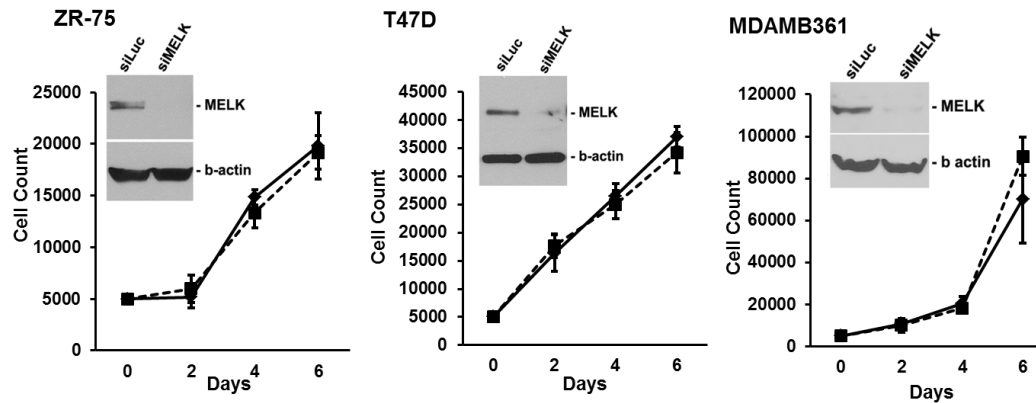
. Speers C. et al. CCR, 2009; Ganguly R et al. MCT, 2014; Wang Y et al. Elife, 2014; Pickard M et al. Breast Ca Res, 2009; Speers C et al. Clin Ca Res, 2016

MELK Knockdown Suppresses TNBC Growth

TNBC

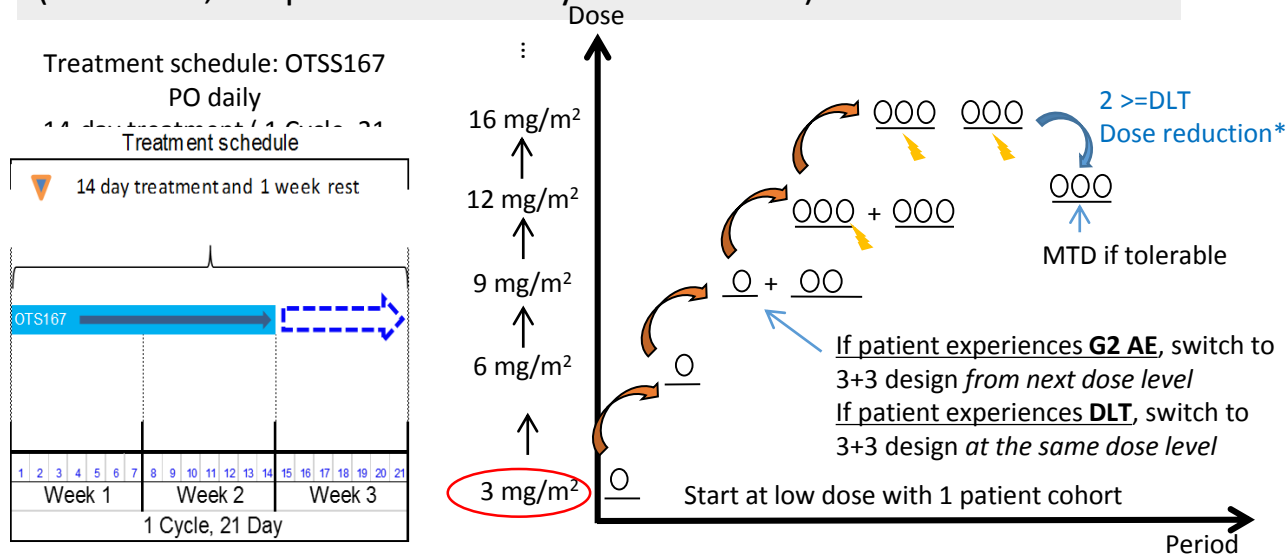


ER-Positive



MELK inhibitor OTS167 PO (Oncotherapy Sciences) Phase I Dose-escalation with Dose-expansion study in patients with Relapsed, Refractory Metastatic TNBC

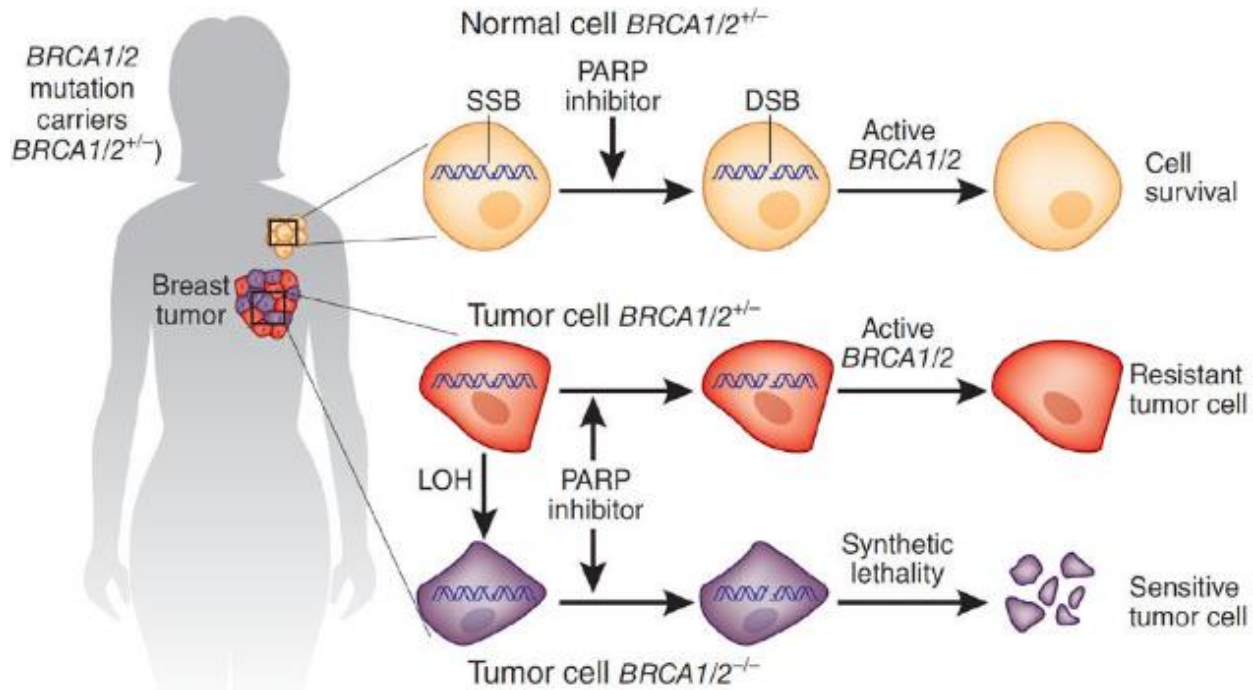
Part A: Phase I dose-escalation : approx. 40 - 50 participants
(advanced, relapsed or refractory breast cancer)



- Starting dose is 5mg (approx. 3mg/m²)
- Calculate actual administration dose based on the patient's BSA
- Doses will be escalated in 100% increments during Stage 1 single patient cohort and in 33% to 100% increments in Stage 2 (3 patients cohort)

