Scientific Publications

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Webinar:

Designing an Effective Scientific Poster

Ann Sutton

Overview

- Planning
- Content
- Design
- Other considerations

Planning

- Read the instructions
- Identify your audience
- Tailor your message
- Create a schedule

Planning

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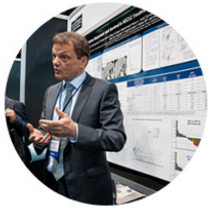
Read the Instructions



Poster Presenter Guidelines

When creating your poster for the ASCO Annual Meeting, please be aware of the following guidelines.

- Format of poster is LANDSCAPE (horizontal).
  - **Regular Poster Size Limitations:** No larger than 47 inches high and 95 inches wide (120 cm high by 240 cm wide). This is the size of the poster board. Do NOT exceed the size of the poster board.
  - **Trials in Progress Poster Size Limitations**: No larger than 42 inches high and 42 inches wide (107 cm high by 107 cm wide). This is half the size of the poster board. You will be sharing the poster board so please do NOT exceed the size limitations.
- **Photos, Charts, and Graphs:** Charts, drawings, and illustrations should be similar to those you would use in making PowerPoint slides. If photographs are used, please have them processed with a matte or dull finish.
- **Contact Information:** Please clearly print 1 email address on your poster for attendees to refer to should they have any questions or comments at a time when you are not standing with your poster. If you do not wish to print your own email address, please list another email address for an appropriate contact person for your abstract.
- **Poster Material:** The poster can either be made on 1 sheet (rollup) or in several small sections. Do NOT mount illustrations on heavy cardboard because they may be difficult to keep in position on the poster board.
- **Federally Funded Research:** Abstract Presenters whose research received federal funding (either in whole or in part) are encouraged to use ASCO's trademarked "Federally Funded Research" badge in their presentation. ASCO created the badge to raise awareness of the importance of federally funded biomedical research. **Download** the badge file and review further information on its use.
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Planning

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Content

- Title and authors
- Background
- Methods and results
- Conclusion
- References
- Contact information and support

Title and Authors

- Title
- Authors
- Affiliations
- Institutional logo

JNK signaling regulates tumor cell–tumor-associated macrophage cross-talk in triple-negative breast cancer

Xuemei Xie[1,2], Shimpei Otsuka[1,2], Evan Cohen[1,3], Khoi Chu[4], Alexander Y. Lu[1,2], Debu Tripathy[1,2], Kevin N. Dalby[5], James M. Reuben[1,3], Walter N. Hittelman[4], Steven Van Laere[6], Chandra Bartholomeusz[1,2], and Naoto T. Ueno[1,2]

[1]Section of Translational Breast Cancer Research, [2]Department of Breast Medical Oncology, [3]Department of Hematopathology, and [4]Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, Texas. [5]Division of Medicinal Chemistry, College of Pharmacy, The University of Texas at Austin, Austin, Texas. [6]Department of Oncology, University of Antwerp, Antwerpen, Belgium.

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Introduction

- Triple-negative breast cancer (TNBC) is more aggressive than other types of breast cancers and has a poor prognosis because of its high proliferation rate, stemness, and tendency to metastasize[1].
- JNK (c-Jun N-terminal kinase) plays a vital role in malignant transformation and stress-induced inflammation[2,3].
- M1 macrophages promote inflammation but suppress tumor progression. M2 macrophages, also termed as tumor-associated macrophages (TAMs), suppress inflammation but promote tumor progression[4].
- In breast cancer, TAMs are associated with high histological grade, large tumor size, high proliferation rate, low ER and PR status, and poor prognosis[5].
- It remains unknown whether JNK plays a role in tumor-TAM cross-talk in TNBC.

Objective

To define the role of JNK signaling in regulation of tumor cell-M2 cross-talk in TNBC.

Hypothesis

JNK contributes to TNBC metastasis by promoting tumor cell-M2 cross-talk through the TGF-β signaling pathway in TNBC.

Results

JNK/c-Jun signaling and M2 cells have clinical impact in TNBC

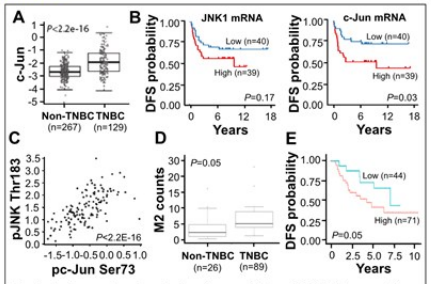

Fig 1. **A**, Expression levels of c-Jun are higher in TNBC tumors than in non-TNBC tumors (MDACC RPPA dataset). **B**, Disease-free survival (DFS) probability by JNK1 and c-Jun status in patients with TNBC (Wang and Mainz dataset). **C**, Expression levels of phospho-c-Jun at Ser73 positively correlate with those of phospho-JNK at Thr183 in TNBC tumors (n=129; MDACC RPPA dataset). In inflammatory breast cancer, (**D**) M2 counts are higher in TNBC tumors than in non-TNBC tumors, and (**E**) M2 counts positively correlate with short DFS.

Differentiation of THP1 monocytes to M1 and M2 macrophages

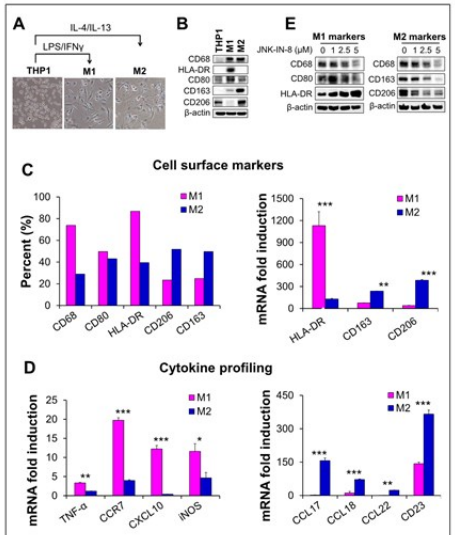

Fig 2. Differentiation of THP1 monocytes to M1 and M2 macrophages, as assessed by (**A**) morphology, (**B** & **C**) cell surface marker expression by Western Blotting, FACS, and qPCR, and (**D**) cytokine profiling by qPCR. **E**, JNK inhibition by JNK-IN-8 promotes M1 differentiation but suppresses M2 differentiation. *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$.

The JNK pathway is involved in M2 macrophage-promoted motility in TNBC cells *in vitro*

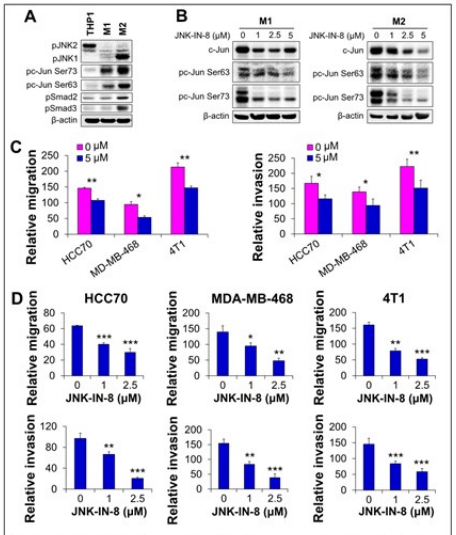

Fig 4. **A**, The JNK/c-Jun and TGF-β pathways are strongly activated in M2 macrophages. **B**, JNK inhibition by JNK-IN-8 suppresses c-Jun activation in both M1 and M2 macrophages at 48 h following treatment. **C** & **D**, JNK inhibition by JNK-IN-8 in (**C**) M2 macrophages or (**D**) TNBC cells leads to a reduction in M2 macrophage-promoted migration and invasion of TNBC cells. *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$.

JNK inhibition suppresses tumor growth and M1/M2 recruitment to tumors in a TNBC mouse model

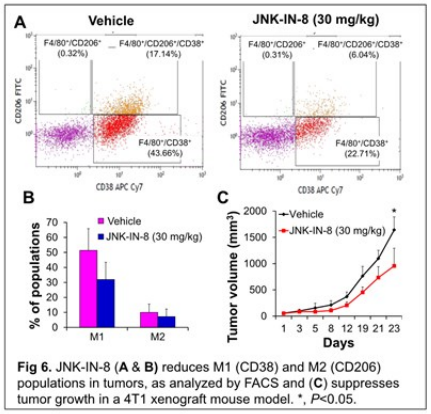

Fig 6. JNK-IN-8 (**A** & **B**) reduces M1 (CD38) and M2 (CD206) populations in tumors, as analyzed by FACS and (**C**) suppresses tumor growth in a 4T1 xenograft mouse model. *, $P<0.05$.

Conclusions

- JNK/c-Jun signaling and M2 macrophages have clinical impact in TNBC.
- M2 macrophages promote migration and invasiveness of TNBC cells possibly through the JNK/c-Jun/TGF-β pathway.
- JNK signaling suppresses M1 macrophage differentiation but promotes M2 macrophage differentiation.

M2 macrophages promote migration and invasion of TNBC cells *in vitro*

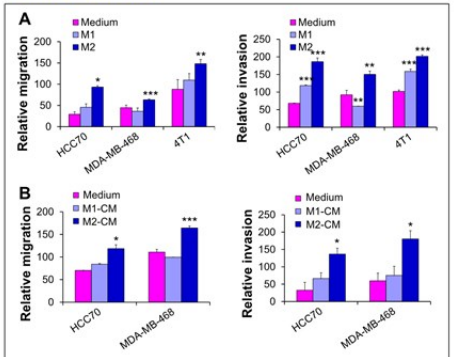

Fig 3. Compared to culture with medium alone or co-culture with (**A**) M1s or (**B**) M1-conditioned medium (CM), co-culture with (**A**) M2s or (**B**) M2-CM significantly enhances migration and invasion of TNBC cells. *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$.

M2 macrophages promote motility of TNBC cells through paracrine signaling *in vitro*

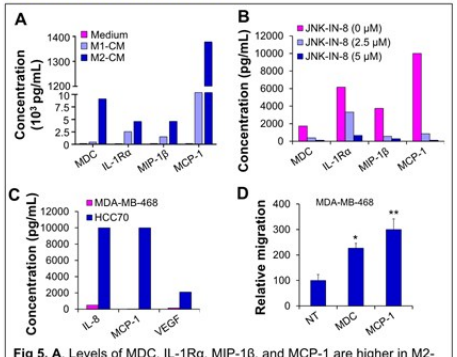

Fig 5. **A**, Levels of MDC, IL-1Rα, MIP-1β, and MCP-1 are higher in M2-CM than in M1-CM. **B**, JNK inhibition by JNK-IN-8 reduces secretion of MDC, IL-1Rα, MIP-1β, and MCP-1. **C**, TNBC cells secret high levels of IL-8, MCP-1, and VEGF. **D**, MDC and MCP-1 enhances migration of TNBC cells. *, $P<0.05$; **, $P<0.01$.

Future Studies

- Determine which JNK isoform plays a predominant role in TNBC-M2 cross-talk.
- Elucidate how the JNK/c-Jun/TGF-β pathway regulates TNBC-M2 cross-talk.
- Assess the impact of M2 macrophages on metastasis of TNBC cells using animal models.
- Determine the clinical significance of M2- and TNBC-derived cytokines/chemokines in TNBC.

Acknowledgements

This work is supported by MDACC Inflammatory Breast Cancer funds (105655) and Nylene Eckles funds (101478) to Naoto T. Ueno; startup funds from MDACC (111411) to Chandra Bartholomeusz; and National Institutes of Health Cancer Center Support Grant to MDACC (CA016672).

References

1. de Ruijter TC *et al.* J Cancer Res Clin Oncol. 2011, 137:183-92.
2. Yoon C-H *et al.* Oncogene. 2012, 31:4655-66.
3. Cubero FJ *et al.* Hepatology. 2011, 54:1470-2.
4. Weagel E et al., J Clin Cell Immunol 2015, 6:4.
5. Zhao X *et al.* Oncotarget. 2017 May 2; 8(18): 30576–30586.

Background

- Why the topic is important (problem or gap in knowledge)
- Essential background information

Background

Background

- Triple-negative breast cancer (TNBC) is among the most aggressive subtypes, accounts for 10-15% of all breast cancer cases and is characterized by the lack of hormone receptors with a low overall survival rate.
- Due to the heterogeneity nature of this disease, the absence of validated molecular targets makes it unresponsive to conventional therapies.
- PI3K/AKT/mTOR pathway is aberrantly activated in TNBC, but single agent therapy is commonly subject to resistance.

