BreastCare
Multidisciplinary Journal for Research, Diagnosis and Therapy

Review Article

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Supplementary Material.

Therapeutic Advances and New Directions for Triple Negative Breast Cancer

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Supplementary Table 1. Summary of clinical and molecular characteristics of TNBC

Clinical

- Accounts for about 15% of all breast cancers in U.S.
- More common in women of black race and/or Hispanic ethnicity
- Younger age at presentation
- Higher risk of visceral metastases, including predilection for brain metastasis and bone marrow involvement
- Associated with germ-line BRCA mutations in about 50% of patients with a strong family history of breast and/or ovarian cancer, and up to 20% of unselected patients

Molecular

- Basal-like subtype and claudin-low subtypes are the most common “intrinsic subtypes” by gene expression
- When present, BRCA mutations are associated with defective DNA repair and sensitivity to DNA damaging agents and PARP inhibitors
- Sporadic cancers not associated with BRCA mutations are often BRCA-like due to methylation-induced silencing of BRCA1 and/or loss of other DNA repair proteins
- Commonly associated with somatic p53 mutations, but “clinically actionable” aberrations occur in < 20% (*BRAF* V600E, high-level *EGFR* amplifications, and *ERBB2* and *ERBB3* mutations) and may not be driver aberrations
- PI3K pathway activation despite low PI3K mutation rate due to *PTEN* and *INPP4B* loss and/or amplification of *PIK3CA*
- PD-L1 gene is expressed in about 20%-30% newly diagnosed early stage breast cancer, primarily in TNBC

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Supplementary Table 2. Novel agents in clinical development for treatment of TNBC

Therapeutic Target	Agents	Phase of Study
DNA Repair Pathway: PARP	ABT-888 (veliparib), AZD2281 (olaparib), BMN763	I/II/III
EGFR	erlotinib, cetuximab, panitumumab	II
Angiogenesis	Bevacizumab	III
	sunitinib, pazopanib	II
HDAC	vorinostat, entinostat	II
Hsp90	Ganetespib	II
AR	bicalutamide, enzalutamide	II
PI3K/AKT/mTOR	GDC-0941	II
	ipatasertib (GDC-0068), GSK2141795,	
	everolimus, temsirolimus	
MEK	trametinib (GSK1120212)	presurgical/II
Src	Dasatinib	II
Stem Cell Pathways:		
Notch	R04929097, MK-0752	I
Wnt	LGK974	I
CXCR1/2	Reparixin	presurgical/Ib
CDKs	P276-00, dinaciclib	I/II
c-Met	onartuzumab, ARQ197, foretinib	II
Aurora kinase	ENMD-2076	II
DNA Repair pathway:	PF-00477736, CHIR-124	Preclinical
Checkpoint kinase 1	SAR-020106, AZD7762	
Death receptors	piperine	Preclinical
	tigatuzumab	II
Inhibitors of apoptosis	YM155	I
	LCL161	II
Immune	MUC-1 vaccine, DC-CIK	0/I
	Pembrolizumab, atelolizumab	I/II
CSF1 receptor, c-kit	PLX 3397	Ib/II

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Therapeutic Target	Agents	Phase of Study
Targeted Cytotoxic	glembatumumab vedotin (CDX-011)	II
Anti-Trop-2-SN-38	Sacituzumab govitecan/ IMMU-132	I/II

Abbreviations: EGFR epidermal growth factor receptor; AR androgen receptor; mTOR mammalian target of rapamycin; CDK cyclin dependent kinase; PARP poly ADP ribose polymerase; MEK mitogen-activated protein/extracellular signal regulated kinase; Src sarcoma; DC-CIK Dendritic cell - cytokine-induced killer cell; CSF1 colony stimulating factor 1

Supplementary Table 3. Revised Molecular Subtype of TNBC (TNBCtype-4)

TNBCtype-4 Designation	"Driver" pathway(s) inferred by Gene Ontology	Estimated Prevalence in TNBC (%)¶	% Patients Achieving pCR§	Putative Therapeutic Intervention
BL1	cell cycle, DNA damage response	35	46	platinum agents, PARP inhibitors (veliparib, olaparib)
BL2	cell cycle, DNA damage response, growth factor signaling	22	12	
M	cell motility, ECM receptor interactions, cell differentiation	25	29	Abl/Src inhibitor (dasatinib), PI3K/mTOR inhibitor (NVP-BEZ235)
LAR	steroid synthesis and metabolism	16	15	bicalutamide, Hsp90 inhibitor (17-DMAG), PI3K/mTOR inhibitor (NVP-BEZ235)

¶ 2% assigned to 'unclassified' molecular subtype.