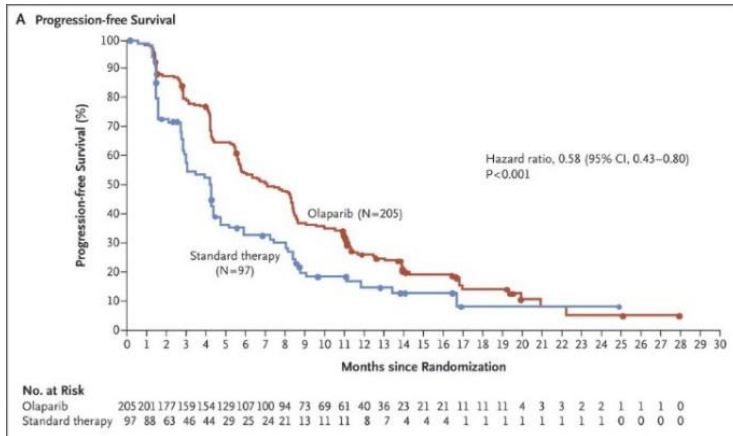
*Dose will be reduced 5mg from administered dose
For example:
Cohort: 50 mg -> 5mg reduction (50 mg to 45 mg)
Cohort: 40 mg -> 5mg reduction (40 mg to 35 mg)

Targeting DNA Damage Repair Defects



Nature

PARP Inhibitors in Germline Mutant Patients



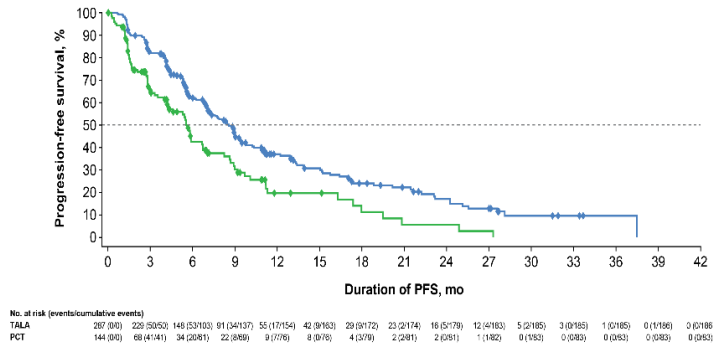
Olaparib Phase III trial

Response rate:

59.9% on olaparib Vs 28.8% in the standard-therapy

Median PFS 7.0 months vs. 4.2 months (P<0.001)

Robson et al NEJM, 2017

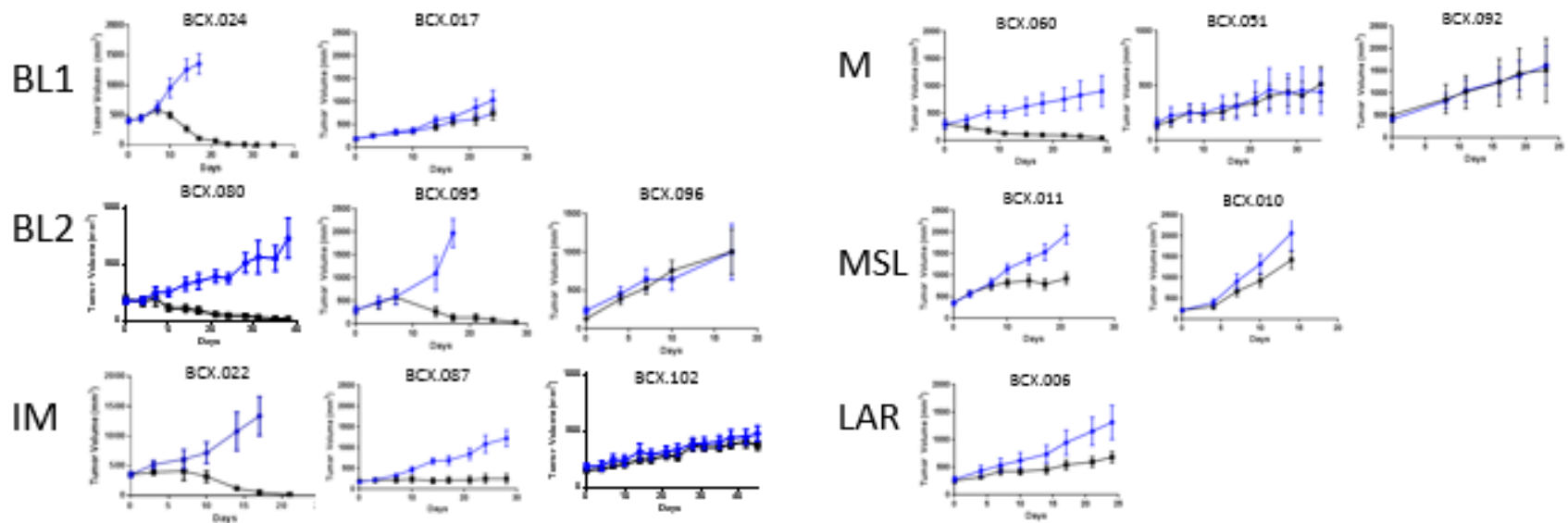


Talazoparib Phase III trial

	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
Hazard ratio, 0.54, 95% CI, 0.41, 0.71 P < .0001		

Litton et al SABCS 2017

Response of PDXs to PARP inhibitor Talazoparib: Activity Beyond BL1 subtype and Germline BRCA



Phase II Histology Agnostic Trial of Talazoparib for Homolog Recombination Defects

Somatic <i>BRCA 1 or 2</i> mutations
<i>BRCA 1 or 2</i> Deletion
Mut or Del of <i>ATM, PALB2, MER11, RAD50, NBS1,ATR;</i> Fanconi Anemia Genes, Amplif <i>EMSY,</i>
<i>PTEN</i> mutation, deletion or loss of expression
Germline <i>BRCA1 or 2</i> Mutation in Non-Breast/Ovarian Cancer

PIs: Sarina Piha-Paul; Meric-Bernstam

Novel PARP combinations

- Target mechanisms of acquired and intrinsic resistance in BRCA germline tumors
- Generate BRCA-ness in germline BRCA1/2 wildtype tumors
 - PARP+ angiogenesis
 - PARP inh+ PD1
 - PARP + PI3K/Akt/mTOR
 - PARP+ MEK
 - PARP+ BET
 - ...

Outline

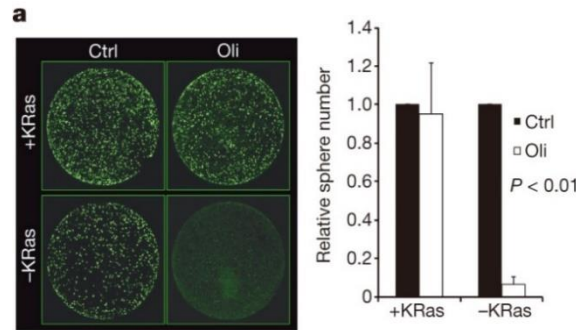
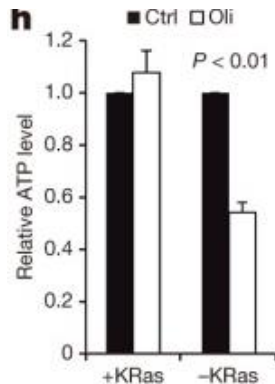
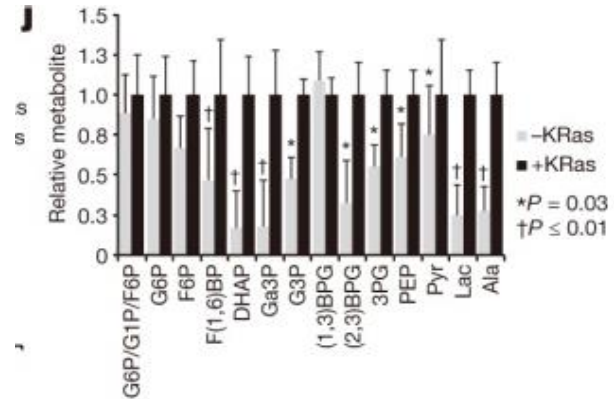
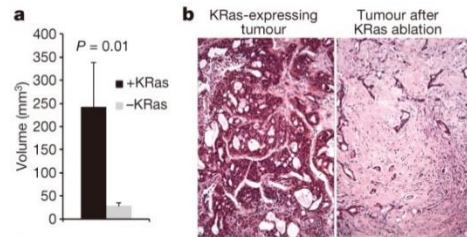
- Tumor Heterogeneity
- DNA damage repair
- **Cancer metabolism**
- Antibody drug conjugates
- Other

