Emerging therapeutic strategies for TNBC

Molecular Triaging as a Clinical Trial Tool

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Basic Facts

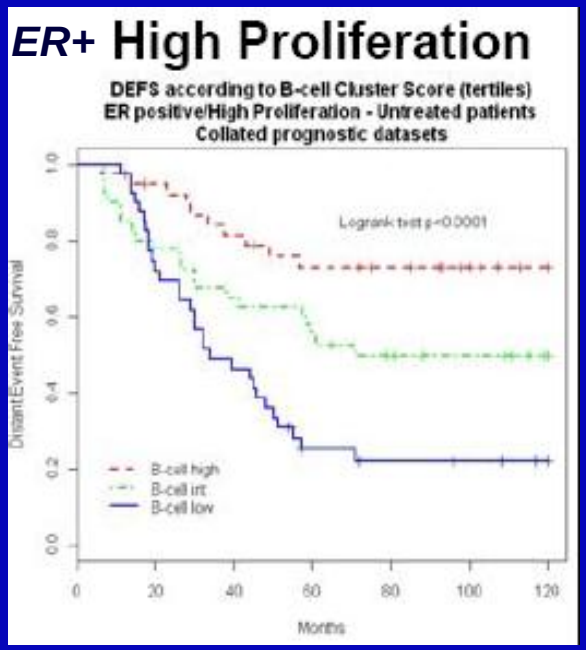
- We do not have many good drugs for metastatic TNBC (chemotherapy).
- We have many good, although untested, therapeutic ideas.

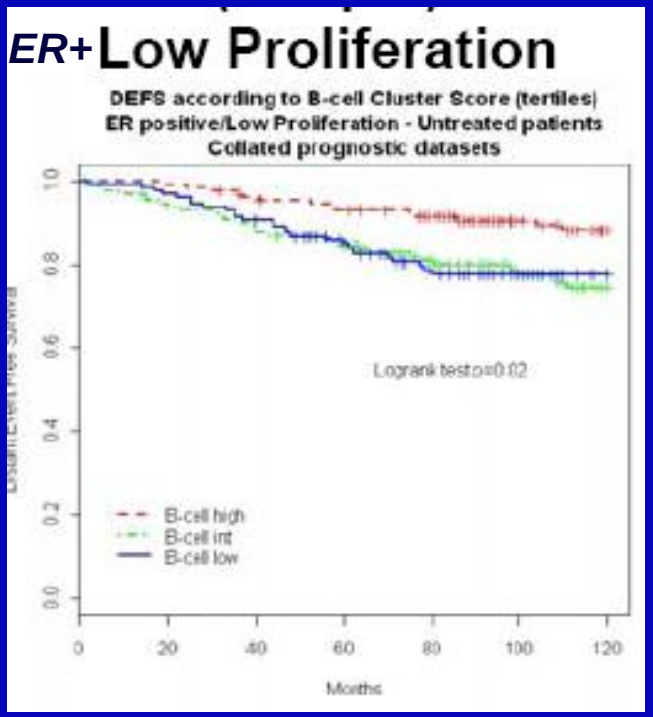
Where do good ideas come from?

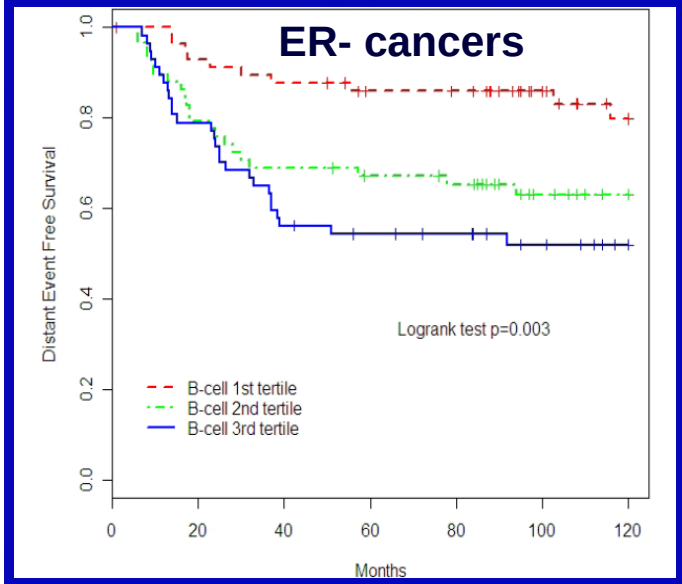
- Preclinical model systems (e.g. PARP inhibitors, chemo drugs).
- Find novel targets through analysis of the cancer genome (e.g. trastuzumab, crizotinib, imatanib)

Genomic observations with potential therapeutic value

Immune cell presence is prognostic in ER+ highly proliferative and ER- cancers only