§ Response to neoadjuvant ACT

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Supplementary Table 4. Platinum Trials in the Neoadjuvant Setting in TNBC and BRCA-Associated Breast Cancer

Phase	N	BRCA status	Regimen	pCR Rate	3y - EFS	Reference
II	28	unselected	cisplatin	21%		Silver et al., JCO, 2010
II	25	mutant	cisplatin	72%		Gronwald et al., JCO, 2009
randomized phase II	454	unselected	weekly paclitaxel, dose-dense AC, +bevacizumab, +carboplatin, or +carboplatin/bevacizumab	60% (+ carboplatin) 46% (- carboplatin)	HR 0.84 (0.58-1.22) P=0.36	Sikov et al., SABCC, 2013 & 2015
randomized phase II	315	unselected	anthracycline/taxane ± carboplatin	59% (+ carboplatin) 38% (- carboplatin)	HR 0.56 (0.33-0.96) p=0.0350	Von Minckwitz et al., Lancet Oncol. 2014 & SABCC, 2015

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Supplementary Table 5. Selected active clinical trials for TNBC or BRCA-associated breast cancer

Clinical Trial Title	Phase	Cancer.gov
Platinum containing regimens		
A randomized phase III postoperative trial of cisplatin vs capecitabine vs observation in patients with residual basal like triple negative breast cancer following neoadjuvant chemotherapy. (E1113)	III	NCT02445391
PARP inhibitors		
Olaparib as Adjuvant Treatment in Patients With Germline BRCA Mutated High Risk HER2 Negative Primary Breast Cancer (OlympiA)	III	NCT02032823
A Study Evaluating Safety and Efficacy of the Addition of ABT-888 Plus Carboplatin Versus the Addition of Carboplatin to Standard Chemotherapy Versus Standard Chemotherapy in Subjects With Early Stage Triple Negative Breast Cancer (Brightness)	III	NCT02032277
A Pilot Study of Talazoparib as a Neoadjuvant Study in Patients With a Diagnosis of Invasive Breast Cancer and a Deleterious BRCA Mutation	II	NCT02282345
Phase II Randomized Placebo-Controlled Trial of Cisplatin With or Without ABT-888 (Veliparib) in Metastatic Triple-Negative Breast Cancer and/or BRCA Mutation-Associated Breast Cancer	II	NCT02595905
Phase I Study of the Oral PI3kinase Inhibitor BKM120 or BYL719 and the Oral PARP Inhibitor Olaparib in Patients With Recurrent Triple Negative Breast Cancer or High Grade Serous Ovarian Cancer	I	NCT01623349
A Phase III, Randomized, Open Label, Multicenter, Controlled Trial of Niraparib Versus Physician's Choice in Previously-treated, HER2 Negative, Germline BRCA Mutation-positive Breast Cancer Patients	III	NCT01905592
A Phase II Multiple-Arm, Open-Label, Randomized Study of PARP Inhibition (Veliparib; ABT-888) and Anti-PD-L1 Therapy (Atezolizumab; MPDL3280A) Either Alone or in Combination in Homologous DNA Repair (HDR) Deficient Triple Negative Breast Cancer (TNBC)	II	NCT02849496
Phase 1/2 Clinical Study of Niraparib in Combination With Pembrolizumab in Patients With Advanced or Metastatic Triple-Negative Breast Cancer and in Patients With Recurrent Ovarian Cancer	I/II	NCT02657889
Phase I/II Study of the Anti-Programmed Death Ligand-1 Antibody MEDI4736 in Combination With Olaparib or Cediranib for Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancer	I/II	NCT02484404
Phase II Sudy of Rucaparib plus cisplatin in BRCA1/2 mutant TNBC	II	NCT01074970
PI3K/AKT/mTOR inhibitors		
Trametinib and Akt Inhibitor GSK2141795 in Treating Patients With Metastatic Triple-Negative Breast Cancer	II	NCT01964924
PIPA: A Phase Ib Study to Assess the Safety, Tolerability and Efficacy of the PI3K Inhibitors, Taselisib (GDC-0032) or Pictilisib (GDC-0941), in Combination With PAlbociclib, With the Subsequent Addition of Fulvestrant in PIK3CA-mutant Breast Cancers	I	NCT02389842
Other targeted agents		
Study of Glembatumumab Vedotin (CDX-011) in Patients With Metastatic, gpNMB Over-Expressing, Triple Negative Breast Cancer (METRIC)	II	NCT01997333