OXPHOS as a Novel Target



G. Draetta

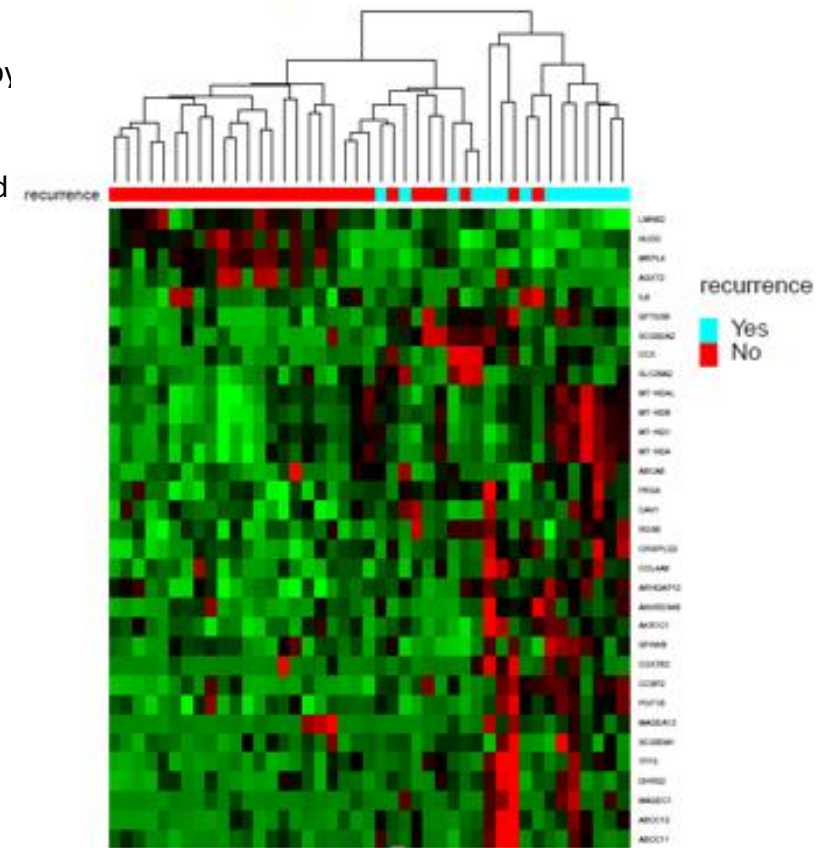
Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function



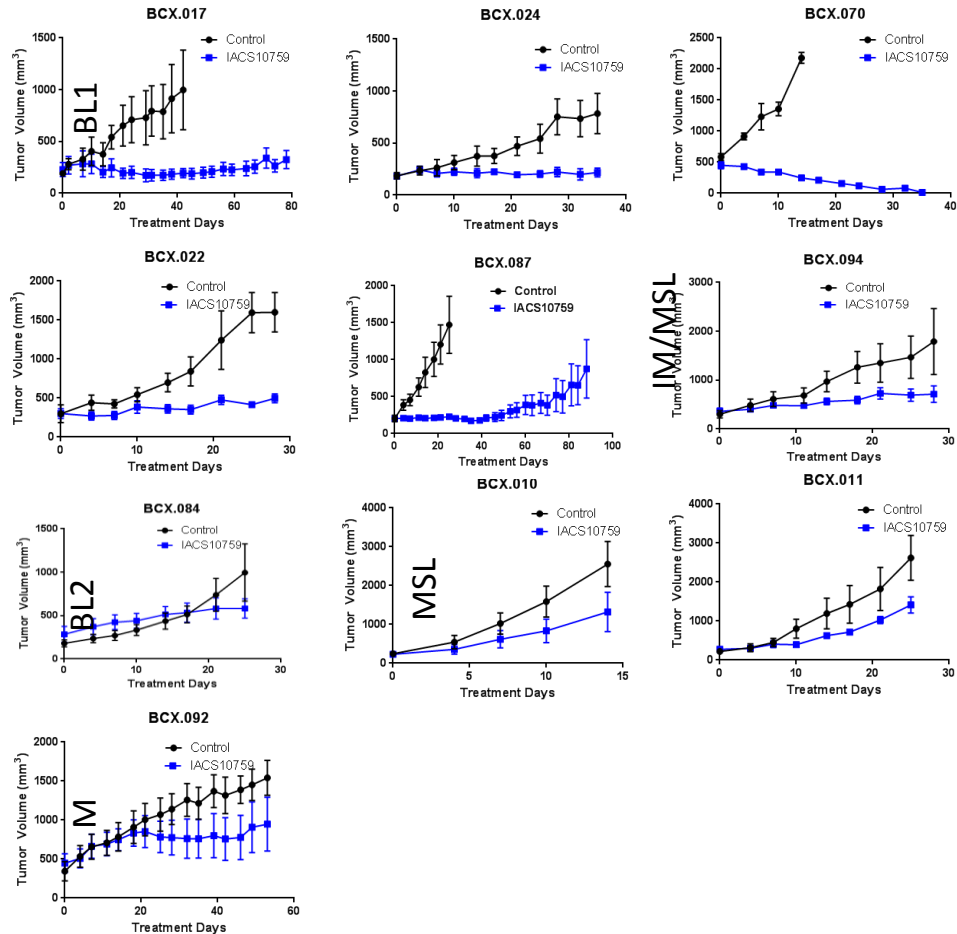
- Pancreatic tumor cells surviving Kras ablation are dependent upon electron transport and oxidative phosphorylation for survival
- Treatment with inhibitors of OXPHOS are capable of eradicating surviving cells
- OXPHOS is a novel target for development of inhibitors