Objective

- The goal of this study is to identify the genes that can be targeted to enhance the efficacy of mTOR inhibitor TAK228, an agent that is being investigated as a treatment for advanced solid tumors, in TNBC with PI3K pathway activation.

Methods and Results

- Experimental approach
- Most important findings

Identification of optimal combination therapy partners for PI3K/AKT/mTOR pathway inhibitor in triple negative breast cancer

Maryam Shariati[1], Natalia Paez-Arango[1], Christopher A. Bristow[2], Kurt W. Evans[1], Erkan Yuca[1], Michael D. Peoples[2], Alessandro Carugo[2],Tim P. Heffernan[2], Funda Meric-Bernstam[1]

1) Investigational Cancer Therapeutics (Phase I Trials Program). 2) Center for Co-Clinical Trials and Institute for Applied Cancer Science, The University of Texas MD Anderson Cancer Center, Houston.

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

San Antonio Breast Cancer Symposium

December 4-8, 2018

Program Number: P6-18-13

Background

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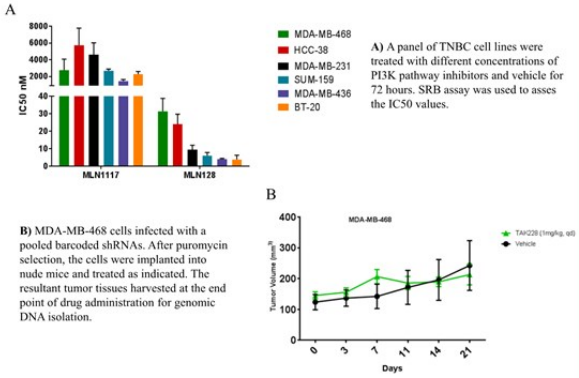
- The goal of this study is to identify the genes that can be targeted to enhance the efficacy of mTOR inhibitor TAK228, an agent that is being investigated as a treatment for advanced solid tumors, in TNBC with PI3K pathway activation.

Methods

- Measuring the cytotoxicity of TAK228 (MLN128) inhibitor in a panel of TNBC cell lines to select the optimal cell for in vivo screening.
- Utilizing an *in vivo* pooled barcoded FDAome shRNA library screening to determine the genes that have the potential for TAK228 synthetic lethal partners.
- Performing sulforhodamine B colorimetric (SRB) and colony formation viability assays to validate the top screening hits using inhibitors targeting the candidate genes.
- Silencing the target genes in MDA-MB-468 cell lines with shRNA to establish xenograft tumors for TAK228 treatment.

Results

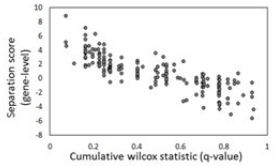
Figure 1: MDA-MB-468 cell line was selected for *in vivo* shRNA screening in the presence of TAK228.



A) A panel of TNBC cell lines were treated with different concentrations of PI3K pathway inhibitors and vehicle for 72 hours. SRB assay was used to asses the IC50 values.

B) MDA-MB-468 cells infected with a pooled barcoded shRNAs. After puromycin selection, the cells were implanted into nude mice and treated as indicated. The resultant tumor tissues harvested at the end point of drug administration for genomic DNA isolation.

Figure 2: Identification of the top hits in TAK228 treated MDA-MB-468 derived xenograft through deep sequencing.

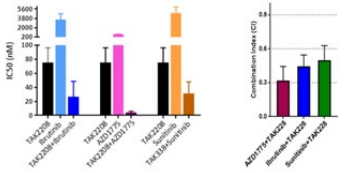


A) MDA-MB-468 xenografts were used to perform deep sequencing to determine shRNA abundance on the basis of shRNA performance supervised analysis. Cumulative wilcox test was done to score statistical gene level significance

B) List of the essential genes whose loss of function conferred lethality in the presence of TAK228 though comparing the representation of shRNA profiles in the tumor tissues to the reference controls.

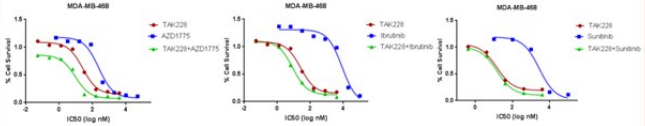
	wilcox.p	wilcox.q	diffScore
MAPK12	0.0008	0.07	8.81
WEE1	0.0006	0.07	5.14
BMX	0.0012	0.08	4.57
CDK7	0.0023	0.11	2.12

Figure 3: Synergistic combination of TAK228 with inhibitors targeting the candidate synthetic lethal partners.



A) MDA-MB-468 cells were treated with various concentrations of each inhibitor and vehicle for 72 hours to asses growth rate through SRB assay. IC50 and CI values were calculated using CalcuSyn 2.0 software (CI>1: synergy; CI=1: addition; CI<1: antagonism).

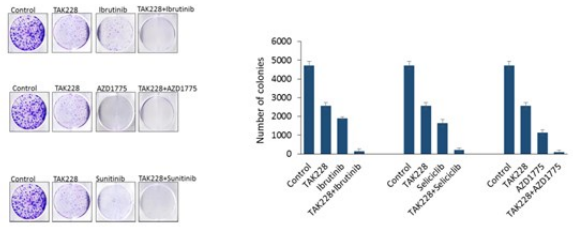
B) Dose response curves for the indicated drug combination treatment created using GraphPad Prism software.



C) List of agents targeting the candidate hits. Ibrutinib and Sunitinib are FDA approved and AZD1775 is in clinical development.

Gene	Agent	Target
MAPK12 (ERK6, p38γ)	Pirfenidone	TGF-β1, TNF-α
WEE1	AZD1775 (MK-1775)	Wee1
BMX	Ibrutinib	BTK
CDK7	Sunitinib, Seliciclib	CDK2, CDK7 and CDK9

Figure 4: Synergistic effect of TAK228 combination with Ibrutinib, AZD1775, and Sunitinib on colony formation growth. Cells were seeded at 1,000 cells/well of 6-well plate in triplicate and treated with TAK228 (50 nM), Ibrutinib (1500 nM), AZD1775 (100 nM) and sunitinib (700 nM) for 3 weeks. Colonies were stained with crystal violet and counted using NIH ImageJ v.1.46 software.



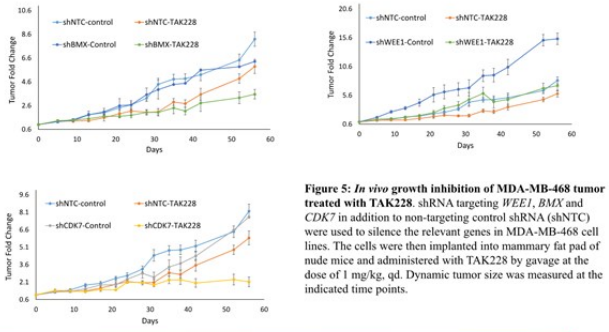


Figure 5: *In vivo* growth inhibition of MDA-MB-468 tumor treated with TAK228. shRNA targeting *WEE1*, *BMX* and *CDK7* in addition to non-targeting control shRNA (shNTC) were used to silence the relevant genes in MDA-MB-468 cell lines. The cells were then implanted into mammary fat pad of nude mice and administered with TAK228 by gavage at the dose of 1 mg/kg, qd. Dynamic tumor size was measured at the indicated time points.

Summary

- This study indicates that TAK228, an agent being investigated as a treatment for advanced solid tumors, has a promising rational strategy in combination of other drugs for the treatment of TNBC with PI3K pathway aberrations. Investigating the activation of relevant survival signaling pathways will further elucidate the mechanism of synergy and synthetic lethality interaction.

Funding

- This work was supported by Takeda Pharmaceutical Company and the Nellie B. Connally Breast Cancer Research Endowment.

Post Contrast FSE-based 3D T1-Weighted MRI for the Evaluation of Brain Metastases and Brain Tumors

Brandy J Willis, MBA RT(R)(MR), Ho-Ling Anthony Liu, PhD, Ping Hou, PhD,
R. Jason Stafford, PhD, Abraham Padua, RT(R)(MR), Linda Chi, MD.
Facilitator: Ashok J Kumar, MD

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What are we trying to accomplish?

The aim of this project is to evaluate the 3D T1W SPACE sequence on Siemens scanners as a post-contrast T1-weighted scan in our routine brain MRI protocol, and to determine whether it is superior to the 3D gradient-recalled echo (GRE) sequence that we currently use.
On alternating weeks, either the 3D T1W FSE sequence or the 3D GRE sequence will be acquired first after contrast bolus to off-set any potential change in contrast enhancement due to time delay between contrast bolus and scan acquisition.

How will we know improvement was made?

3D SPACE and GRE images acquired during two weeks will be blindly evaluated by at least 2 radiologists (Drs. Linda Chi and Ashok J. Kumar) and a scoring sheet will be provided for quantitative comparison.

What changes can we make?

Conventional 2D spin-echo (SE) sequence has been the standard imaging protocol for post-contrast T1-weighted MRI. However, flow-related motion artifacts often compromise lesion detection in these images, particularly in the posterior fossa. The flow related artifacts can be minimized by adding flow compensation during image acquisition. One major limitation to using flow compensation is the accentuation of small vessel enhancement, which can mimic leptomeningeal disease (LMD). This potentially can lead to either over-calling (false positive) or miss-diagnosing (false negative) LMD with serious clinical consequences.
Metastatic disease, such as from breast, lung, kidney and melanoma primary is often small in size measuring less than 3 mm in diameter. These small lesions can be missed on the routine 2D SE sequence obtained at 5 mm slice thickness.

PLAN the improvement

In order to improve lesion detection for small lesions and to increase conspicuity of lesions in the posterior fossa, we replaced a 2D SE sagittal post contrast sequence with a 3D GRE sequence, with or without inversion-recovery (IR) T1 preparation as part of our routine brain protocol. We found the 3D gradient-echo sequence to be useful in lesion detection and mitigated the flow- related artifacts in the posterior fossa. However, we noted that the contrast is very different from the spin-echo sequence and this sequence is more sensitive to field inhomogeneity. In addition, some flow-related artifacts remained.
Recent development of fast spin echo (FSE)-based 3D pulse sequences has facilitated T1-weighted imaging, implemented as T1 SPACE on Siemens and T1 CUBE in GE. This sequence has been proposed as being superior to the magnetization prepared rapid gradient echo (MPRAGE), an IR-prepared 3D gradient-echo sequence, in the detection of brain metastasis.

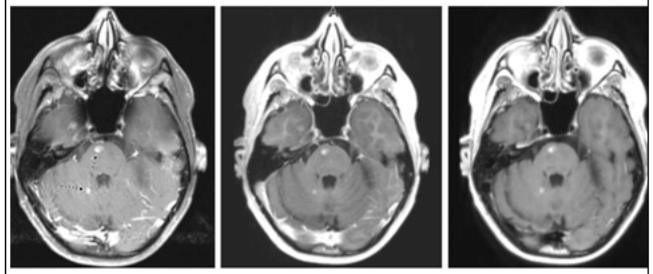
Radiologist Process Analysis Tool

MRN	MRI date	Sequence	Number of metastases	Severity of artifact 1: minimal; 2: moderate; 3: severe
		2D Ax SE		
		3D GRE		
		T1 SPACE		

Physicist Measurement Form

MRN	MRI date	Sequence	SNR	Contrast of T1 enhancement (lesion-normal)/normal
		2D Ax SE		
		3D GRE		
		T1 SPACE		

Image Comparison



DO the implementation

We plan to add 3D T1W SPACE sequence to the routine brain protocol on two of our scanners at ROC and collect data for two weeks. During the first week the sequence will be scanned right before the 3D GRE, and then during the second week it will be scanned right after. Imaging physicists (Drs. H. L. Anthony Liu, Ping Hou and R. Jason Stafford) and Siemens Specialist (Abraham Padua) will be responsible for optimizing sequence parameters and medical imaging technologist supervisor (Brandy J. Willis) will implement the sequence on scanners and coordinate the data collection and reporting.