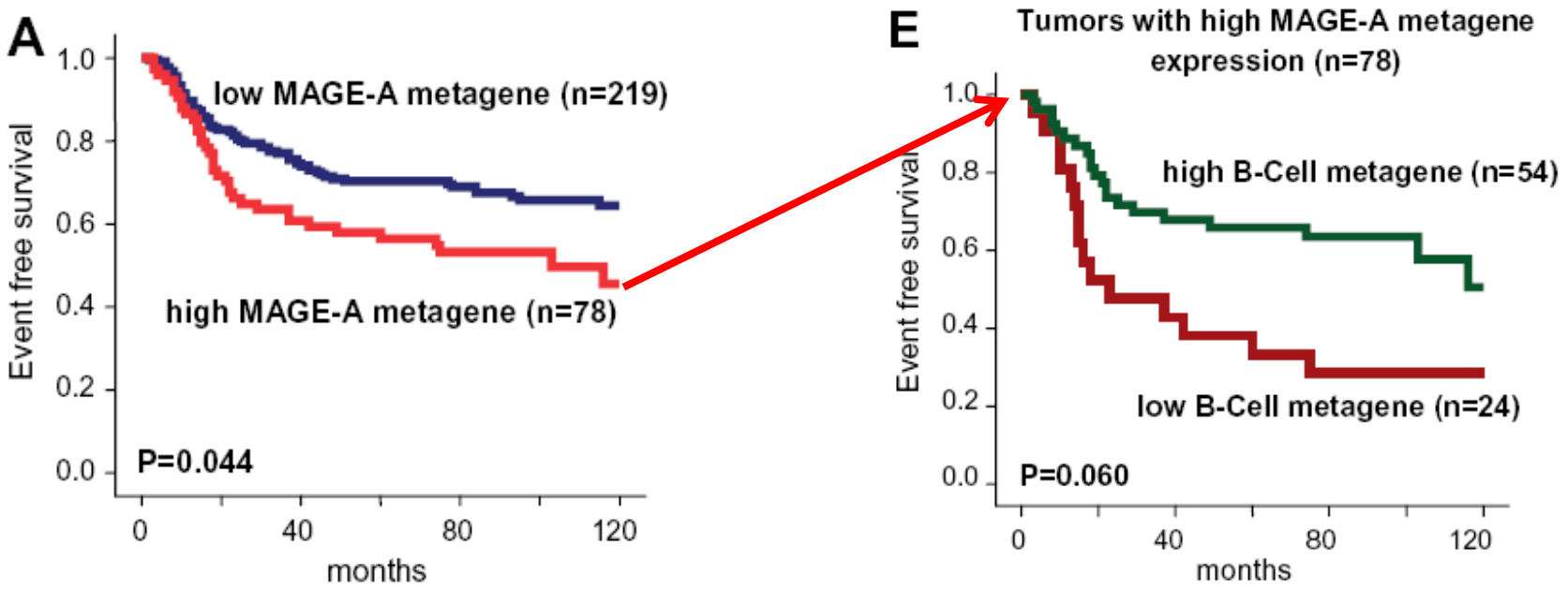




G Bianchini et al JCO 28(28):4316-4323, 2010

Genomic observations with potential therapeutic value

Identify bimodally expressed genes in TNBC
(Wang J et al Cancer Inform 7:199-216, 2009) and test their prognostic value



These and similar results suggest that augmenting the immune response might improve survival for ER- (and high risk ER+) cancers in the adjuvant setting

Karn T, et al. Eur J Cancer:doi:10.1016/j.ejca.2011.06.025, 2011.

Kinase expression differences across breast cancer subtypes

Table 1. Differentially expressed kinases between ER-positive and ER-negative cancers (adjusted for HER2 status) and between HER2-positive and HER2-negative cancers (adjusted for ER status) in the three clinical validation data sets and a cohort of 51 breast cancer cell lines