OXPHOS and TNBC Prognosis

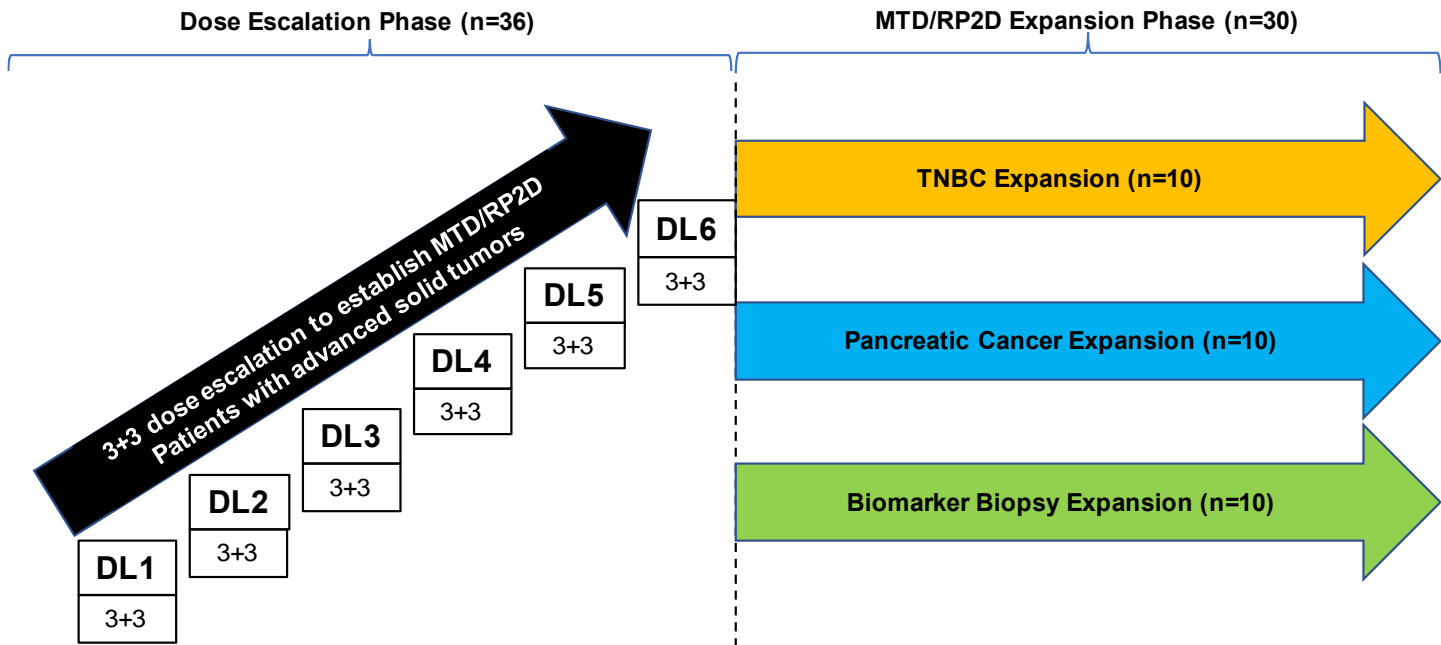
- Pretreatment biopsies from patients with TNBC (n=43)
 - Sequential taxane and anthracycline based therapy
 - > 5 years median follow up
- 14 patients recurred and all but 2 of these patients died
- 33 genes differentially expressed in patients with and without recurrence
- Top canonical pathways that differed:
 - oxidative phosphorylation ($p < 0.0001$)
 - mitochondrial dysfunction ($p < 0.0001$)
- Patients that recurred had significantly higher levels of mitochondrial genes:
 - MT-ND1 (adjusted p or FDR-BH=0.007)
 - MT-ND5 (adjusted p=0.03)
 - MT-ND4 (adjusted p=0.04).



Efficacy of OX PHOS inhibitor IACS-10759 Against TNBC PDXs



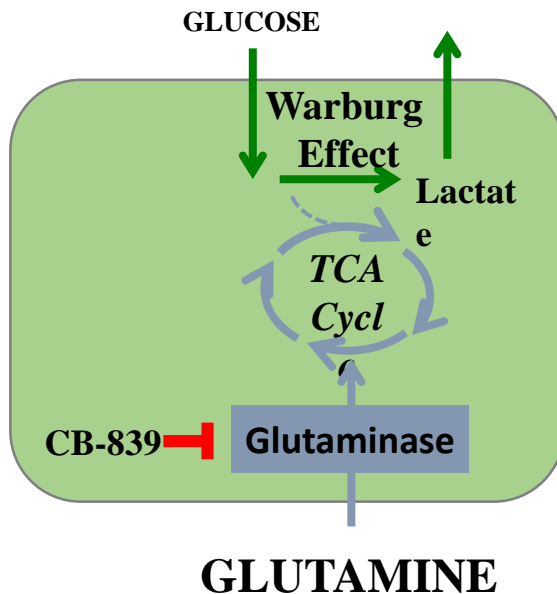
Phase I Clinical Trial Design



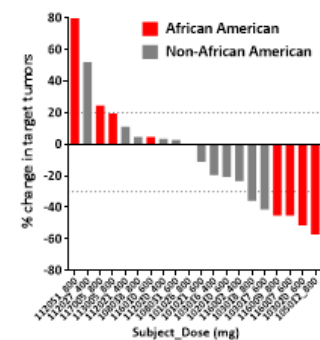
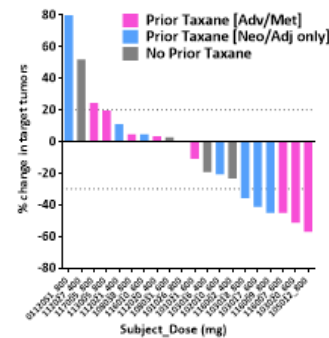
PI: Tim Yap
Co-Pis: Meric-Bernstam
Varadhachari

Targeting Tumor Glutamine Metabolism

Blocking Glucose and Glutamine Metabolism in Tumors



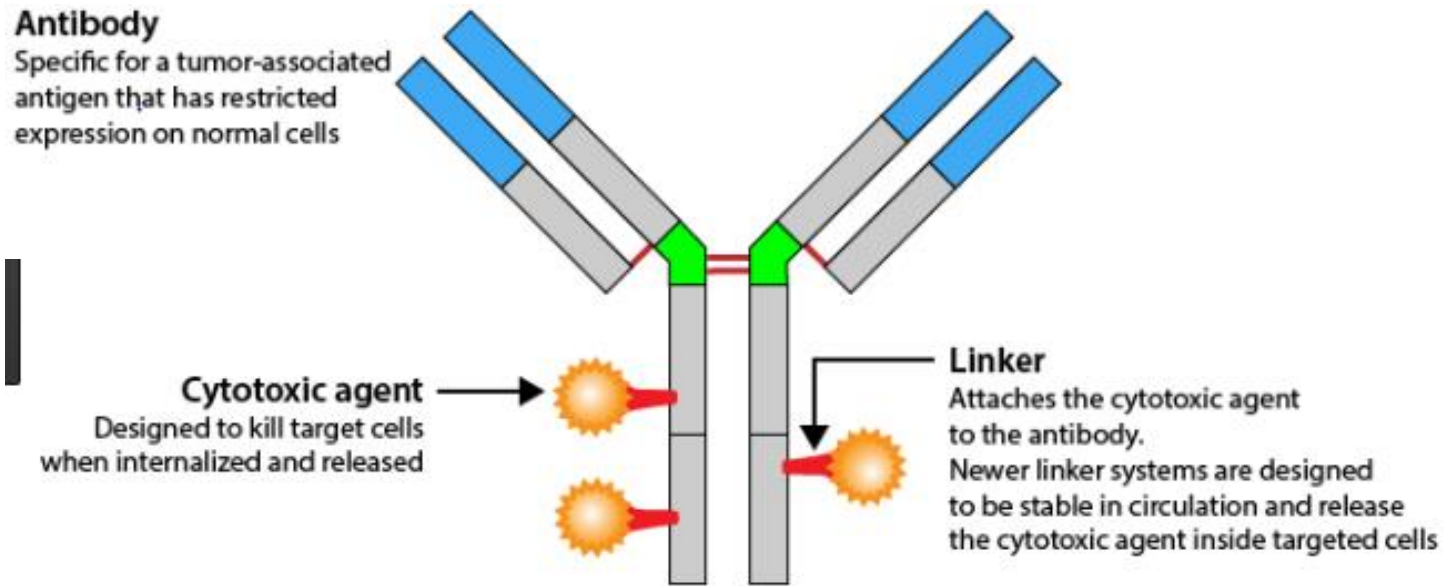
- Cancer cells require both glucose and glutamine for growth and survival
- The TCA cycle is a critical source of ATP for cellular energy, and key biosynthetic intermediates for production of amino acids, nucleotides and fatty acid
- Glutaminase is a mitochondrial enzyme that catalyzes the conversion of glutamine to glutamate. Glutamate subsequently is converted to alpha-ketoglutarate, entering TCA cycle.
- CB-839 is a first in class, small molecule, oral, highly specific, reversible, inhibitor of glutaminase.