STUDY the results

Radiologists & Physicist will blindly review the images and provide measurements. Scores of the two sequences, as well as the conventional Ax SE will be compared statistically.

ACT: maintain/rollout improvement

The goal of this project is to assess the artifact reduction and lesion detection of a FSE-based 3D T1W post contrast sequence by comparing to a 3D GRE sequence that is currently in use. Sequence-related artifacts, overall quality of the study, and radiologists' preference will be assessed.
Once results are compiled and analyzed, it will be determined if a change in the current protocol is required. If deemed necessary, all of the MRI scanners will be updated with the improved sequence, the eProtocol system & technical datasheets will be updated.

Conclusion

- Main message (answer to your research question)
- Implications
- Future research

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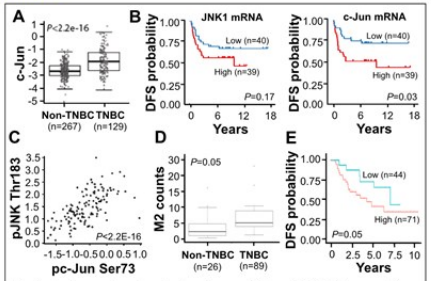

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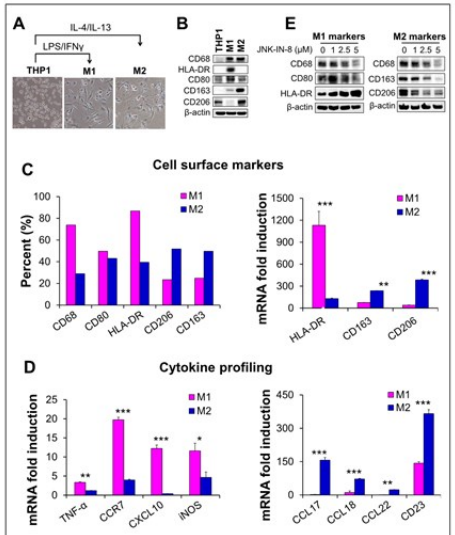

Fig 2. Differentiation of THP1 monocytes to M1 and M2 macrophages, as assessed by (**A**) morphology, (**B** & **C**) cell surface marker expression by Western Blotting, FACS, and qPCR, and (**D**) cytokine profiling by qPCR. **E**, JNK inhibition by JNK-IN-8 promotes M1 differentiation but suppresses M2 differentiation. *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$.

M2 macrophages promote migration and invasion of TNBC cells *in vitro*

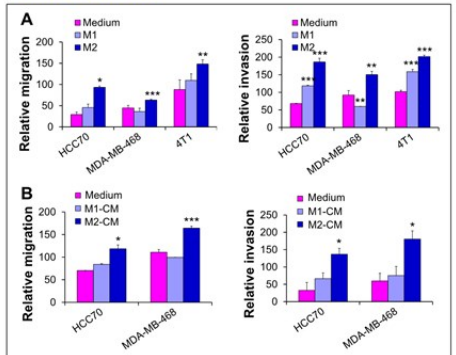

Fig 3. Compared to culture with medium alone or co-culture with (**A**) M1s or (**B**) M1-conditioned medium (CM), co-culture with (**A**) M2s or (**B**) M2-CM significantly enhances migration and invasion of TNBC cells. *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$.

The JNK pathway is involved in M2 macrophage-promoted motility in TNBC cells *in vitro*

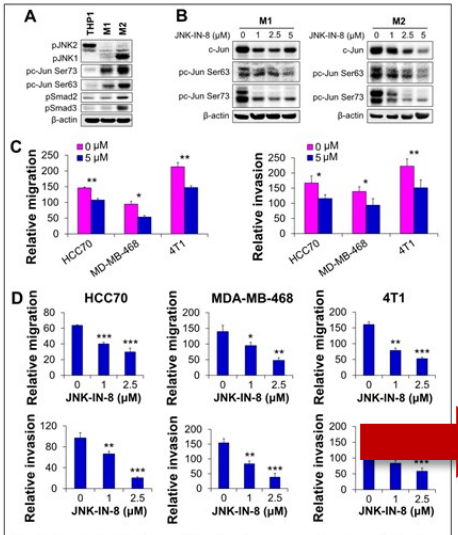

Fig 4. **A**, The JNK/c-Jun and TGF-β pathways are strongly activated in M2 macrophages. **B**, JNK inhibition by JNK-IN-8 suppresses c-Jun activation in both M1 and M2 macrophages at 48 h following treatment. **C** & **D**, JNK inhibition by JNK-IN-8 in (**C**) M2 macrophages or (**D**) TNBC cells leads to a reduction in M2 macrophage-promoted migration and invasion of TNBC cells. *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$.

M2 macrophages promote motility of TNBC paracrine signaling *in vitro*

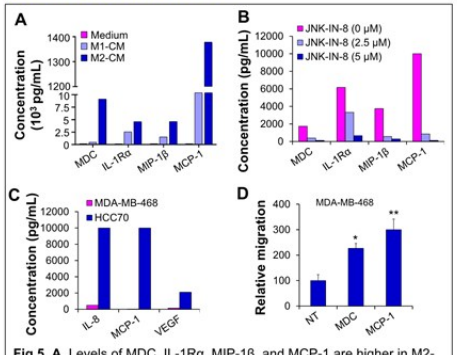

Fig 5. **A**, Levels of MDC, IL-1Rα, MIP-1β, and MCP-1 are higher in M2-CM than in M1-CM. **B**, JNK inhibition by JNK-IN-8 reduces secretion of MDC, IL-1Rα, MIP-1β, and MCP-1. **C**, TNBC cells secret high levels of IL-8, MCP-1, and VEGF. **D**, MDC and MCP-1 enhances migration of TNBC cells. *, $P<0.05$; **, $P<0.01$.

JNK inhibition suppresses tumor growth and M1/M2 recruitment to tumors in a TNBC mouse model

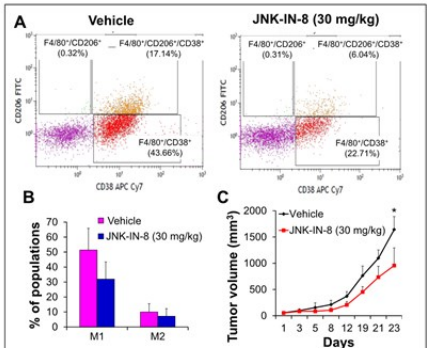

Fig 6. JNK-IN-8 (**A** & **B**) reduces M1 (CD38) and M2 (CD206) populations in tumors, as analyzed by FACS and (**C**) suppresses tumor growth in a 4T1 xenograft mouse model. *, $P<0.05$.

Conclusions

- JNK/c-Jun signaling and M2 macrophages have clinical impact in TNBC.
- M2 macrophages promote migration and invasiveness of TNBC cells possibly through the JNK/c-Jun/TGF-β pathway.
- JNK signaling suppresses M1 macrophage differentiation but promotes M2 macrophage differentiation.

Future Studies

- Determine which JNK isoform plays a predominant role in TNBC-M2 cross-talk.
- Elucidate how the JNK/c-Jun/TGF-β pathway regulates TNBC-M2 cross-talk.
- Assess the impact of M2 macrophages on metastasis of TNBC cells using animal models.
- Determine the clinical significance of M2- and TNBC-derived cytokines/chemokines in TNBC.

Acknowledgements

This work is supported by MDACC Inflammatory Breast Cancer funds (105655) and Nylene Eckles funds (101478) to Naoto T. Ueno; startup funds from MDACC (111411) to Chandra Bartholomeusz; and National Institutes of Health Cancer Center Support Grant to MDACC (CA016672).

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Identification of optimal combination therapy partners for PI3K/AKT/mTOR pathway inhibitor in triple negative breast cancer

Maryam Shariati[1], Natalia Paez-Arango[1], Christopher A. Bristow[2], Kurt W. Evans[1], Erkan Yuca[1], Michael D. Peoples[2], Alessandro Carugo[2],Tim P. Heffernan[2], Funda Meric-Bernstam[1]

1) Investigational Cancer Therapeutics (Phase I Trials Program). 2) Center for Co-Clinical Trials and Institute for Applied Cancer Science, The University of Texas MD Anderson Cancer Center, Houston.

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Background

- Triple-negative breast cancer (TNBC) is among the most aggressive subtypes, accounts for 10-15% of all breast cancer cases and is characterized by the lack of hormone receptors with a low overall survival rate.
- Due to the heterogeneity nature of this disease, the absence of validated molecular targets makes it unresponsive to conventional therapies.
- PI3K/AKT/mTOR pathway is aberrantly activated in TNBC, but single agent therapy is commonly subject to resistance.

Objective

- The goal of this study is to identify the genes that can be targeted to enhance the efficacy of mTOR inhibitor TAK228, an agent that is being investigated as a treatment for advanced solid tumors, in TNBC with PI3K pathway activation.

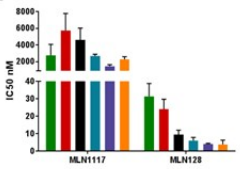
Methods

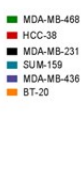
- Measuring the cytotoxicity of TAK228 (MLN128) inhibitor in a panel of TNBC cell lines to select the optimal cell for in vivo screening.
- Utilizing an *in vivo* pooled barcoded FDAome shRNA library screening to determine the genes that have the potential for TAK228 synthetic lethal partners.
- Performing sulforhodamine B colorimetric (SRB) and colony formation viability assays to validate the top screening hits using inhibitors targeting the candidate genes.
- Silencing the target genes in MDA-MB-468 cell lines with shRNA to establish xenograft tumors for TAK228 treatment.

Results

Figure 1: MDA-MB-468 cell line was selected for *in vivo* shRNA screening in the presence of TAK228.

A





A) A panel of TNBC cell lines were treated with different concentrations of PI3K pathway inhibitors and vehicle for 72 hours. SRB assay was used to asses the IC50 values.

B) MDA-MB-468 cells infected with a pooled barcoded shRNAs. After puromycin selection, the cells were implanted into nude mice and treated as indicated. The resultant tumor tissues harvested at the end point of drug administration for genomic DNA isolation.

B

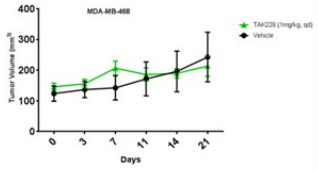
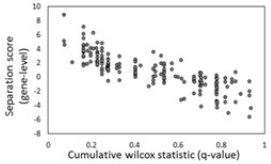


Figure 2: Identification of the top hits in TAK228 treated MDA-MB-468 derived xenograft through deep sequencing.

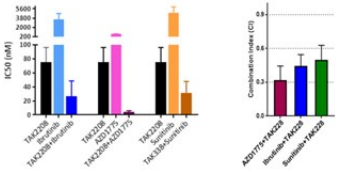


A) MDA-MB-468 xenografts were used to perform deep sequencing to determine shRNA abundance on the basis of shRNA performance supervised analysis. Cumulative wilcox test was done to score statistical gene level significance

B) List of the essential genes whose loss of function conferred lethality in the presence of TAK228 though comparing the representation of shRNA profiles in the tumor tissues to the reference controls.

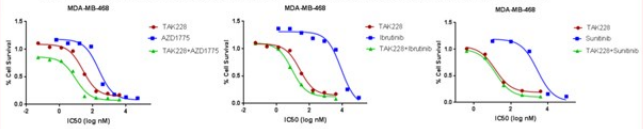
	wilcox.p	wilcox.q	diffScore
MAPK12	0.0008	0.07	8.81
WEE1	0.0006	0.07	5.14
BMX	0.0012	0.08	4.57
CDK7	0.0023	0.11	2.12

Figure 3: Synergistic combination of TAK228 with inhibitors targeting the candidate synthetic lethal partners.



A) MDA-MB-468 cells were treated with various concentrations of each inhibitor and vehicle for 72 hours to asses growth rate through SRB assay. IC50 and CI values were calculated using CalcuSyn 2.0 software (CI>1: synergy; CI=1: addition; CI<1: antagonism).

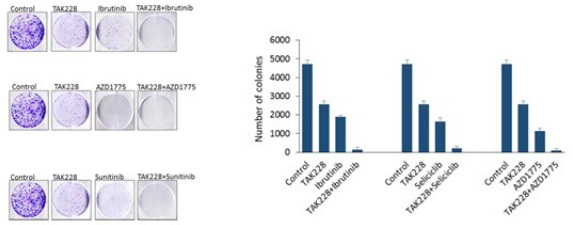
B) Dose response curves for the indicated drug combination treatment created using GraphPad Prism software.