Probe set	Gene symbol	Primary tumors (validation data sets)						Cell lines	
		Ratio, Wang and colleagues	*P*	Ratio, TRANSBIG	*P*	Ratio,* Mainz	*P*	Ratio,* 51 cells	*P*
Kinases overexpressed in ER-positive									
203628_at	*IGF1R*	2.54	<1E–07	4.59	<1E–07	4.86	<1E–07	1.96	**0.01**
219686_at	*STK32B*	4.46	<1E–07	5.16	<1E–07	7.55	<1E–07	1.46	0.24
214053_at	*ERBB4*	4.67	<1E–07	7.24	<1E–07	6.01	<1E–07	1.99	**0.0006**
204379_s_at	*FGFR3*	2.3	**5.00E–06**	2.86	**1.00E–06**	2.68	**6.00E–05**	3.74	**0.004**
210523_at	*BMPR1B*	2.94	<1E–07	4.58	<1E–07	2.61	**0.001**	1.3	0.29
222348_at	*MAST4*	2.67	<1E–07	3.4	<1E–07	2.82	**8.00E–07**	0.99	0.95
221667_s_at	*HSPB8*	2.03	**3.00E–07**	2.53	<1E–07	2.64	**2.00E–06**	3.18	**0.02**
209341_s_at	*IKBKB*	2.01	<1E–07	2	<1E–07	2.57	<1E–07	1.49	0.07
205399_at	*DCLK1*	2.12	<1E–07	2.04	<1E–07	2.05	**1.00E–05**	1.03	0.92
202454_s_at	*ERBB3*	2.05	<1E–07	2.28	<1E–07	1.99	<1E–07	5.32	<1E–07
202786_at	*STK39*	1.88	<1E–07	1.98	<1E–07	1.87	<1E–07	1.07	0.76
214786_at	*MAP3K1*	1.18	0.2	1.9	**2.00E–06**	1.56	**0.0001**	2.12	**0.004**
206482_at	*PTK6*	2.45	<1E–07	2.59	<1E–07	2.2	**0.0001**	3.97	**0.0001**
201939_at	*PLK2*	1.47	**5.00E–05**	1.63	**3.00E–06**	1.51	**0.0009**	1.02	0.93
221035_s_at	*TEX14*	1.58	**0.002**	1.31	0.13	1.44	0.1	0.91	0.75
205614_x_at	*MST1*	1.95	<1E–07	1.8	**1.00E–05**	2.03	<1E–07	1.07	0.7
Kinases overexpressed in ER-negative									
201983_s_at	*EGFR*	2.63	<1E–07	2.64	<1E–07	2.57	**1.00E–06**	8.6	**2.00E–06**
204825_at	*MELK*	2.27	<1E–07	2.55	<1E–07	2.87	<1E–07	1.56	**0.009**
204822_at	*TTK*	2.47	<1E–07	3.12	<1E–07	2.67	<1E–07	1.8	**0.0004**
203213_at	*CDC2*	1.44	**2.00E–05**	2.1	<1E–07	1.79	**3.00E–05**	1.05	0.74
209642_at	*BUB1*	1.91	<1E–07	2.68	<1E–07	2.45	<1E–07	1.68	**5.00E–07**
208079_s_at	*AURKA*	1.85	<1E–07	2.3	<1E–07	2.12	**3.00E–07**	1.58	**0.009**
204641_at	*NEK2*	1.55	**8.00E–05**	1.91	<1E–07	1.74	**0.0006**	1.23	0.1
204061_at	*PRKX*	2.05	<1E–07	2.32	<1E–07	2.11	<1E–07	1.26	0.39
206571_s_at	*MAP4K4*	1.7	<1E–07	1.57	<1E–07	1.47	**1.00E–06**	5.28	<1E–07
205805_s_at	*ROR1*	1.26	**0.002**	1.43	**0.003**	1.29	**0.009**	2.7	**0.0003**
209464_at	*AURKB*	1.59	<1E–07	1.88	<1E–07	2.16	<1E–07	1.7	**5.00E–05**
202933_s_at	*YES1*	1.58	<1E–07	2.01	<1E–07	1.52	**1.00E–07**	1.41	**0.03**
207011_s_at	*PTK7*	1.65	<1E–07	1.33	**0.002**	1.21	**0.04**	2.2	**0.0004**
205394_at	*CHEK1*	1.73	<1E–07	2.43	<1E–07	2.18	<1E–07	1.76	**0.0002**
202240_at	*PLK1*	1.61	<1E–07	2.26	<1E–07	2.25	<1E–07	1.57	**0.001**
203139_at	*DAPK1*	1.6	<1E–07	1.77	<1E–07	1.96	<1E–07	1.16	0.51
221215_s_at	*RIPK4*	1.83	<1E–07	1.53	**7.00E–05**	1.41	**0.003**	1.71	0.06
204891_s_at	*LCK*	1.93	**1.00E–07**	1.71	**8.00E–05**	2.24	**4.00E–06**	0.98	0.91
218236_s_at	*PRKD3*	1.62	<1E–07	1.71	<1E–07	1.71	<1E–07	2.93	**7.00E–05**
204887_s_at	*PLK4*	1.34	**0.0001**	1.7	**2.00E–06**	1.4	**0.002**	1.19	0.13
202626_s_at	*LYN*	1.92	<1E–07	1.79	<1E–07	2.03	<1E–07	6.07	<1E–07
202200_s_at	*SRPK1*	1.59	<1E–07	1.75	<1E–07	1.62	<1E–07	1.6	**3.00E–05**
203755_at	*BUB1B*	1.49	<1E–07	1.82	<1E–07	1.82	<1E–07	1.4	**0.003**
201587_s_at	*IRAK1*	1.46	<1E–07	1.51	<1E–07	1.49	<1E–07	1.94	**3.00E–05**

Directly testable therapeutic hypotheses (HER3,-4, FGFR3)

Potential new drug targets ? (TTK, PTK7)