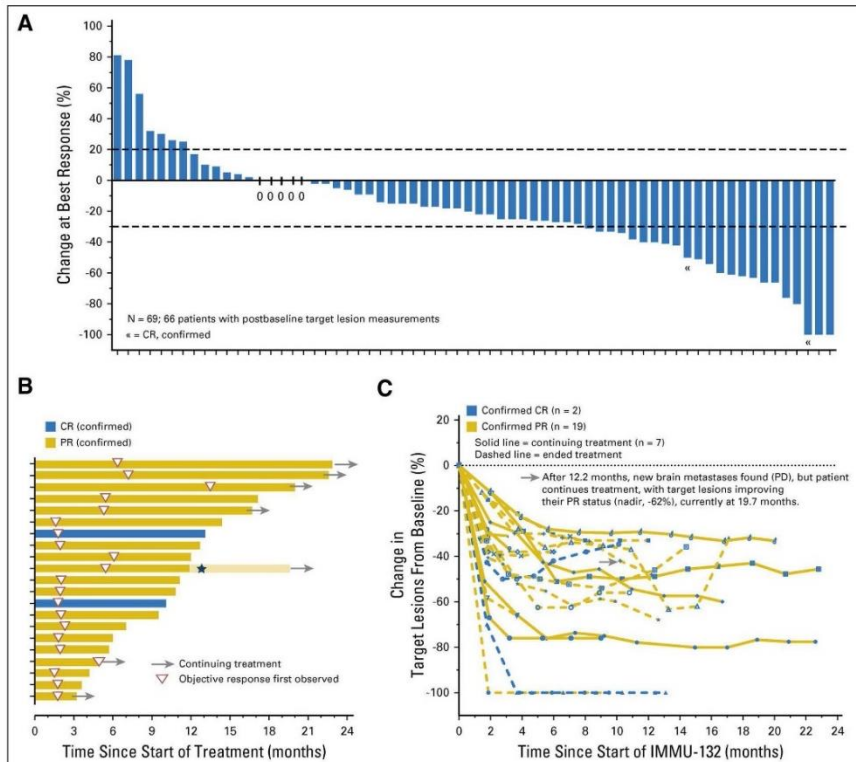
Outline

- Tumor Heterogeneity
- DNA damage repair
- Cancer metabolism
- **Antibody drug conjugates**
- **Other**

Antibody Drug Conjugates



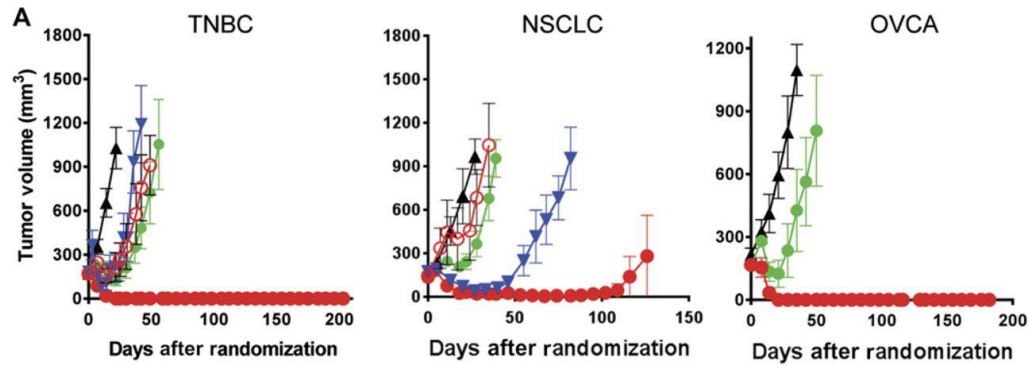
Sacituzumab govitecan (IMMU-132), an anti-Trop-2-SN-38 antibody



- Trop-2 is a calcium signal transducer that drives tumor growth
- 69 patients who received a median of five prior therapies (range, one to 12) since diagnosis
- Confirmed objective response rate was 30% (partial response, n = 19; complete response, n = 2),
- Median response duration was 8.9 months
- Clinical benefit rate (CR+ PR+ SD ≥ 6 months) was 46%

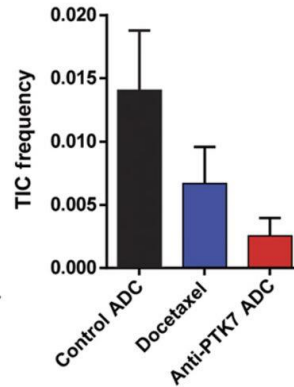
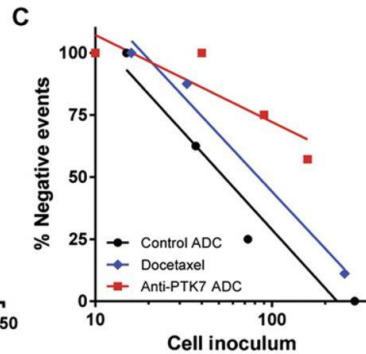
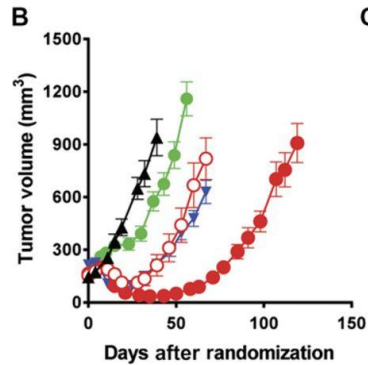
The majority of archival tumor specimens (88%) were moderately to strongly positive for Trop-2 IHC

Targeting PTK7



PTK7 ADC :

- Decreased tumor growth in TNBC, NSCLC and OVCA
- Reduced tumor initiating cell frequency

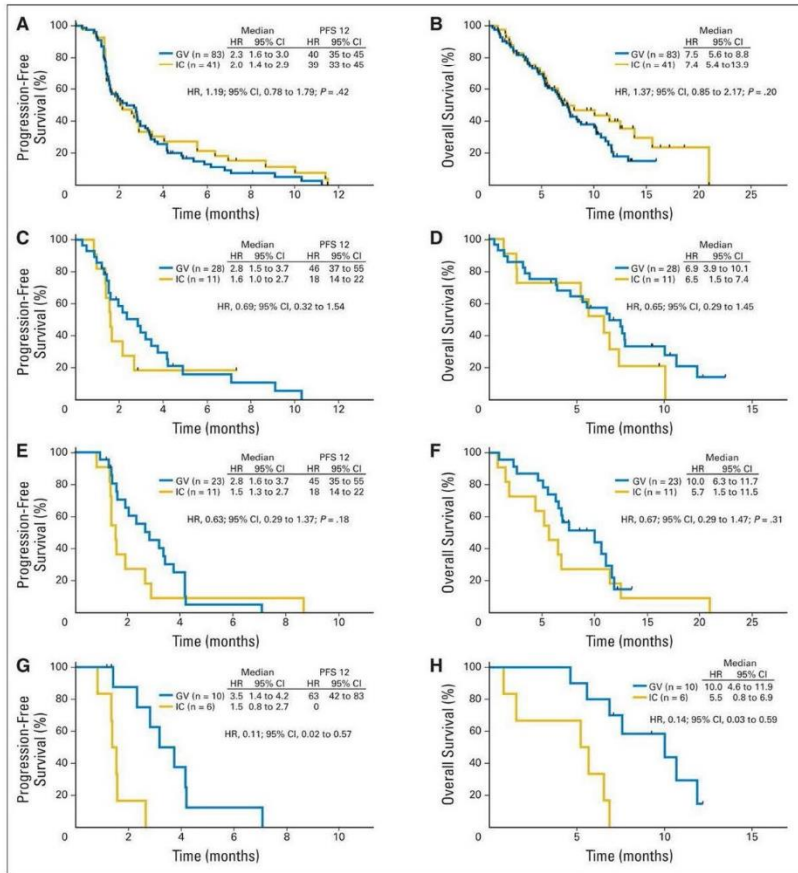


Glycoprotein nonmetastatic B (GPNMB)