C) List of agents targeting the candidate hits. Ibrutinib and Sunitinib are FDA approved and AZD1775 is in clinical development.

Gene	Agent	Target
MAPK12 (ERK6, p38γ)	Pirfenidone	TGF-β1, TNF-α
WEE1	AZD1775 (MK-1775)	Wee1
BMX	Ibrutinib	BTK
CDK7	Sunitinib, Seliciclib	CDK2, CDK7 and CDK9

Figure 4: Synergistic effect of TAK228 combination with Ibrutinib, AZD1775, and Sunitinib on colony formation growth. Cells were seeded at 1,000 cells/well of 6-well plate in triplicate and treated with TAK228 (50 nM), Ibrutinib (1500 nM), AZD1775 (100 nM) and sunitinib (700 nM) for 3 weeks. Colonies were stained with crystal violet and counted using NIH ImageJ v.1.46 software.



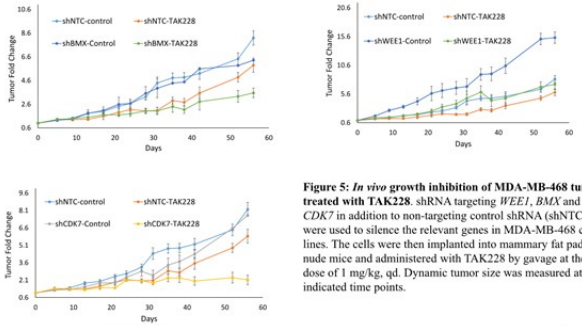


Figure 5: *In vivo* growth inhibition of MDA-MB-468 tumor treated with TAK228. shRNA targeting *WEE1*, *BMX* and *CDK7* in addition to non-targeting control shRNA (shNTC) were used to silence the relevant genes in MDA-MB-468 cell lines. The cells were then implanted into mammary fat pad of nude mice and administered with TAK228 by gavage at the dose of 1 mg/kg, qd. Dynamic tumor size was measured at the indicated time points.

Summary

- This study indicates that TAK228, an agent being investigated as a treatment for advanced solid tumors, has a promising rational strategy in combination of other drugs for the treatment of TNBC with PI3K pathway aberrations. Investigating the activation of relevant survival signaling pathways will further elucidate the mechanism of synergy and synthetic lethality interaction.

Funding

- This work was supported by Takeda Pharmaceutical Company and the Nellie B. Connally Breast Cancer Research Endowment.

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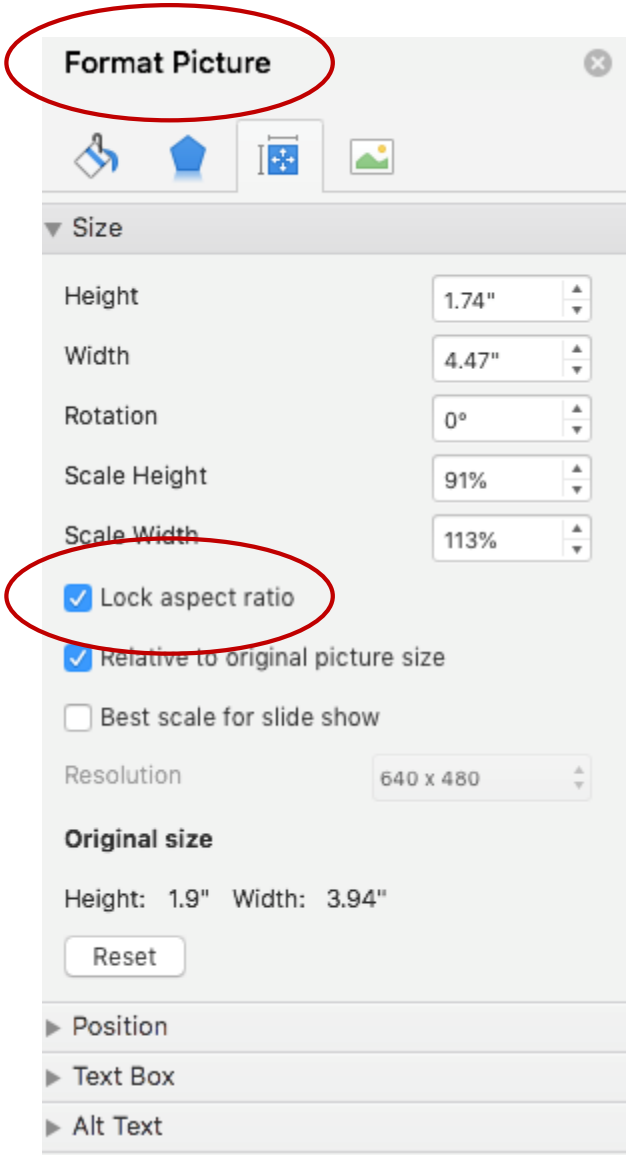

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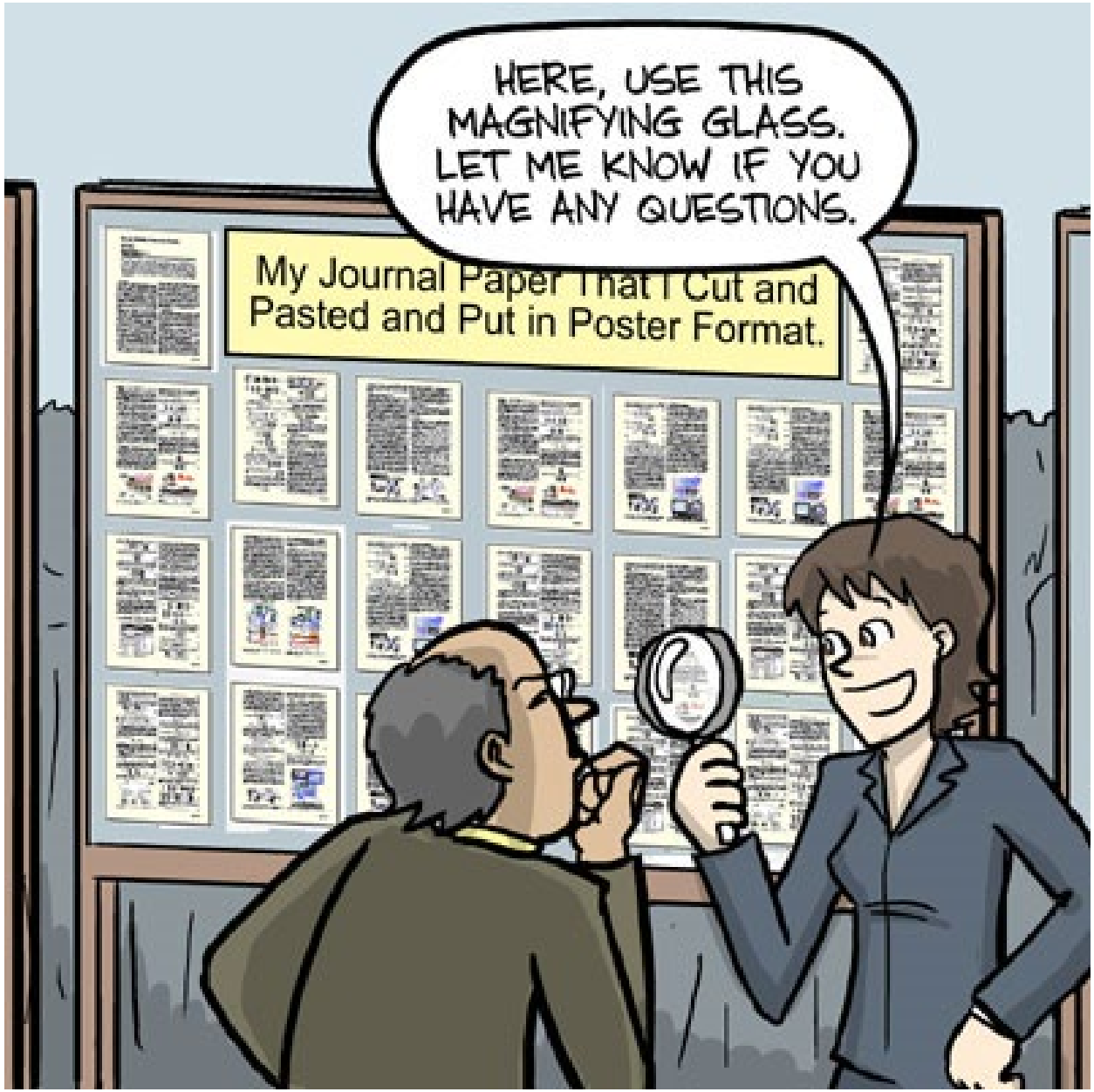

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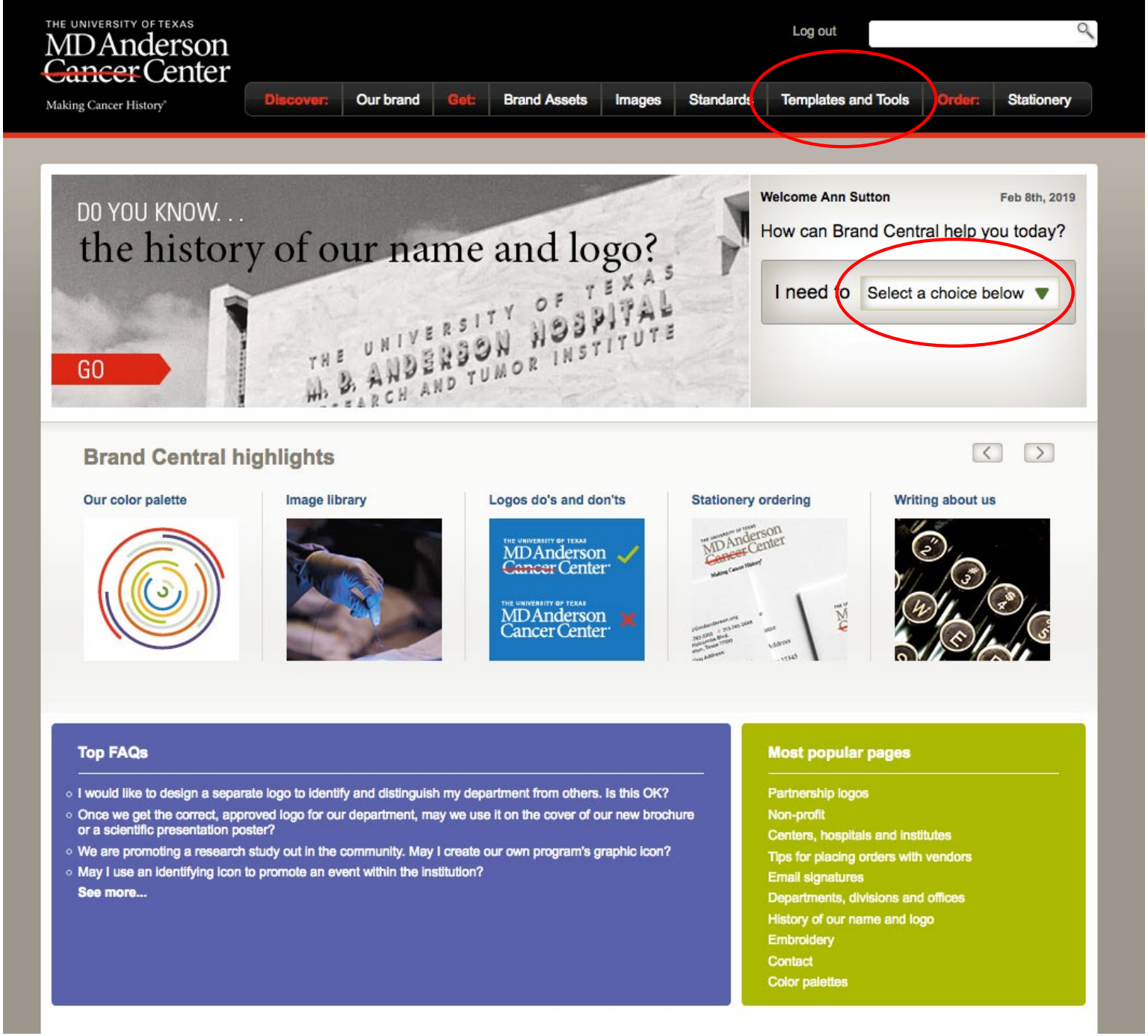