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Clinical Trial Title	Phase	Cancer.gov
Safety and Efficacy Study of Enzalutamide in Patients With Advanced, Androgen Receptor-Positive, Triple Negative Breast Cancer	II	NCT01889238
Immunotherapy		
Targeted T Cells After Neoadjuvant Chemotherapy in Treating Women With Stage II or Stage III Breast Cancer Undergoing Surgery	II	NCT01147016
A Randomized Open-Label Phase III Study of Single Agent Pembrolizumab Versus Single Agent Chemotherapy Per Physician's Choice for Metastatic Triple Negative Breast Cancer (mTNBC) - (KEYNOTE-119)	III	NCT02555657
A Phase II Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy for Metastatic Triple-Negative Breast Cancer (mTNBC) - (KEYNOTE-086)	II	NCT02447003
Phase 1/2a Study of Double-Immune Suppression Blockade By Combining a CSF1R Inhibitor (PLX3397) With An Anti-PD-1 Antibody (Pembrolizumab) To Treat Advanced Melanoma And Other Solid Tumors	I/IIA	NCT02452424
This Phase 1/2 study will evaluate the safety and efficacy of combination treatment with niraparib and pembrolizumab (MK-3475) in patients with advanced or metastatic triple-negative breast cancer or recurrent ovarian cancer. (KEYNOTE-162)	I/II	NCT02657889
Adaptive Phase II Randomized Non-comparative Trial of Nivolumab After Induction Treatment in Triple-negative Breast Cancer (TNBC) Patients: TONIC-trial	II	NCT02499367
A Phase 1 Study Evaluating Safety, Tolerability, and Preliminary Antitumor Activity of Entinostat and Nivolumab With or Without Ipilimumab in Advanced Solid Tumors	I	NCT02453620
A Phase 1, Open-Label, Dose Escalation Study of MGA271 in Combination With Ipilimumab in Patients With B7-H3-Expressing Melanoma, Squamous Cell Cancer of the Head and Neck, Non Small Cell Lung Cancer, and Other B7H3 Expressing Cancers	I	NCT02381314
A Phase II, Multi-Center, Open-Label Study of Tremelimumab Monotherapy in Patients With Advanced Solid Tumors	II	NCT02527434
A Phase III, Multicenter, Randomized Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) in Combination With Nab Paclitaxel Compared With Placebo With Nab Paclitaxel for Patients With Previously Untreated Metastatic Triple Negative Breast Cancer	III	NCT02425891
Open Label Multicenter Phase I/II Study of the Safety and Efficacy of PDR001 Administered to Patients With Advanced Malignancies	I/II	NCT02404441

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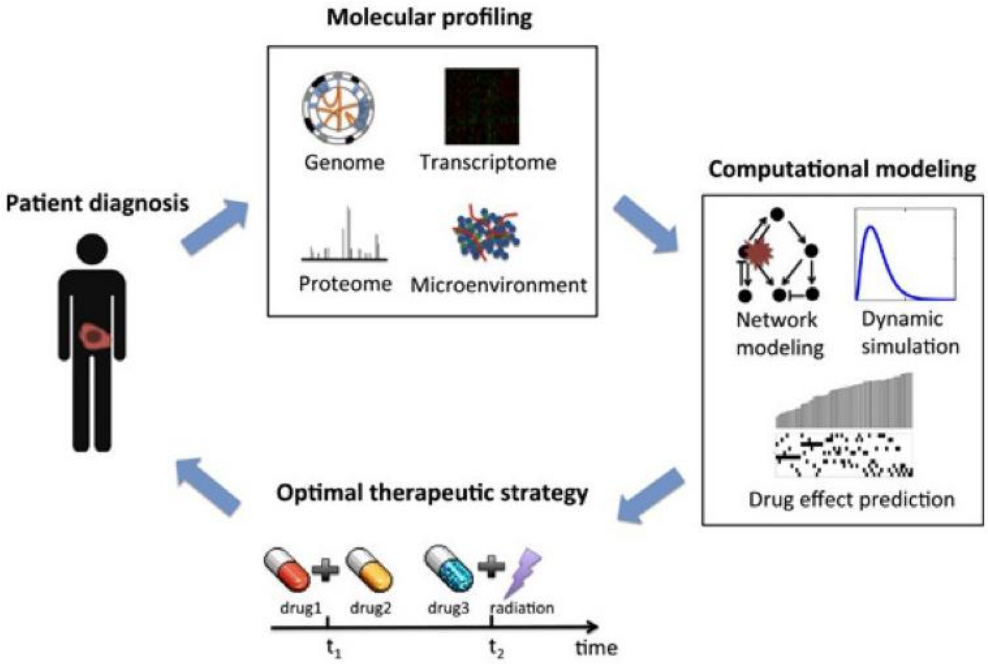