- Murine steoactivin as a protein that is expressed in aggressive human breast cancers and is capable of promoting breast cancer metastasis to bone.
- GPNMB expression correlates with shorter recurrence times and reduced overall survival of breast cancer
- GPNMB staining GPNMB is highly expressed in basal and triple-negative breast cancers (and some other tumors such as melanoma)
- GPNMB expression confers a more migratory and invasive phenotype on breast cancer cells
- GPNMB sensitizes them to killing by CDX-011 (glembatumumab vedotin), a GPNMB-targeted ADC (anti gpnMB Ab conjugated with cleavable linker to monomethyl auristatin E.

Rose A, MCR, 2007, Rose A, CCR, 2010

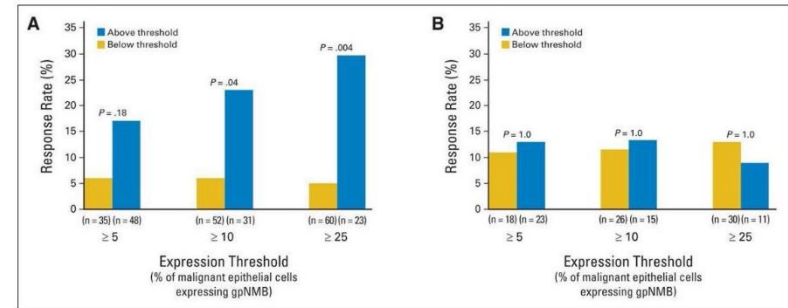
EMERGE: Randomized Phase II with gpNMB ADC Glembatumumb Vedotin



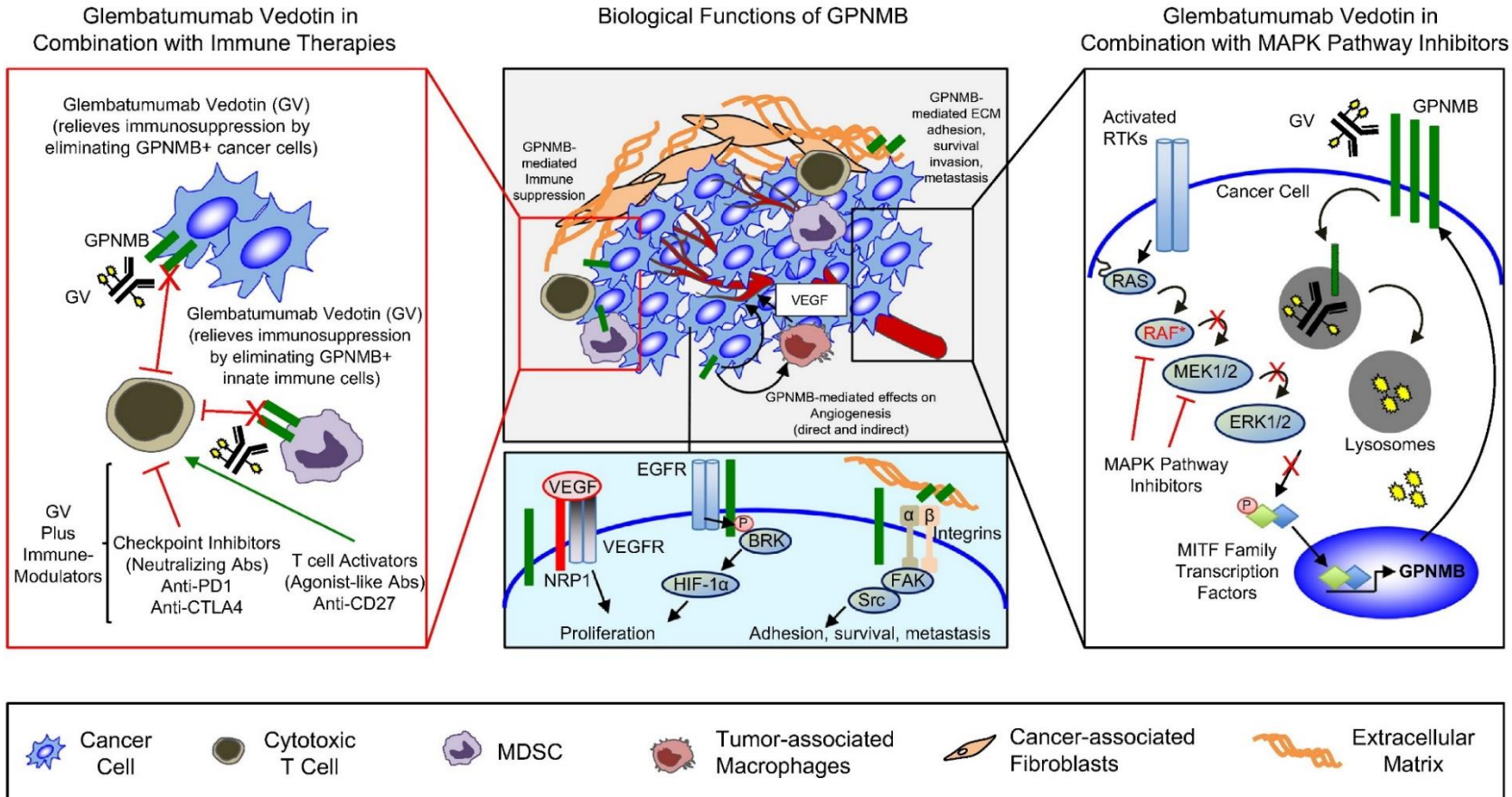
- Patient randomized 2:1 to glemba vs investigator choice
- ORR was 6% vs 7% overall
- ORR 30% vs 9% for gpNMB overexpression ($\geq 25\%$)
- Unplanned analysis showed 40% vs 0% in gpNMB overexpressing TNBC