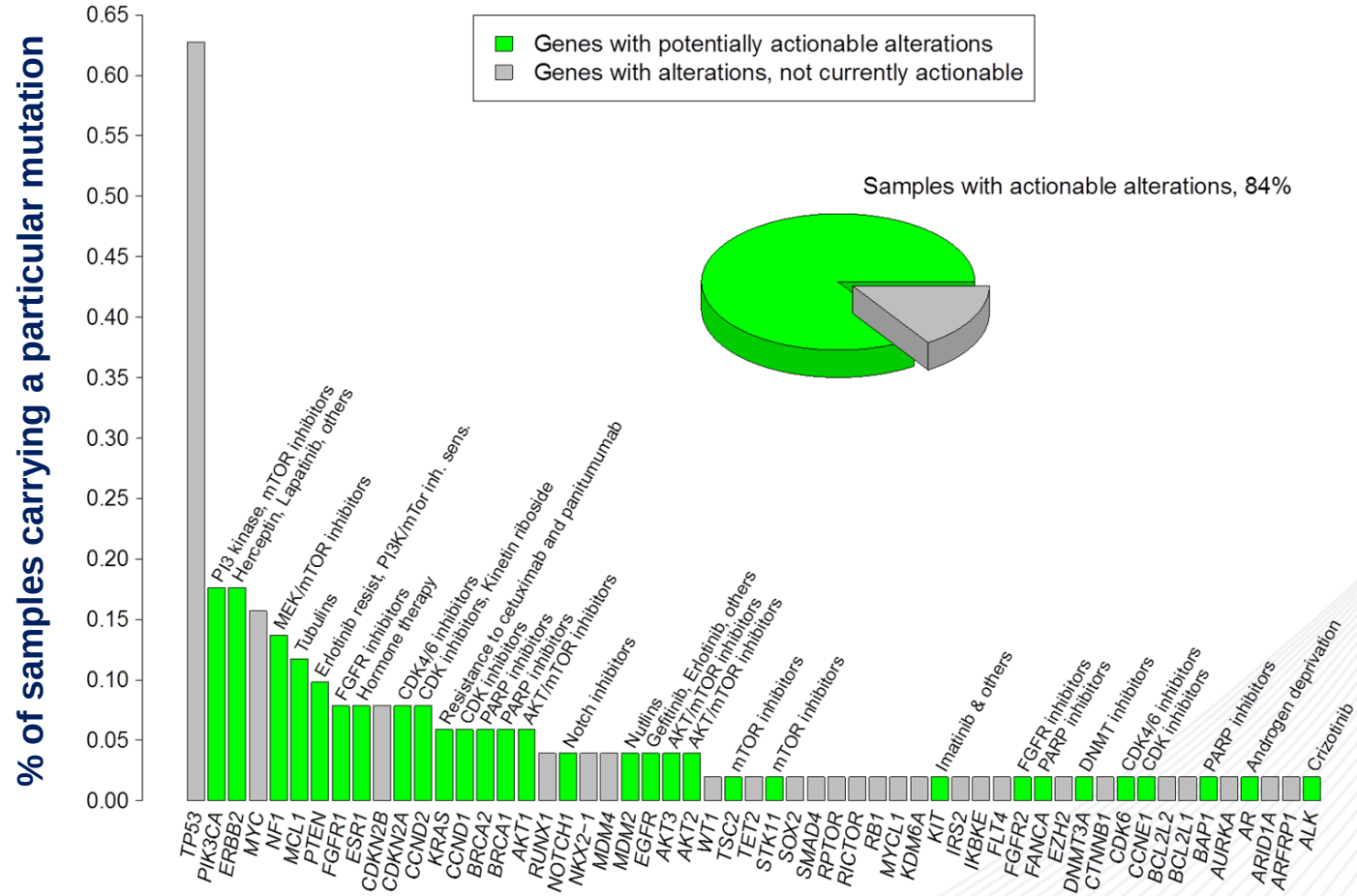
G Bianchini et al. Cancer Res 70:8852, 2010

Drugable mutations in breast cancer

Gene symbol	Genomic and codon positions, base and amino acid substitutions*	Number (%) of cases with mutations at allele level	Number (%) of cases with mutation at gene level	Drugs that inhibit gene function or block the involved signaling pathway
AKT1	c.49G > A/p.E17K[1]	5 (1.9 %)	5 (**1.9** %)	MK2206, GSK690693, KRX-041 (Perifosine), GSK2141795
BRAF	c.1391G > T/p.G464V[1]	1 (0.4 %)	8 (**3** %)	Sorafenib Tosylate (Nexavar, or Bay 43-9006), CI-1040 (PD184352), PLX4720, GDC0879, AZD6244 (Selumetinib), PD98059, SL327, PD0325901, BIRB796 (Doramapimod), SD169, SB202190, SB203580, PD169316, PLX4032, AS703026
	c.1397G > T/p.G466V[1]	1 (0.4 %)		
	c.1396G > C/p.G466R[1]	4 (1.5 %)		
	c.1798G > A/p.V600M[1]	1 (0.4 %)		
	c.1799T > A/p.V600E[1]	1 (0.4 %)		
CTNNB1	c.101G > T/p.G34V[1]	1 (0.4 %)	5 (**1.9** %)	AVN316, inhibitors of beta catenin—Wnt signaling
	c.121A > G/p.T41A[1]	4 (1.5 %)		
EGFR	c.2573T > G/p.L858R[1]	7 (2.6 %)	7 (**2.6** %)	Erlotinib Hydrochloride (Tarceva, CP-358774, OSI-774, NSC 718781), Lapatinib Ditosylate (Tykerb, Tyverb, o GW-572016), Gefitinib (Iressa o ZD-1839), Cetuximab (IMC-C225 o Erbitux), CI-1033 (Canertinib, PD-183805, CI1033, o PD183805), ZD6474 (Vandetanib), BIBW-2992 (Afatinib, INN, Tovok o Tomtovok), XL647, CUDC101, AG-1478 (NSC 693255, Tyrphostin AG-1478), PD153035 hydrochloride, AG-18 (RG-50810, Tyrphostin AG-18, Tyrphostin 23, TX 825, RG-50858), AG-213 (Tyrphostin AG-213), NVP-AEE788
FBXW7	**c.1436G > T/p.R479L[2]**	1 (0.4 %)	21 (**7.9** %)	Tumor cell with *FBXW7* mutation are particularly sensitive to inhibitors of the mTOR pathway
	c.1514G > A p.R505H[2] or			
	c.1514G > T/p.R505L[2] or			
	c.1514G > C/p.R505P[2]	14 (5.1 %)		
	c.1745C > T/p.S582L[2]	4 (1.5 %)		
	c.1379A > G/p.H460R[2]	2 (0.7 %)		
HIF1-α	c.2089C > G/p.Q697E[3]	1 (0.4 %)	1 (**0.4** %)	PX478, RX0047, SF1126, 2 methoxyestradiol (2-ME2)
IDH2	c.515G > A/p.R172K[1]	1 (0.4 %)	1 (**0.4** %)	Gliomas with IDH2 mutation may have higher sensitivity to temazolamide
KIT	c.2446G > C/p.D816H[1]	1 (0.4 %)	4 (**1.5** %)	Imatinib mesylate (Gleevec), Nilotinib (AMN107), Axitinib (AG-013736), XL184, Masitinib mesylate, Dasatinib (BMS-354825, Sprycel, o BMS354825), AZD0530 (Saracatinib)
	c.1924A > G/p.K642E[1]	1 (0.4 %)		
	c.1727T > C/p.L576P[1]	2 (0.7 %)		
KRAS	c.35G > A/p.G12D[1]	1 (0.4 %)	4 (**1.5** %)	AZD6244 (Selumetinib), U0126-EtOH, PD98059, AS703026, MEK pathway inhibitors
	c.181C > A/p.Q61K[1]	1 (0.4 %)		
	c.182A > T/p.Q61L[1]	1 (0.4 %)		
	c.183A > C/p.Q61H[1]	1 (0.4 %)		
PDGFR-α	c.1977C > A/p.N659K[1]	1 (0.4 %)	3 (**1.1** %)	IMC-3G3[a], MEDI 575[a], Pazopanib Hydrochloride (GW786034, VOTRIENT), Sunitinib Malate (Sutent), PKC412 (Midostaurin o CGP 41251), Gleevec (Imatinib mesylate, STI-571), Axitinib (AG-013736), ZD6474 (Vandetanib), Sorafenib Tosylate (Nexavar, or Bay 43-9006), Dasatinib (BMS-354825, Sprycel, o BMS354825), Nilotinib (AMN107), MP470, Masitinib mesylate (AB1010), Tandutinib, Vargatef (BIBF1120), AG18, AG-213 (Tyrphostin AG 213), TSU-68 (SU6668), AP24534 (Ponatinib), Imatinib mesylate (Gleevec)
	c.2470G > C/p.V824L[1]	2 (0.7 %)		