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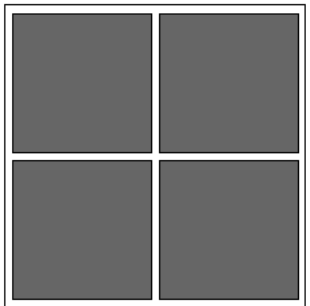

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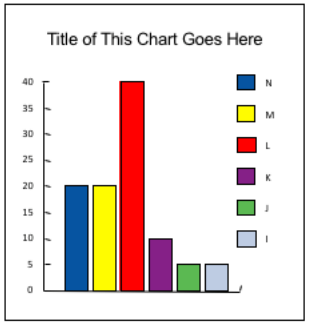

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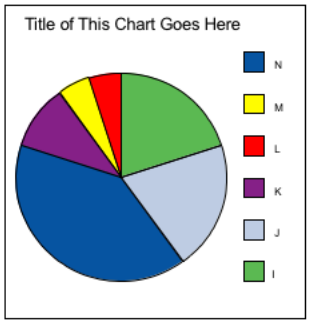

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Llrw	321	567	098
Ghlu	345	567	986
Bvcm	222	367	087
Total	321	567	098

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2) Porta et al. Pain Digest Pain 1998;8:346-352
3) Porta et al. Pain Digest Pain 1998;8:346-352
4) Porta et al. Pain Digest Pain 1998;8:346-352

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A phase II study of Atezolizumab, Cobimetinib and Eribulin (ACE) in patients with recurrent/metastatic inflammatory breast cancer

A Alexander[1,10], A Marx[1,10], SM Reddy[1], JM Reuben[2], H Le-Petross[3,10], D Lane[3], ML Huang[3], S Krishnamurthy[4,10], Y Gong[4,10], DS Gombos[5], N Patel[5], CI Tung[5], RC Allen[5], TJ Kandl[5], J Wu[6], S Liu[6], AB Patel[7], A Futreal[8], I Wistuba[9], R Layman[1], V Valero[1,10], D Tripathy[1], NT Ueno[1,10], B Lim[1,10]
Departments of [1]Breast Medical Oncology, [2] Hematopathology [3] Diagnostic Radiology-Breast Imaging, [4] Pathology, [5] Opthalmology, [6] Biostatistics, [7] Dermatology, [8] Genomic Medicine, [9] Translational Molecular Pathology and [10] Morgan Welch Inflammatory Breast Cancer Research Program and Clinic University of Texas MD Anderson Cancer Center, Houston, TX

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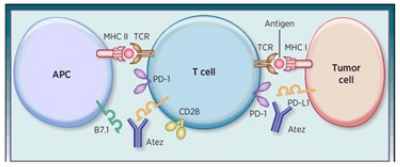
Background

- Inflammatory breast cancer (IBC) is a rare but aggressive subtype of breast cancer.
- Deregulated immune pathways are commonly found in IBC patient samples, particularly those that do not fully respond to chemotherapy.
- There is increasing evidence for the role of the microenvironment in promoting therapy resistance and metastasis in IBC.
- Novel combination therapies are needed to improve the outcomes in metastatic inflammatory breast cancer – single agent chemotherapy tends to only work for a few months in most HER2-negative IBC patients.

PD-L1, Atezolizumab and TNBC

- PD-1 is a receptor on antigen-stimulated T-cells that when bound to its ligands PD-L1 and PD-L2 maintains T-cells in an inactive state, therefore allowing tumor evasion from immune destruction.
- PD-L1 is expressed in many tumor cells, including IBC as well as on antigen-presenting cells such as dendritic cells.
- PD-L1 is expressed in about one third of all IBC tumors, and is enriched in hormone-receptor negative and high-grade proliferative tumors. Expression is correlated with the amount of TIL infiltration.
- PD-L1 is the target of Atezolizumab, a monoclonal antibody that inhibits the interaction of PD-L1 with its receptor PD1 or B7.1. Atezolizumab blocks this inhibitory regulation of T cell function.
- Recent phase 3 data in the first line setting in metastatic TNBC has demonstrated an improvement in PFS when Atezolizumab is added to Abraxane versus Placebo and Abraxane in both the intent-to-treat and PD-L1 positive population. (1.7mth benefit for ITT and 1.5mth for PD-L1+). (*Schmid P et al, NEJM 2018*)
  - Overall survival was also significantly longer for the Atezolizumab treated patients who had PD-L1+ tumors.
- Atezolizumab is currently FDA approved in the metastatic non-small cell lung cancer setting as well as for advanced/metastatic urothelial carcinoma and under investigation in various other cancers including breast cancer.



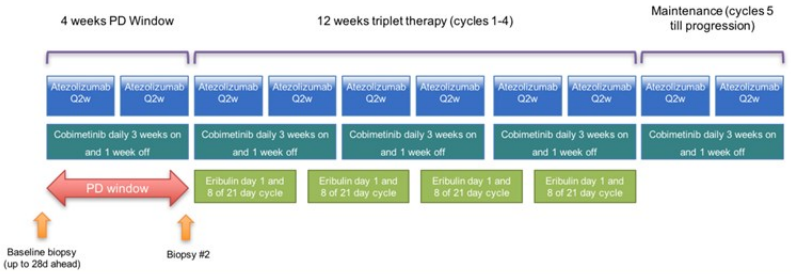
Brant A. Inman et al. Clin Cancer Res 2017;23:1886-1890

Figure 1: Mechanism of Action of Atezolizumab ("Atez")

Cobimetinib/MAPK pathway

- Cobimetinib is an oral MEK1/2 inhibitor that is FDA approved for patients with BRAF mutant melanoma in combination with Vemurafenib.
- MAPK is a survival pathway in many cancers, and has been shown to regulate metastasis in preclinical TNBC models.
- MEK inhibition has been shown to have immune-modulating properties including the upregulation of PD-L1 expression - hence the combination of Cobimetinib and Atezolizumab is thought to be synergistic. Preliminary evidence of these biomarker changes have been demonstrated in a prior study in colorectal cancer.

Trial Schema



Hypothesis & Objectives

Atezolizumab and Cobimetinib will induce synergy and potentiate the effects of Eribulin to control metastatic inflammatory breast cancer.

Primary Objective:

- To determine the objective response rate of recurrent/metastatic inflammatory breast cancer treated with this proposed combinatorial therapy

Secondary Objectives:

- To further characterize the safety and tolerability of triple combination (ACE) therapy
- To determine the duration of response
- To determine the progression free survival
- To determine the 2-year overall survival rate

Exploratory Objectives:

- To determine the changes in biomarkers induced by therapy in both tissue and blood (see correlative science section)
- To determine immune pathway related cytokine changes during treatment using multiplex serum cytokine assays.

Patient Population & Main Criteria

Inclusion Criteria

- Adult patient (male/female, age >18) with a clinical diagnosis of inflammatory breast cancer by international consensus criteria below:
  - Rapid onset of breast erythema, edema and/or peau d'orange, and/or warm breast, with/without an underlying breast mass
  - Duration of symptoms no more than 6 months
  - Erythema occupying at least 1/3 of the whole breast
  - Pathological confirmation of invasive carcinoma is required
- Patients with recurrent or metastatic IBC after standard systemic therapy.
  - Any number of prior lines of treatment for metastatic disease is allowed.
  - Prior Eribulin is allowed.
- Any subtype of IBC. HER2+ patients must have received Pertuzumab and T-DM1.
- Measurable disease (per RECIST 1.1), local or distant
- At least one site of metastatic disease amenable for biopsy
- Patients with treated brain metastases must be stable, confirmed by CNS study ≥ 4 weeks from completion of radiation and have completed any steroids ≥ 2 weeks prior to study treatment.
- Adequate organ and bone marrow function as measured by laboratory values. Normal cardiac function (LVEF ≥50% by MUGA or echocardiogram)
- Patient must not be pregnant and agree to use an acceptable birth control method while on the study.

Exclusion Criteria

- Ongoing serious AEs from prior therapy such as grade 2+ neuropathy.
- No prior PD-1/PD-L1 inhibitor exposure. Prior anti-CTLA4 treatment is allowed but a minimum of 12 weeks must have elapsed from the 1st dose and >6 weeks washout is required and no severe (grade 3 or 4) immune-related adverse events occurred.
- History of extensive interstitial lung disease e.g. pneumonitis, pulmonary fibrosis, organizing pneumonia, however a history of radiation pneumonitis is permitted.
- Known clinically significant liver disease including viral, alcoholic or other hepatitis (hepatitis B/C infection), cirrhosis; fatty liver and inherited liver diseases.
- Active or history of autoimmune diseases or immune deficiency such as myasthesia gravis, myositis, autoimmune hepatitis, lupus, rheumatoid arthritis, inflammatory bowel disease or known HIV infection.
- Other known significant medical or psychiatric condition that would make assessment of toxicity or efficacy difficult or place the patient at high risk for treatment complications.
- Other malignancies within 5 years except those with a negligible risk of metastasis or death and with expected curative outcome such as adequately treated cervical carcinoma-in-situ, DCIS, basal/squamous cell carcinomas of the skin.

Trial Design

- Single-arm phase I/II investigator initiated trial
- Only open at MD Anderson.
- Enrollment target – 33 patients in total, up to 9 in phase 1 and 24 in phase II to assess the efficacy.
- Phase 1 portion is to determine the MTD of Cobimetinib in combination with Atezolizumab and Eribulin. The starting dose is the FDA approved combination dose in melanoma (60mg/day), and there are 2 lower doses possible.
- Phase 2 portion is to assess the efficacy.
- Atezolizumab is dosed at a flat dose (840mg), Cobimetinib starting dose is 60mg/day (21 days on, 7 days off) and Eribulin dosing is per standard of care, starting at full dose (1.4mg/m^2)
- Radiographical imaging responses will be based on RECIST1.1
- Safety endpoints will be assessed using CTCAE v4.0
- The first 4 weeks of study treatment is the pharmacodynamic window, when patients receive only targeted therapy and pre- and post- biopsies (liquid & tissue) are obtained for translational studies.

Statistical Considerations

- The phase 1 lead in phase to establish the MTD of Cobimetinib in combination with Atezolizumab and Eribulin includes up to 9 patients.
  - The design is a Bayesian optimal interval design (BOIN) that is similar to a 3+3 design but more flexible and possess superior operating characteristics that are comparable to more complex model-based designs such as the continual reassessment method.
  - The target toxicity rate is 0.3 and cohorts of 3 patients will be analyzed for each dose.
- The phase II portion to assess the efficacy of the combination at the MTD of Cobimetinib includes up to 24 additional patients. The final analysis will be conducted at 12 months after the last patient is treated, and all patients who receive the MTD of Cobimetinib will be included in the data.
- The sample size overall provides 80% power to detect an improved objective response rate of 25% compared to historic rate of 10%.

Planned Correlative Science

- Biopsies taken prior to treatment with the first cycle of Atezolizumab and Cobimetinib will be used for IHC, immune-profiling, and transcriptomic analysis
- WES sequencing and RNAseq will be performed on tumor samples, and cfDNA sequencing is planned.
- Immune-profiling via flow cytometry for T cell markers
- Cytokine/chemokine analysis.
- Multiplex immunofluorescence imaging will be performed to examine tumor microenvironment markers and cancer stem cell phenotypes.
- Liquid biopsies:
  - CTC gene-expression analysis for signatures of EMT and stemness via qRT-PCR or ddPCR and
  - cfDNA sequencing
  - Exosome analysis.

Current Status

- Trial activation date: 8/11/2017
- Current enrolled patients: 9 evaluable patients have been enrolled in the phase 1 and the DLT period has elapsed for all patients. 2 additional patients are in screening for phase 2.