High gpNMB

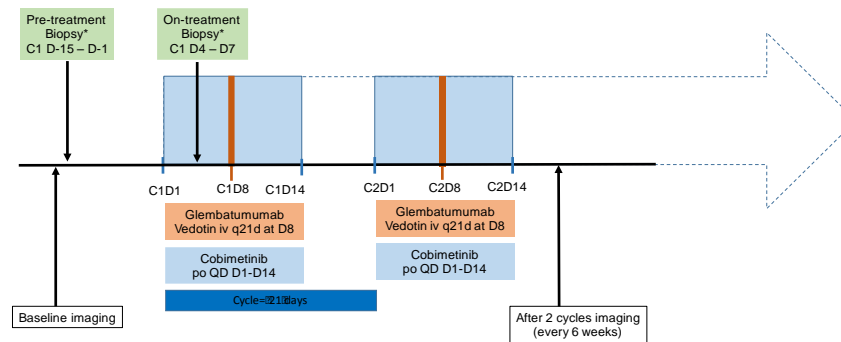
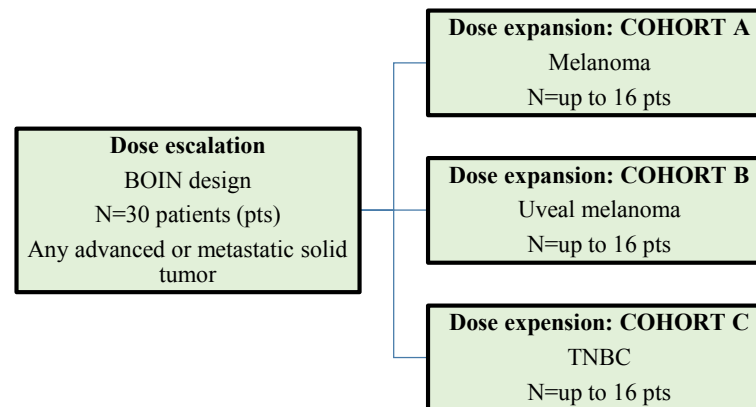
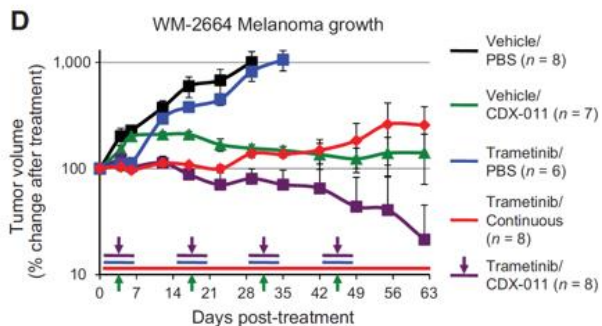
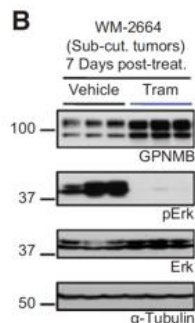
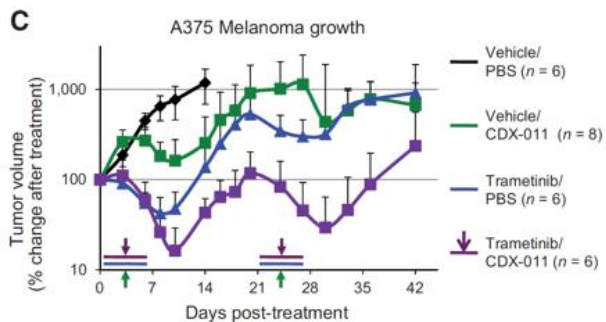
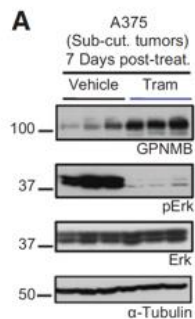
TNBC and high gpNMB



Rationale Combinations with Glebatumumab

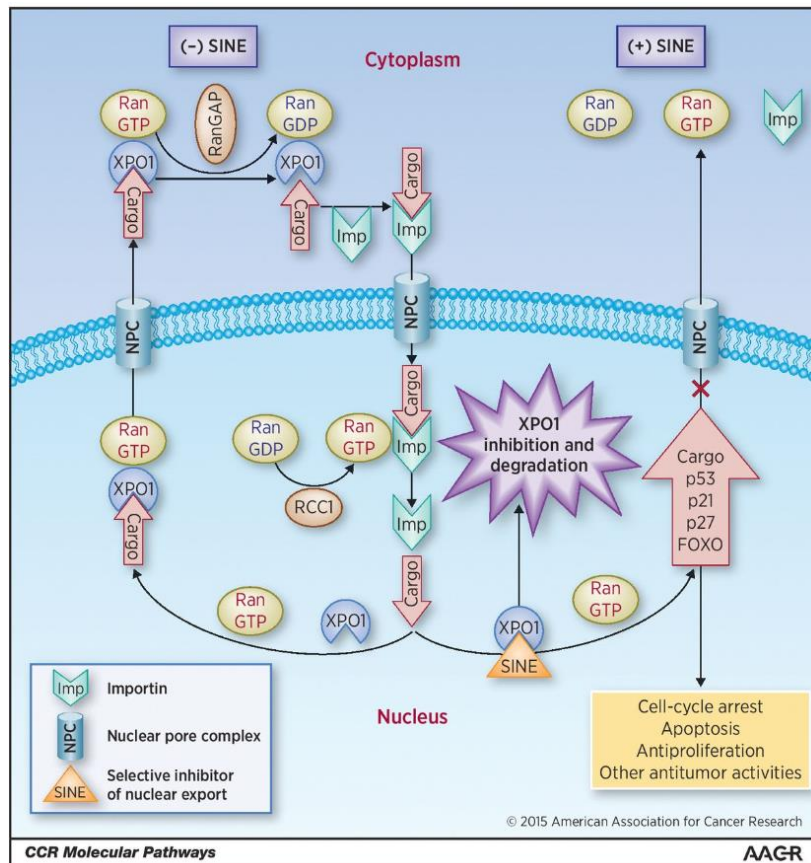


Modulating ADC targets



* Biopsies are optional in dose escalation, but mandatory in dose expansion phase

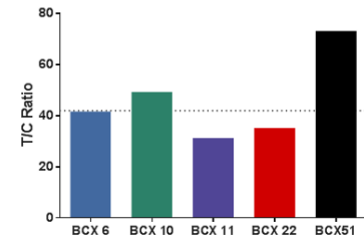
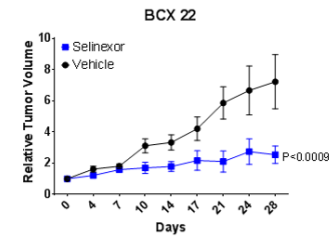
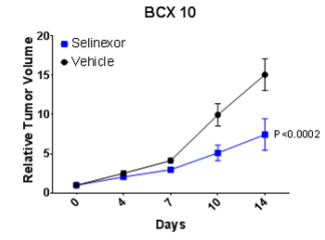
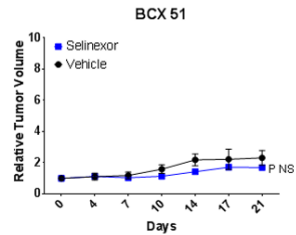
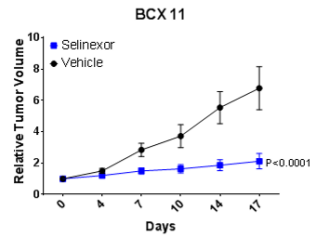
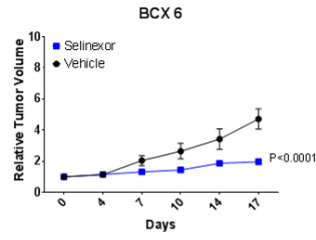
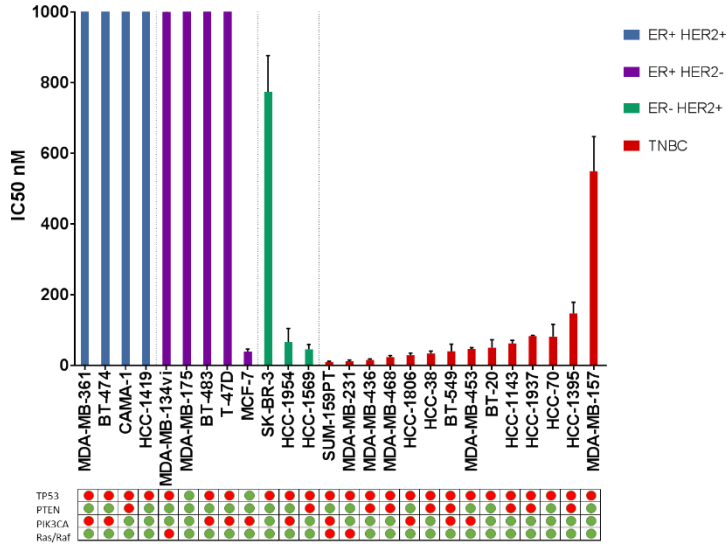
XPO1 as a Target in TNBC