Santarpia et al. Breast Cancer Res Treat (doi:10.1007/s10549-012-2035-3), 201

Currently drugable abnormalities are individually rare but collectively effect more than 50% of breast cancers



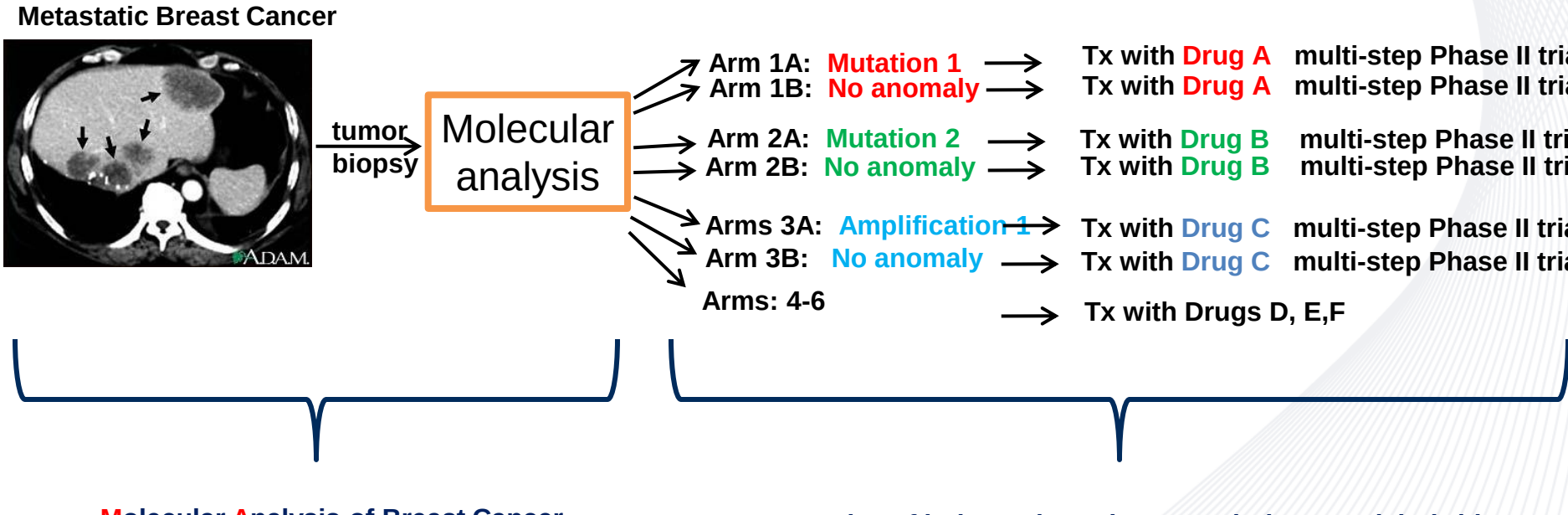
Pusztai. L. et al J Clin Oncol 30(15S):670S (#10559), 2012