Acknowledgments

- Trial design and oversight: University of MD Anderson Cancer Center IND Office
- Atezolizumab and Cobimetinib provided by Genentech, through rare tumor alliance with MD Anderson

Contact for more information:

- Trial PI: Bora Lim MD – blim@mdanderson.org
- Study Coordinator: Angela Alexander PhD– aalexand@mdanderson.org

Proximity

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- Keep graphics and tables from breaking across columns

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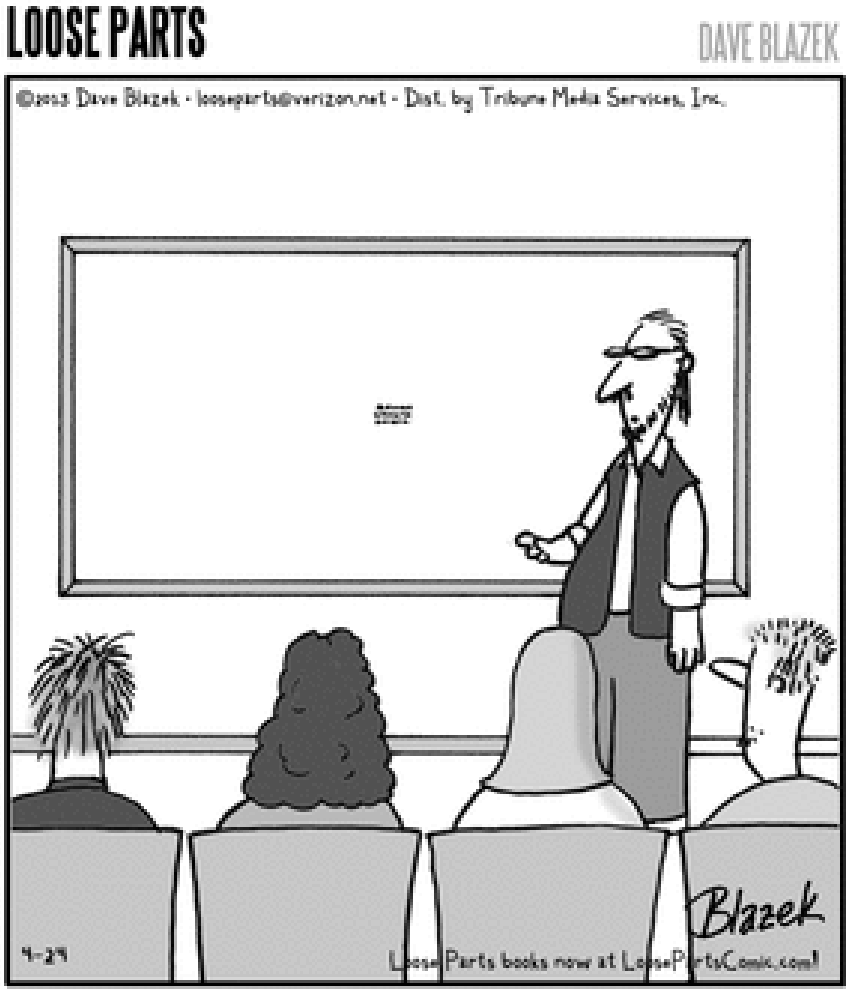

"Welcome to today's design class on the use of white space in layouts. The notes are on the board."

Association of Body Mass Index (BMI) with chemotherapy administration and emergency room (ER) visits among breast cancer patients.

Sharon H. Giordano[1,2], Jiangong Niu[1], Hui Zhao[1], Daria Zorzi[1], and Mariana Chavez Mac Gregor [1,2]

[1]Department of Health Services Research, [2] Department of Breast Medical Oncology, The University of Texas M.D. Anderson Cancer Center

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Making Cancer History®

Background

- Obese post-menopausal women have a higher risk of breast cancer compared to their normal weight peers[1]
- Obesity is associated with poor breast cancer outcomes. In a meta-analysis obese women had a 35% higher breast-cancer specific mortality compared with normal weight women.[2]
- The cause of worse outcomes in unknown. Possible mechanisms include higher estrogen, higher levels of insulin and insulin like growth factor, inflammatory cytokines, and chemotherapy under-dosing due to concerns about toxicity.
- Current guidelines recommend standard weight-based dosing for obese patients.[3]

Objective

To determine if BMI has an effect on the rates of emergency room (ER) visits, all cause hospitalizations, and chemotherapy-related hospitalizations among breast cancer patients.

Materials & Methods

- Female breast cancer patients 18 years or older, diagnosed between 2009 and 2014.
- We identified beneficiaries from the commercial MarketScan Health Risk Assessment database.
- All patients underwent mastectomy or lumpectomy and had self-reported BMI data available.
- BMI was categorized as normal (<25), overweight (≧25 and <30) and obese (≥30).
- Descriptive statistics were used to compare patient and treatment variables by BMI. ER visits, all hospitalizations, and chemotherapy related hospitalizations were identified in the 6 months after diagnosis.
- Cox regression models were used to identify factors associated with ER visits and hospitalizations.
- 7,830 breast cancer patients met the inclusion criteria.

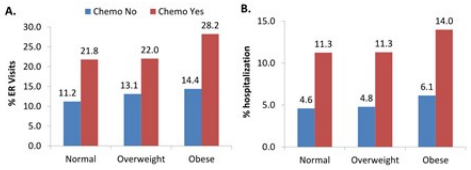
Results

Table 1. Patient characteristics among 7,830 breast cancer patients

	Normal	Overweight	Obese		Total
Variables	n (%)	N (%)	n (%)	p value	n (%)
All subjects	2602 (100)	2313 (100)	2915 (100)		7830 (100)
Age at diagnosis				<0.001	
Range	25-69	23-69	24-70		23-70
Mean	51±8	52±8	53±8		52±8
Median	51	53	53		52
<45	586 (22.5)	404 (17.5)	443 (15.2)		1433 (18.3)
45-49	558 (21.5)	409 (17.7)	482 (16.5)		1449 (18.5)
50-54	599 (23)	551 (23.8)	689 (23.6)		1839 (23.5)
55-59	485 (18.6)	577 (25)	706 (24.2)		1768 (22.6)
60+	374 (14.4)	372 (16.1)	595 (20.4)		1341 (17.1)
Region				<0.001	
North Central	609 (23.4)	545 (23.6)	756 (25.9)		1910 (24.4)
Northeast	451 (17.3)	340 (14.7)	271 (9.3)		1062 (13.6)
South	1162 (44.7)	1134 (49)	1612 (55.3)		3908 (49.9)
West	379 (14.6)	294 (12.7)	276 (9.5)		949 (12.1)
Charlson Comorbidity Score				<0.001	
0	2334 (89.7)	1982 (85.7)	2201 (75.5)		6517 (83.2)
1	239 (9.2)	290 (12.5)	590 (20.2)		1119 (14.3)
2+	29 (1.1)	41 (1.8)	124 (4.3)		194 (2.5)
Radiation therapy				<0.001	
No	1093 (42)	784 (33.9)	932 (32)		2809 (35.9)
Yes	1509 (58)	1529 (66.1)	1983 (68)		5021 (64.1)
Chemotherapy				<0.001	
No	1740 (66.9)	1419 (61.4)	1743 (59.8)		4902 (62.6)
Yes	862 (33.1)	894 (38.7)	1172 (40.2)		2928 (37.4)
Surgery				<0.001	
ALND	19 (0.7)	19 (0.8)	24 (0.8)		62 (0.8)
BCS	1389 (53.4)	1376 (59.5)	1784 (61.2)		4549 (58.1)
Mastectomy	1194 (45.9)	918 (39.7)	1107 (38)		3219 (41.1)
Hormone therapy				0.320	
No	1274 (49)	1116 (48.3)	1466 (50.3)		3856 (49.3)
Yes	1328 (51)	1197 (51.8)	1449 (49.7)		3974 (50.7)

*Abbreviations: BCS= breast conserving surgery

Figure-1. A) ER visits and **B)** All hospitalization rates within 6 months of diagnosis according to chemotherapy and BMI status. (ER=Emergency room).



p=0.018 - Chemo No
p<0.001 - Chemo Yes

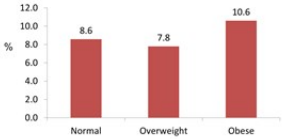
p=0.087 - Chemo No
p=0.091 - Chemo Yes

Table 2. Multivariable Cox regression analysis for factors associated with all ER visits or hospitalizations among 7,830 breast cancer patients

	All Hospitalization		ER Visits	
Variables	Adjusted HR	95% CI	Adjusted HR	95% CI
BMI				
Normal	[reference]		[reference]	
Overweight	1.05	0.85 - 1.30	1.11	0.96 - 1.28
Obese	1.28	1.05 - 1.55	1.32	1.15 - 1.51
Age				
<45	[reference]		[reference]	
45-49	0.80	0.62 - 1.04	0.85	0.72 - 1.01
50-54	0.86	0.68 - 1.10	0.77	0.65 - 0.91
55-59	0.87	0.68 - 1.11	0.81	0.69 - 0.96
60+	0.89	0.68 - 1.16	0.75	0.62 - 0.90
Region				
North Central	[reference]		[reference]	
Northeast	0.79	0.59 - 1.05	0.94	0.79 - 1.13
South	0.86	0.71 - 1.04	0.80	0.70 - 0.91
West	0.67	0.49 - 0.92	0.79	0.65 - 0.96
Comorbidity				
0	[reference]		[reference]	
1	1.31	1.06 - 1.63	1.43	1.24 - 1.65
2+	1.67	1.09 - 2.55	1.60	1.19 - 2.15
Chemotherapy				
No	[reference]		[reference]	
Yes	2.32	1.95 - 2.75	1.90	1.70 - 2.13
Radiation therapy				
No	[reference]		[reference]	
Yes	0.91	0.75 - 1.11	1.04	0.90 - 1.19
Surgery				
BCS	[reference]		[reference]	
ALND	1.66	0.73 - 3.78	1.55	0.89 - 2.71
Mastectomy	1.48	1.22 - 1.80	1.28	1.12 - 1.47
Hormone therapy				
No	[reference]		[reference]	
Yes	0.91	0.77 - 1.07	1.02	0.91 - 1.14

Interaction terms for BMI*chemotherapy were not significant (p=.40 for ER visits; p=0.93 for hospitalization)

Figure 2. Chemo-related hospitalization rates according to BMI



- In a multivariable Cox regression model with chemotherapy-related hospitalizations as the endpoint, obese patients had a non-significant 23% higher risk of hospitalization (HR 1.23, 95% CI 0.90- 1.68) when compared to normal weight patients.

Conclusions

- Obese patients with breast cancer are more likely than normal weight patients to have ER visits and hospitalizations in the 6 months after diagnosis
- Chemotherapy increased the risk of ER visits and hospitalizations
- Chemotherapy-related hospitalizations were not significantly increased in obese patients
- The risk of chemotherapy-related ER visits or hospitalization was independent of BMI

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3. Griggs JJ et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2012 May 1;30(13):1553-61.