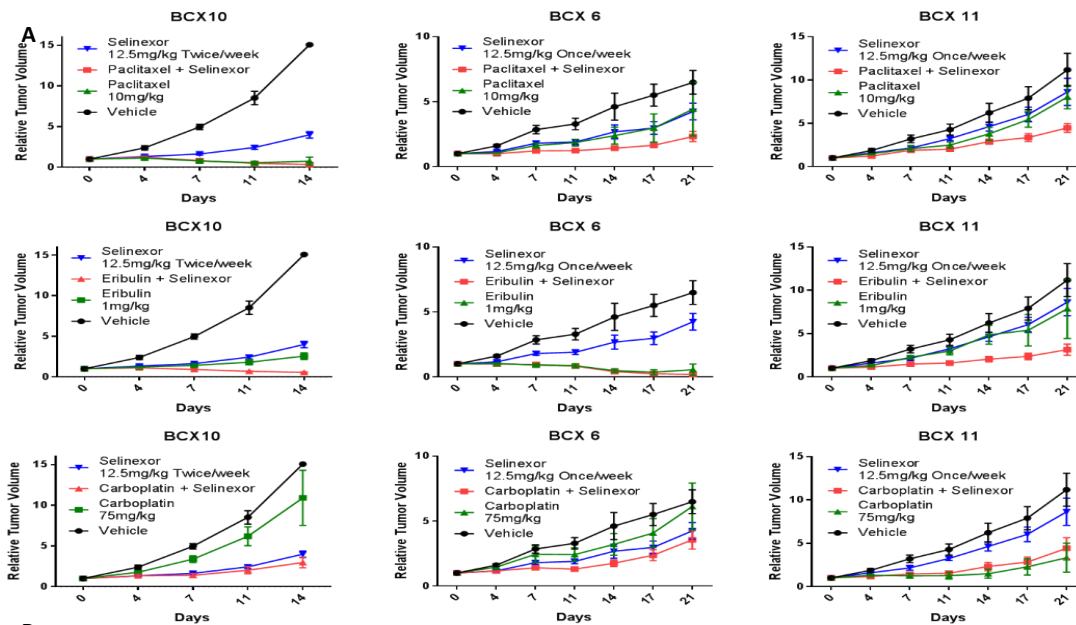
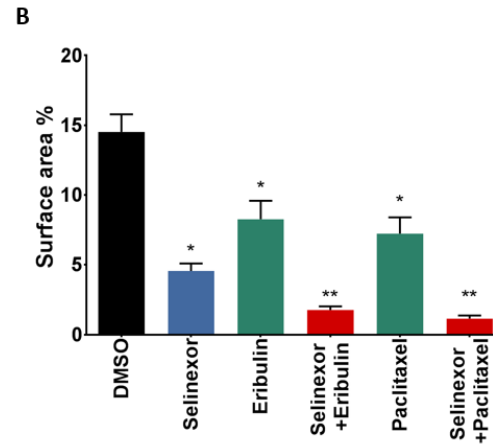
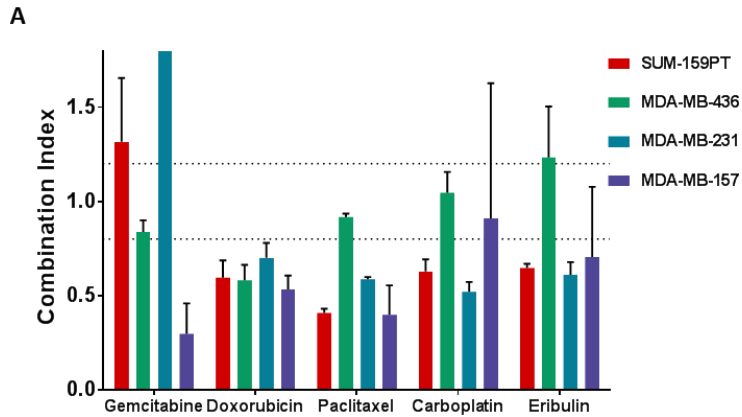


- The nuclear exporter XPO1 (Exportin1 or CRM1) is one of at least seven exportins that mediate the transport of over 200 proteins, including several key regulators of the cell cycle (e.g., p53, STAT3, survivin, FoxO3a, BRCA1, and others)
- Selinexor is an oral inhibitor of XPO1

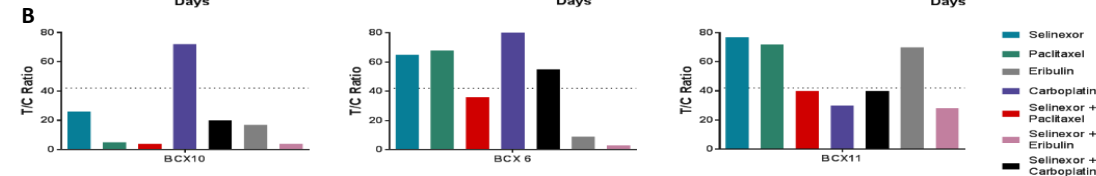
Conforti et al,
CCR, 2015

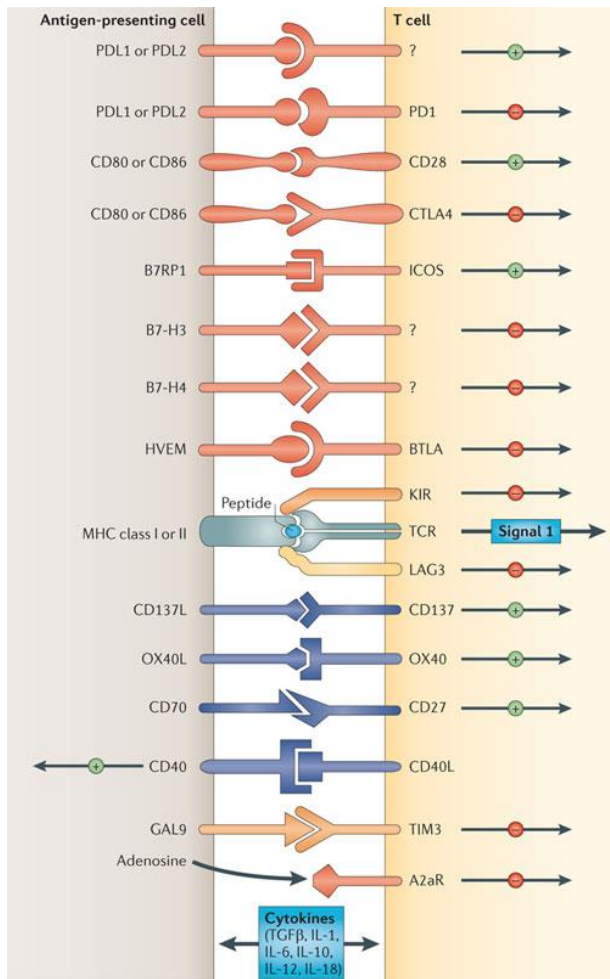
Selinexor in TNBC





Selinexor combinations
in Phase I trials
(PI Naing, co-PI Meric)





Nature Reviews | Cancer

Many immunotherapy efforts

New agents

Novel combinations

Novel/novel IO

Targeted/IO

Chemo/IO

Intratumoral therapies

Markers of response

Summary and Conclusions

- TNBC is a heterogenous disease
- Many new and exciting targets in development
- Systematic efforts are needed to identify effective rational combination therapies and optimize patient selection

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THANK YOU!

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