The new challenge

Way too many good ideas to explore

Molecular triaging

Molecular triaging is one approach to rapidly try to identify promising drugs for a particular molecularly defined patient subset



Molecular **A**nalysis of Breast Cancer **P**rior to **I**nvestigational **T**herapy (MAP-IT)

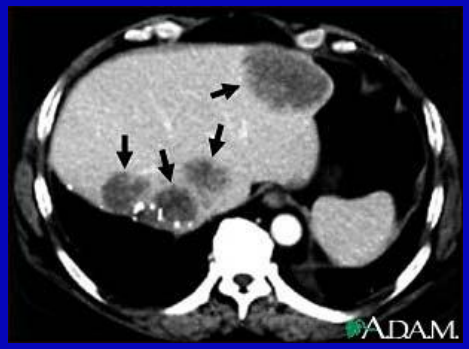
A series of independent Phase I and Phase II trials (with early stopping rules for futility)

www.mycancergenome.org

Does This approach work?

MDACC 2007-0754, Parallel, multi-arm, 2-step Phase II response marker evaluation study for dasatinib

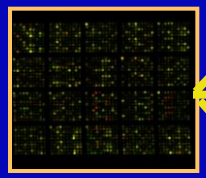
The objective is to assess the PPV of candidate markers and determine if selection of patients by one of 3 a priory defined gene signatures will increase clinical benefit rate (OR + SD > 6 months) to dasatinib.



Day 1

CT-guided FNA

CLIA lab



Day 5-7

Dasatinib target index high → Dasatinib

Src pathway activity high → Dasatinib

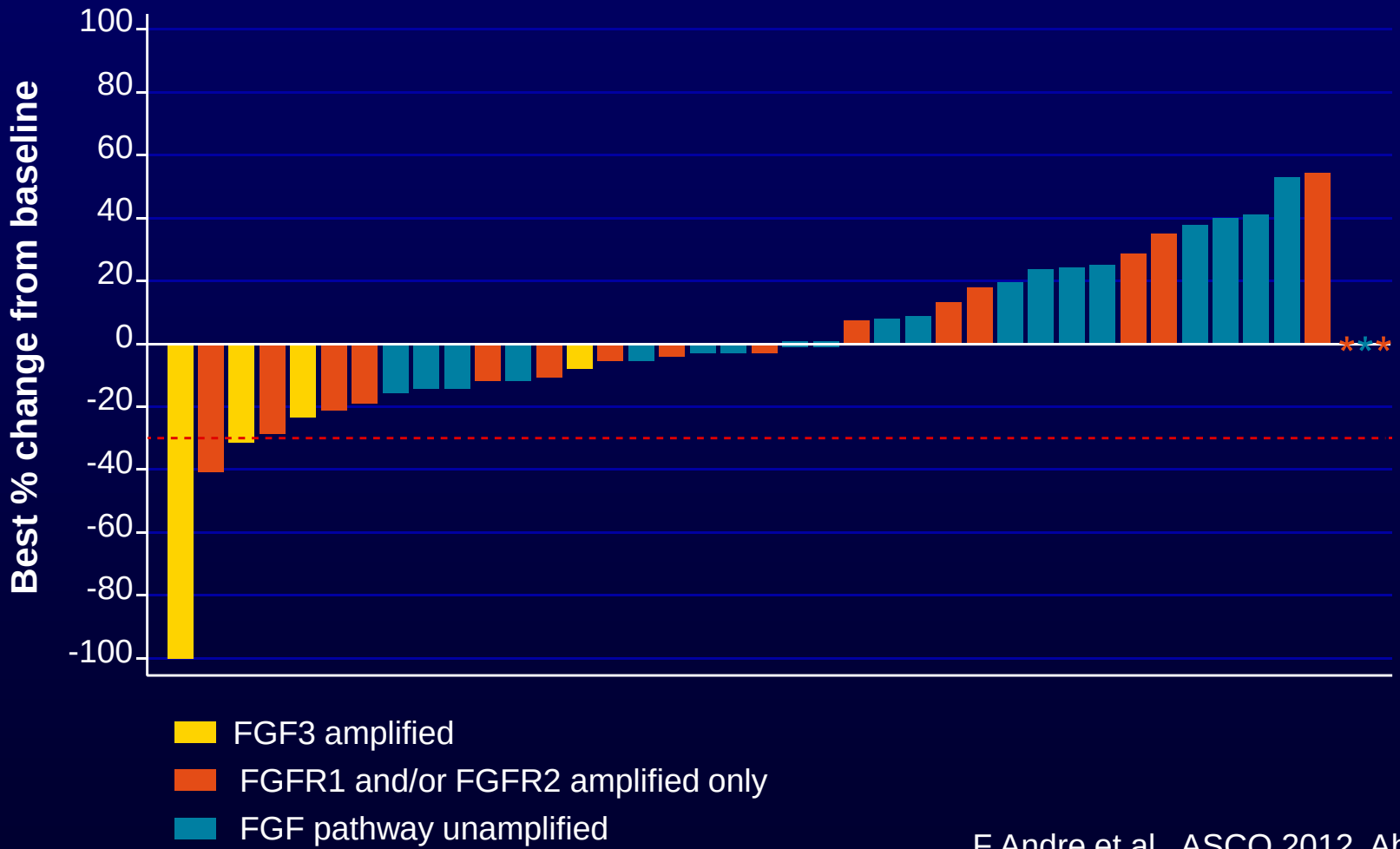
BMS predictor score high → Dasatinib

Each arm accrued 10 patients:
No sufficient clinical benefit in any of the 3 arms to move to next phase

The trial worked, these 3-gene signatures do not warrant further study

Does this approach work?