FUNDING

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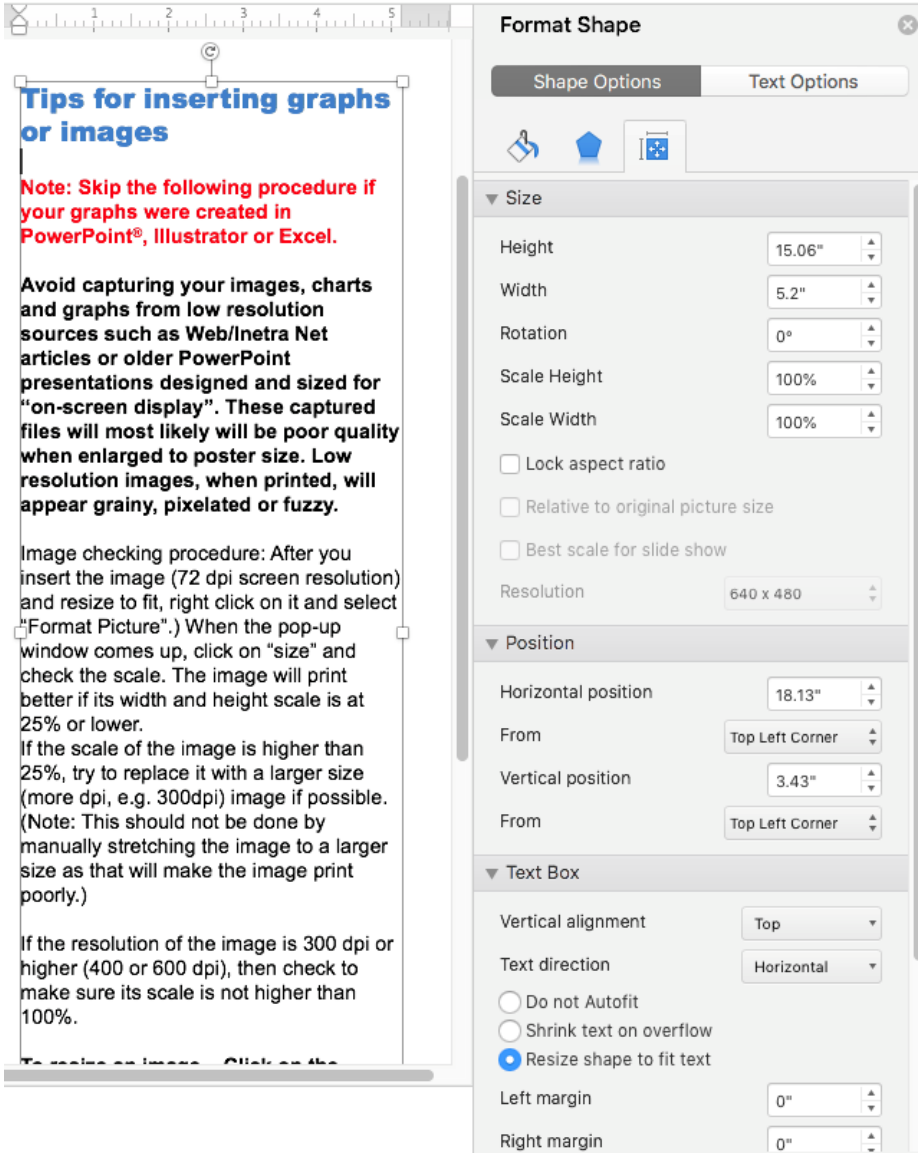
Contacts: Sharon Giordano at sgiordan@mdanderson.org

Alignment

- Graphics and text boxes
- Paragraphs

Alignment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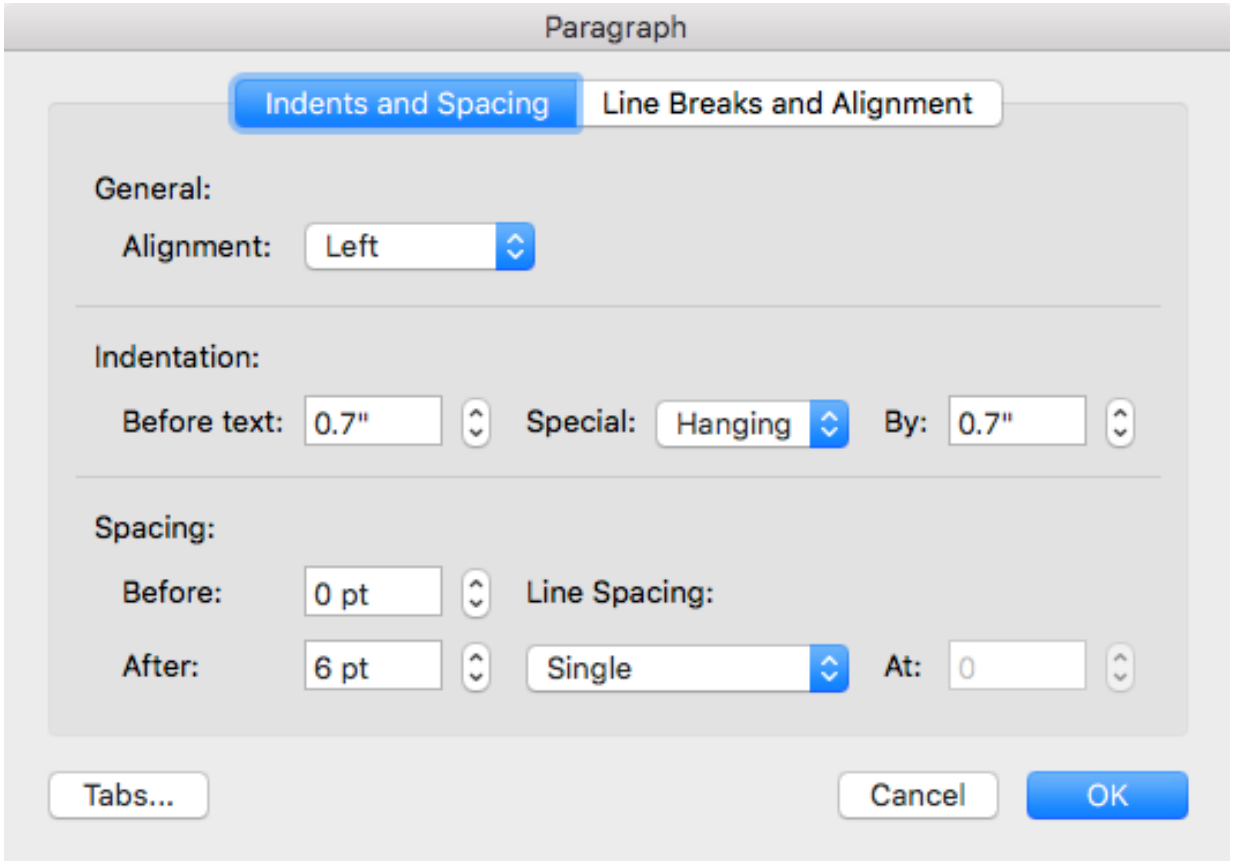
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Consistency

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JNK signaling regulates tumor cell–tumor-associated macrophage cross-talk in triple-negative breast cancer

Xuemei Xie[1,2], Shimpei Otsuka[1,2], Evan Cohen[1,3], Khoi Chu[4], Alexander Y. Lu[1,2], Debu Tripathy[1,2], Kevin N. Dalby[5], James M. Reuben[1,3], Walter N. Hittelman[4], Steven Van Laere[6], Chandra Bartholomeusz[1,2], and Naoto T. Ueno[1,2]

[1]Section of Translational Breast Cancer Research, [2]Department of Breast Medical Oncology, [3]Department of Hematopathology, and [4]Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, Texas. [5]Division of Medicinal Chemistry, College of Pharmacy, The University of Texas at Austin, Austin, Texas. [6]Department of Oncology, University of Antwerp, Antwerpen, Belgium.

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Introduction

- Triple-negative breast cancer (TNBC) is more aggressive than other types of breast cancers and has a poor prognosis because of its high proliferation rate, stemness, and tendency to metastasize[1].
- JNK (c-Jun N-terminal kinase) plays a vital role in malignant transformation and stress-induced inflammation[2,3].
- M1 macrophages promote inflammation but suppress tumor progression. M2 macrophages, also termed as tumor-associated macrophages (TAMs), suppress inflammation but promote tumor progression[4].
- In breast cancer, TAMs are associated with high histological grade, large tumor size, high proliferation rate, low ER and PR status, and poor prognosis[5].
- It remains unknown whether JNK plays a role in tumor-TAM cross-talk in TNBC.

Objective

To define the role of JNK signaling in regulation of tumor cell-M2 cross-talk in TNBC.

Hypothesis

JNK contributes to TNBC metastasis by promoting tumor cell-M2 cross-talk through the TGF-β signaling pathway in TNBC.

Results

JNK/c-Jun signaling and M2 cells have clinical impact in TNBC

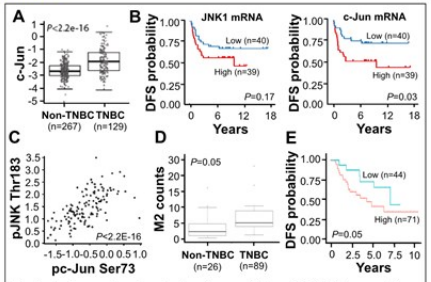

Fig 1. **A**, Expression levels of c-Jun are higher in TNBC tumors than in non-TNBC tumors (MDACC RPPA dataset). **B**, Disease-free survival (DFS) probability by JNK1 and c-Jun status in patients with TNBC (Wang and Mainz dataset). **C**, Expression levels of phospho-c-Jun at Ser73 positively correlate with those of phospho-JNK at Thr183 in TNBC tumors (n=129; MDACC RPPA dataset). In inflammatory breast cancer, (**D**) M2 counts are higher in TNBC tumors than in non-TNBC tumors, and (**E**) M2 counts positively correlate with short DFS.

Differentiation of THP1 monocytes to M1 and M2 macrophages

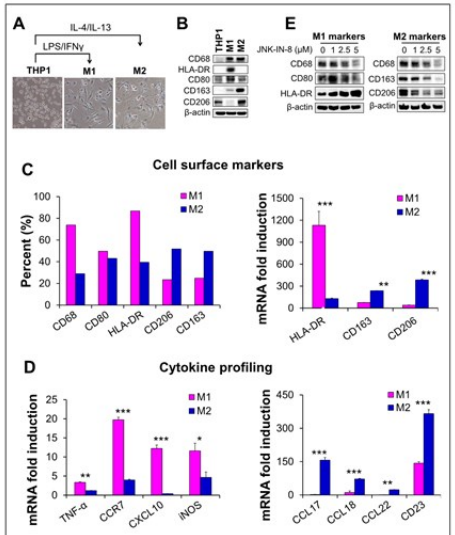

Fig 2. Differentiation of THP1 monocytes to M1 and M2 macrophages, as assessed by (**A**) morphology, (**B** & **C**) cell surface marker expression by Western Blotting, FACS, and qPCR, and (**D**) cytokine profiling by qPCR. **E**, JNK inhibition by JNK-IN-8 promotes M1 differentiation but suppresses M2 differentiation. *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$.

M2 macrophages promote migration and invasion of TNBC cells *in vitro*

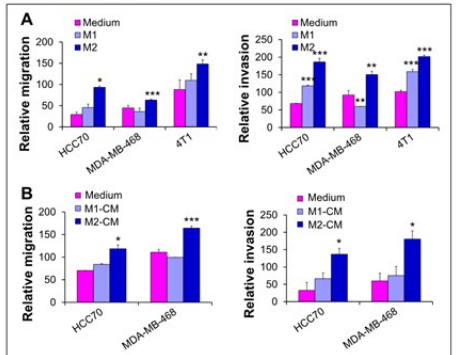

Fig 3. Compared to culture with medium alone or co-culture with (**A**) M1s or (**B**) M1-conditioned medium (CM), co-culture with (**A**) M2s or (**B**) M2-CM significantly enhances migration and invasion of TNBC cells. *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$.

The JNK pathway is involved in M2 macrophage-promoted motility in TNBC cells *in vitro*

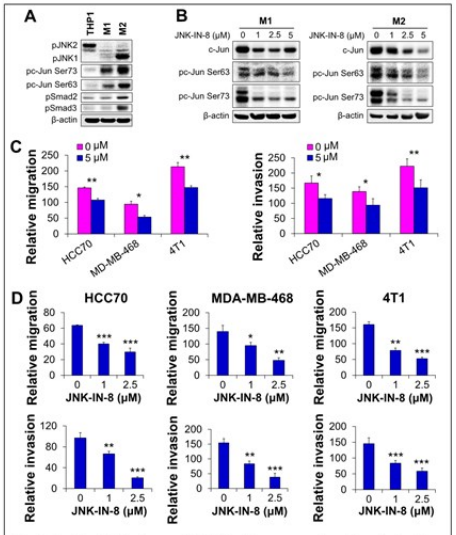

Fig 4. **A**, The JNK/c-Jun and TGF-β pathways are strongly activated in M2 macrophages. **B**, JNK inhibition by JNK-IN-8 suppresses c-Jun activation in both M1 and M2 macrophages at 48 h following treatment. **C** & **D**, JNK inhibition by JNK-IN-8 in (**C**) M2 macrophages or (**D**) TNBC cells leads to a reduction in M2 macrophage-promoted migration and invasion of TNBC cells. *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$.