Supplementary Figure 1. Cancer Systems Biology: embracing complexity to develop better anticancer therapeutic strategies. (Du, W. and Elemento, O. 2015. Oncogene 34(25): 3215-25). *Courtesy - Olivier Elemento*

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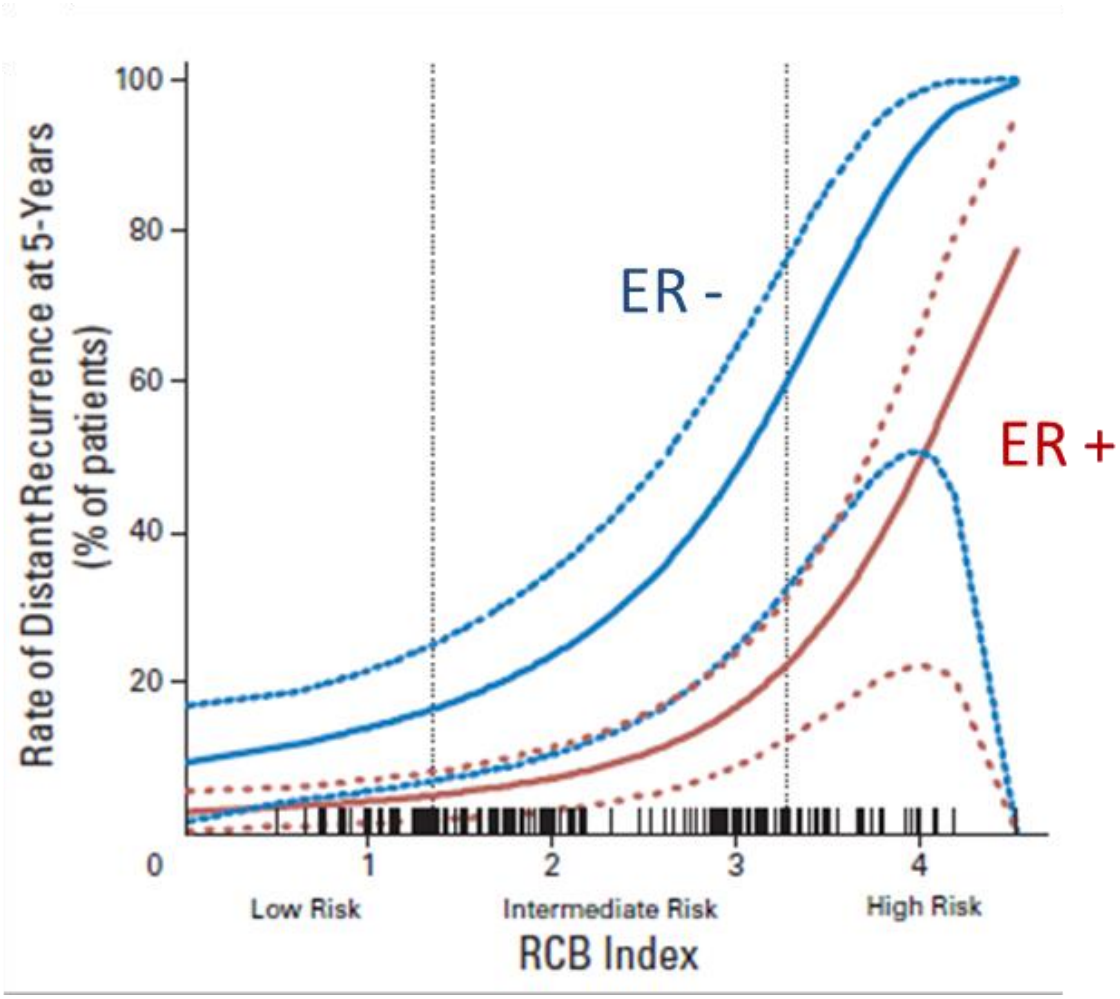

Supplementary Figure 2. Residual Cancer Burden (RCB) Index, a measure of the residual tumor burden after neoadjuvant chemotherapy, predicts risk of distant relapse at five years. For a given RCB score, ER- patients have a higher risk of developing distant metastases than ER+ patients. *Courtesy of W.F. Symmans*

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