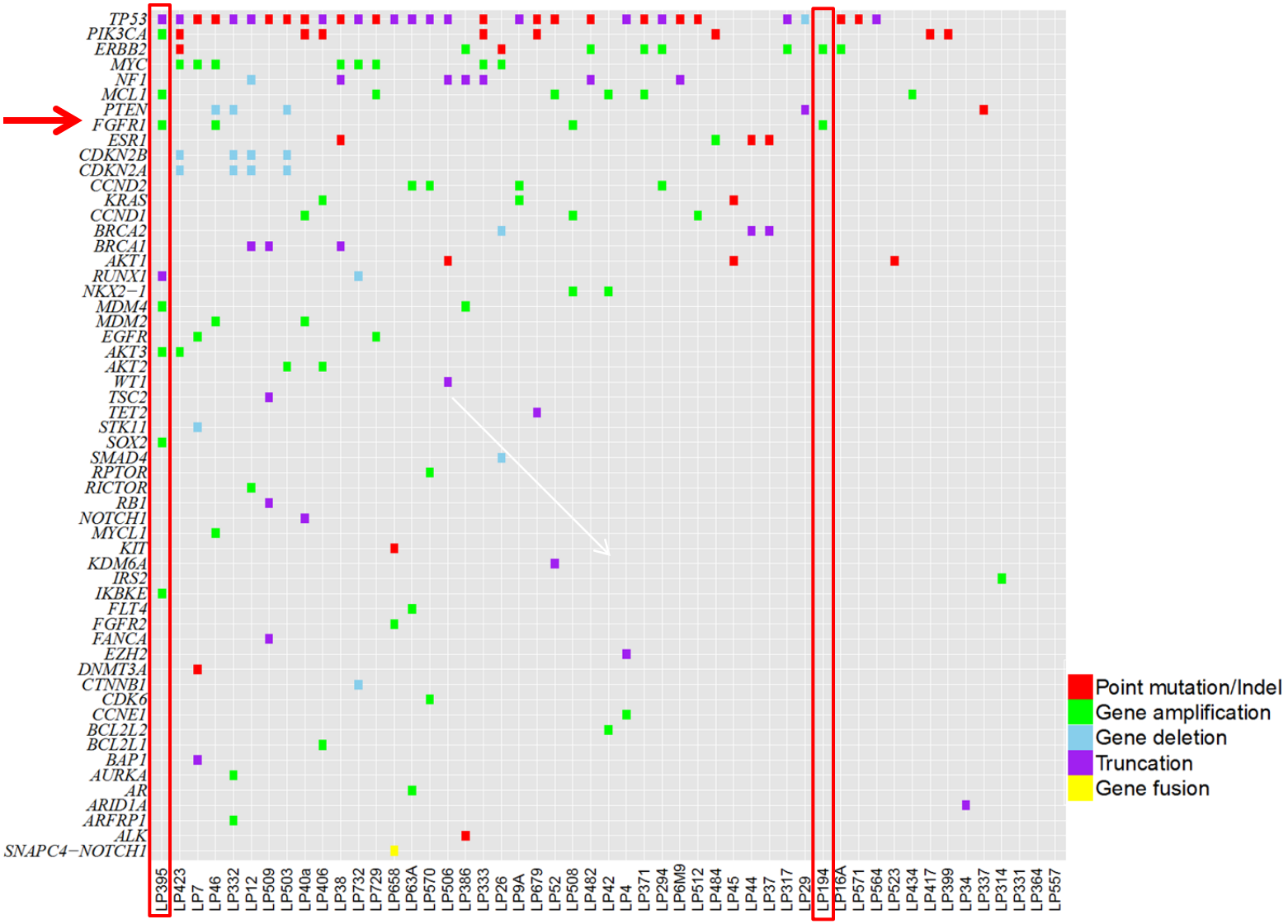
A Multicenter, Open-Label Phase 2 Trial of Dovitinib, an FGFR1 Inhibitor, in *FGFR1*-Amplified and -Nonamplified Metastatic Breast Cancer