M2 macrophages promote motility of TNBC cells through paracrine signaling *in vitro*

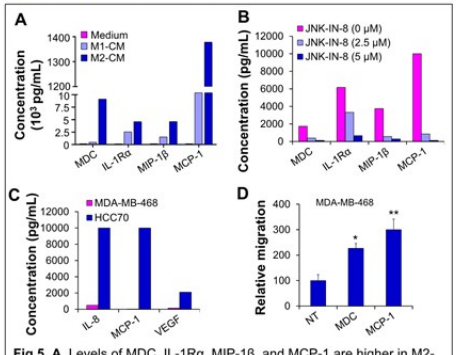

Fig 5. **A**, Levels of MDC, IL-1Rα, MIP-1β, and MCP-1 are higher in M2-CM than in M1-CM. **B**, JNK inhibition by JNK-IN-8 reduces secretion of MDC, IL-1Rα, MIP-1β, and MCP-1. **C**, TNBC cells secret high levels of IL-8, MCP-1, and VEGF. **D**, MDC and MCP-1 enhances migration of TNBC cells. *, $P<0.05$; **, $P<0.01$.

JNK inhibition suppresses tumor growth and M1/M2 recruitment to tumors in a TNBC mouse model

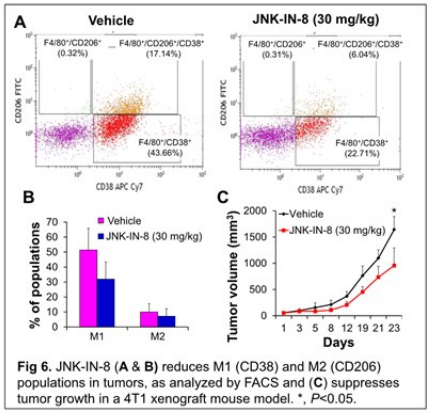

Fig 6. JNK-IN-8 (**A** & **B**) reduces M1 (CD38) and M2 (CD206) populations in tumors, as analyzed by FACS and (**C**) suppresses tumor growth in a 4T1 xenograft mouse model. *, $P<0.05$.

Conclusions

- JNK/c-Jun signaling and M2 macrophages have clinical impact in TNBC.
- M2 macrophages promote migration and invasiveness of TNBC cells possibly through the JNK/c-Jun/TGF-β pathway.
- JNK signaling suppresses M1 macrophage differentiation but promotes M2 macrophage differentiation.

Future Studies

- Determine which JNK isoform plays a predominant role in TNBC-M2 cross-talk.
- Elucidate how the JNK/c-Jun/TGF-β pathway regulates TNBC-M2 cross-talk.
- Assess the impact of M2 macrophages on metastasis of TNBC cells using animal models.
- Determine the clinical significance of M2- and TNBC-derived cytokines/chemokines in TNBC.

Acknowledgements

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Color and Contrast

Color palette

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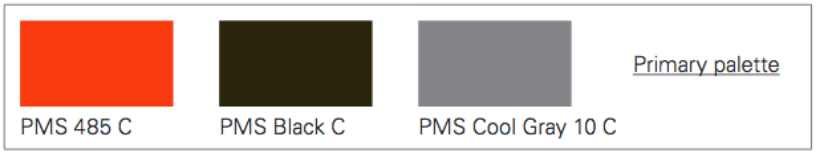
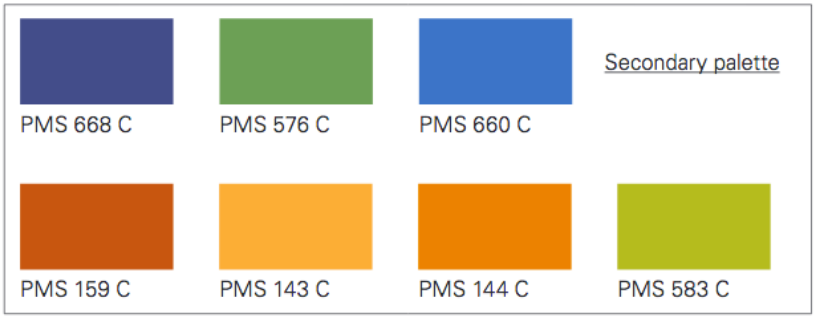
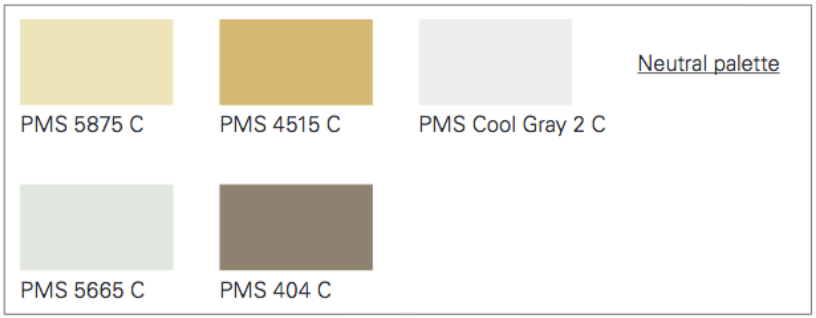
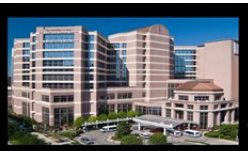






Color and Contrast

- Style and graphic elements
- Color conflicts
- Color blindness



Poster #P6-17-04

3-year relapse-free survival of stage II-III HER2-neu positive breast cancer treated with pertuzumab and trastuzumab-containing neoadjuvant therapy compared to trastuzumab-containing therapy.

Rashmi K. Murthy[1], Akshara S. Raghavendra[1], Kenneth R Hess[2], Carlos H. Barcenas[1], Bora Lim[1], Stacy L. Moulder[1], Sharon H. Giordano[1,4], Elizabeth A. Mittendorf[5,6], Alastair Thompson[5,7], Naoto T. Ueno[1], Vicente Valero[1], Jennifer K. Litton[1], Debu Tripathy[1], Mariana Chavez-MacGregor[1,4]

The University of Texas MD Anderson Cancer Center, Department of Breast Medical Oncology[1], Department of Biostatistics[2], Department of Health Services Research [4], Department of Breast Surgical Oncology [5], Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center[6], Department of Breast Surgical Oncology, Baylor College of Medicine[7]

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Contact: rmurthy1@mdanderson.org

BACKGROUND

- Pertuzumab (P) in combination with trastuzumab (H) based chemotherapy is FDA-approved as a standard neoadjuvant treatment (NAT) for patients with clinical stage II-III HER2-positive (HER2+) breast cancer (BC).
- Patients who achieve pathologic complete response (pCR), after NAT are considered to have improved survival compared to those with residual disease (RD).

OBJECTIVE

- To evaluate the pCR rate for neoadjuvant HP-containing regimens compared to H-containing regimens and report the 3-year relapse-free survival (RFS) for patients who had a pCR compared to those with RD.

METHODS

- Retrospective chart review of a prospectively maintained electronic database at the MD Anderson Caner Center.
- Patients were identified with newly diagnosed non-inflammatory stage II-III HER2+ BC who received neoadjuvant H-containing or HP-containing therapy and underwent definitive breast and axillary surgery from 2005 to 2016.
- Medical records were reviewed to confirm patient demographics, stage of BC, tumor characteristics comprising of histologic type, biomarkers, and grade, systemic therapy received, and pathologic response.
- All patients underwent definitive breast and lymph node surgery.
- pCR was defined as ypT0/is, ypN0.
- RFS was defined as the interval from surgery to date of relapse, last followup or death from any cause.
- Descriptive statistics, Cox proportional hazards, and Kaplan-Meier estimates were used for statistical analysis.

RESULTS

Table 1: pCR rate, median follow-up, and median age in HP and H groups

		HP (n=215)	H (n=807)
pCR rate*		56%	49%
*adjusted OR = 1.55 (0.82, 2.95) p = 0.18			
Median follow-up		1.9 (0-4.2) years	5.3 (0.1-12) years
Median Age		51(22-84) years	50(21-87) years

Table 2 : pCR rate by menopausal status, nodal status, nuclear grade, and HR status in HP and H groups

Variable		HP			H		
		N	pCR	RD	N	pCR	RD
Menopausal Status	Pre-	103	54%	46%	445	48%	52%
	Post-	112	58%	42%	362	52%	48%
Clinical Nodal Status	Node (+)	147	52%	48%	571	48%	52%
	Node (-)	68	66%	34%	236	53%	47%
Nuclear Grade[1]	II	65	49%	51%	200	43%	57%
	III	150	59%	41%	607	51%	49%
HR status	HR(+)	133	47%	53%	483	43%	57%
	HR(-)	82	71%	29%	324	59%	41%

Table 2 Key: (+) – positive; (-) – negative; HR – hormone receptor; ER – estrogen receptor; PR – progesterone receptor; HR(+) - ER+ or PR+; HR(-) – ER(-) and PR (-)

[1] 1 patient in the HP pCR group had nuclear grade 1; 2 patients in the HP RD group had nuclear grade 1 tumors

Figure 1) 3-yr RFS in HP group by PCR vs. RD

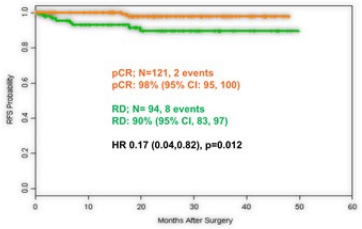


Figure 2) 3-yr RFS in H group by PCR vs. RD

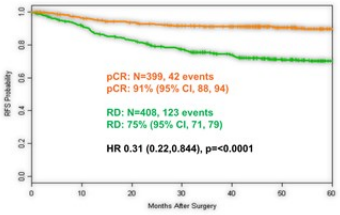
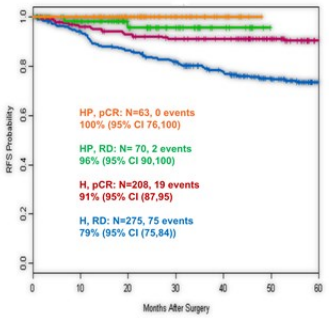


Table 3: 3-yr Kaplan Meier estimates for local recurrence (LR), distant recurrence (DR), and breast cancer-related death (BC death).

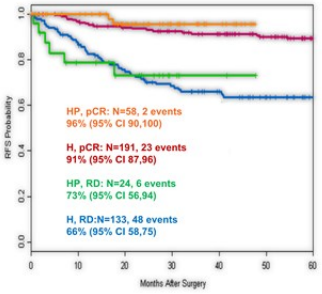
RX	pCR	N	LR	DR	BC death
HP	Y	121	0%(0%,13%)	2%(0%,5%)	0%(0%,13%)
HP	N	94	2%(0%,5%)	8%(2%,15%)	2%(0%,6%)
H	Y	399	0%(0%,1%)	8%(6%,11%)	5%(0%,8%)
H	N	408	2%(0%,4%)	23%(19%,27%)	18%(14%,22%)

Figure 3) 3-yr RFS stratified by HR status, pCR status, and HP/H

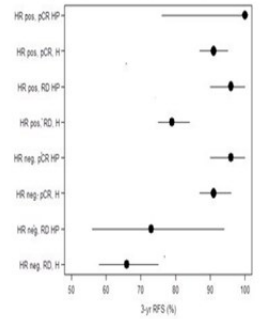
A) 3 yr. RFS stratified by HR Positive



B) 3 yr. RFS stratified by HR Negative



C) 3 yr. RFS with confidence intervals



CONCLUSIONS

- **Treatment with HP-containing neoadjuvant regimens is associated with a high 3-year RFS.**
- **Patients who achieve pCR have an improved 3-year RFS compared to patients who have RD.**
- **An important observation is that patients with RD after HP have a higher 3-yr RFS compared to patients with RD after H alone.**

LIMITATIONS

- **Retrospective analysis**
- **The two groups have very different median follow-up times: 1.9 years (HP) vs. 5.3 years (H).**
- ***Further analysis in larger prospective datasets is needed to confirm findings and to inform design of future trials.***

Other Considerations

- Technical issues
- Discussing your work
- Where to get assistance

Technical Issues

- Software
- QR code or web links

Discussing Your Work

- Prepare a brief speech
- Be prepared to answer questions

Where to Get Assistance

- Creative Communications
  - Design
  - Layout tools
  - Printing
- Scientific Publications
  - Text

Creative Communications

- http://inside.mdanderson.org/departments/creative-communications or https://mdabrandcentral.com
- brandcentral@mdanderson.org
- Tel: 713-745-5054
- 1MC16.2300 (poster printing only)

Creative Communications
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Brand Central
(tools and templates)

Scientific Publications

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- scientificpublications@mdanderson.org
- Tel: 713-792-3305
- 1MC16.3438

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