F Andre et al.. ASCO 2012, Abst #508

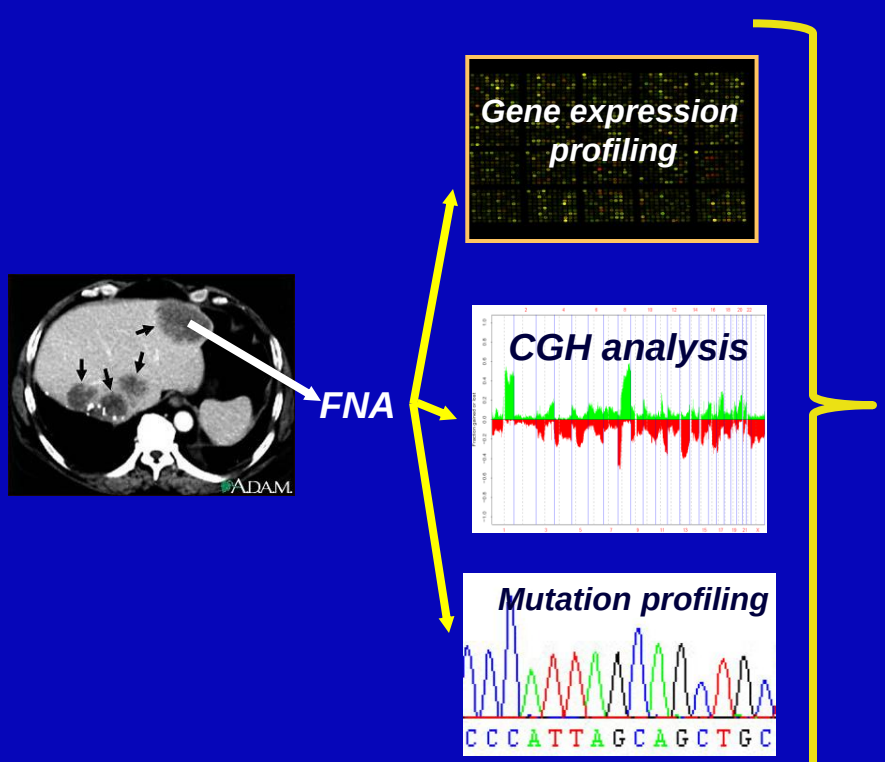
What is next?

Rational individual combination of targeted drugs….

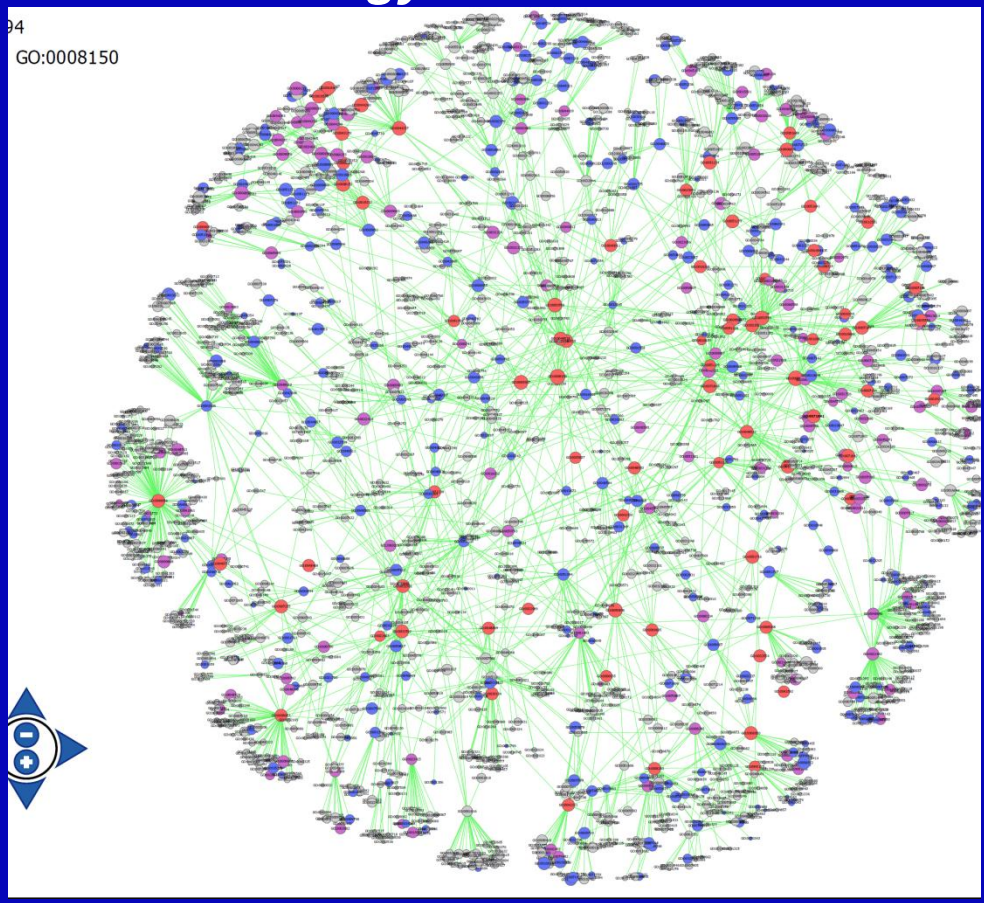


Pusztai. L. et al J Clin Oncol 30(15S):670S (#10559), 2012

Integrated analysis of mutation, gene expression and copy number changes in individual cases (www.NETGOPLOT.org)



Gene Ontology network "skeleton"



Weiwei Shi & L Pusztai

Conclusions

- Molecular markers are increasingly used in clinical trials as patient selection criteria or as an enrichment strategy.

- Due to low marker prevalence (i.e. marker positive status), the most expeditious way to accommodate this important research strategy is to perform multiple tests at once and use the results to triage patients to targeted therapies
  - In-house portfolio
  - www.mycancergenome.org

- One of the most important future challenges is to design tools and obtain proof of concept results on how to combine targeted agents to match the multiple abnormalities that individual cancers have.

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