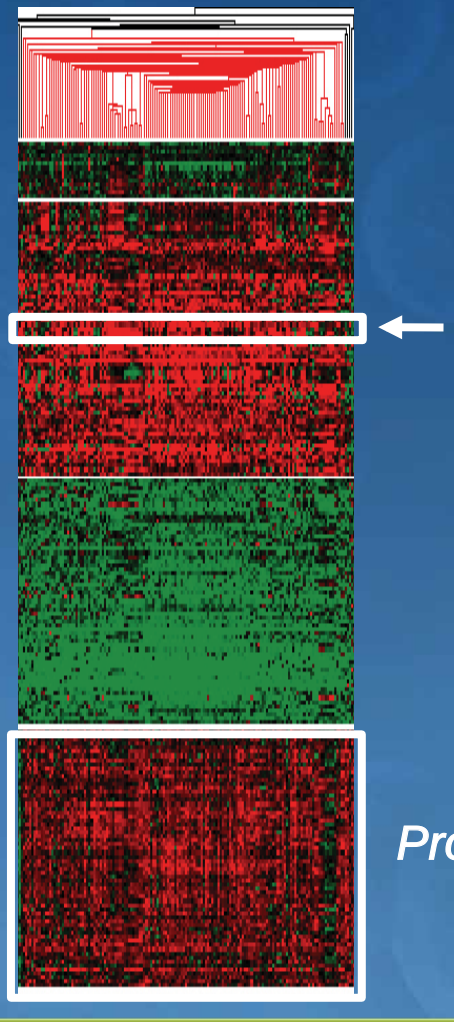
Therapeutic Targets for Triple-Negative Breast Cancer: Focus on Platinums and EGFR Inhibition

Lisa A Carey, MD

Disclosures for Lisa A Carey, MD

No real or apparent conflicts of interest to disclose

Basal-Like Breast Cancer: Biology and Behavior



Proliferation genes

Red = “on”
Green = “off”

- Typically high grade, high expression of proliferation genes
- EGFR is a characteristic of the basal gene cluster
- Short RFS in stage I-III (relapse peak 2-3 y)
- Short PFS in stage IV

Schneider BP et al. *Clin Cancer Res* 2008;14(24):8010-8.

Is Chemosensitivity General or Drug-Specific? (No one knows, there are arguments for both)

BUB1
PLK1
Thymidylate Synthetase = 5-FU
EZH2
DNA Polymerase alpha
Cyclin A2, B2, E1
Tubulin = taxanes, other antitubulins
BRCA1, 2
MCM2, 3, 5, 6, 7, 8, 10
Forkhead Box M1
MAD2
DHFR = methotrexate
MYBL2
Ki-67
PTTG1
Replication Factor C
CENPA, E, F, H
TOP2a = doxorubicin, etoposide
STK6/15
RAD51
FANCA
PCNA
MSH2
Ribonucleotide reductase = HU
CHEK1
CDC1, 2, 7, 8, 20, 25

Chemosensitivity and TNBC

Pathologic complete response (complete tumor eradication) to preoperative anthracycline-taxane-based chemotherapy:

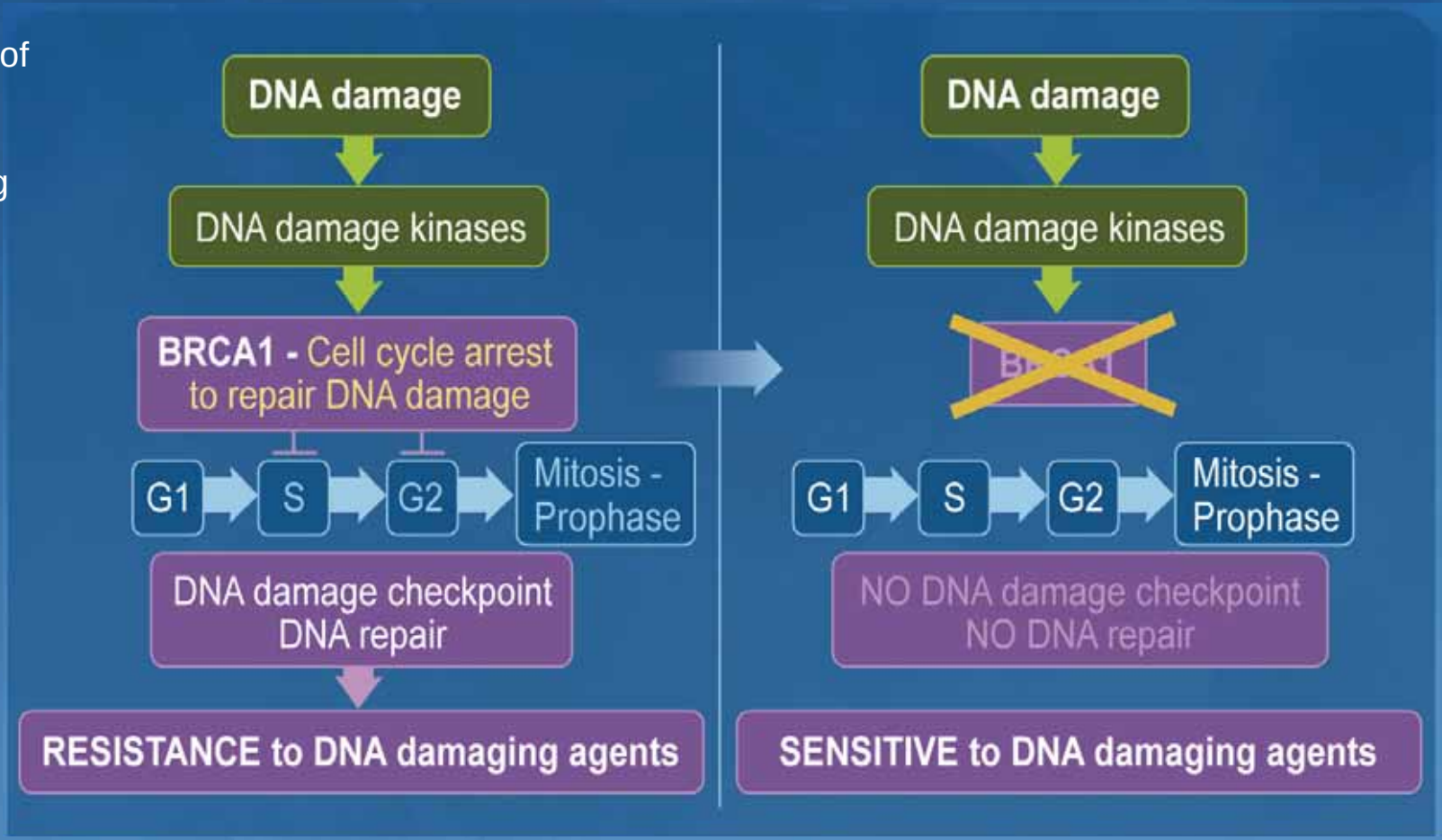
	T-FAC[1] (N = 82)	AC-T[2] (N = 107)
Luminal A/B	7%	7%
Normal-like	0%	NA
HER2+/ER-	45%	36%
Basal-like/triple negative	**45%**	**27%**

- Basal-like/triple negative breast cancer responds to anthracycline-taxane-based chemotherapy.
- Conventional chemotherapy regimens remain standard of care.

[1] Rouzier R et al. *Clin Cancer Res* 2005;11(16):5678-85.
[2] Carey L et al. *Clin Cancer Res* 2007;13(8):2329-34.

Drug-Specific Chemotherapy for TNBC?

- "BRCAness" of TNBC and sensitivity to DNA damaging agents?
- Platinums classic
- Others, e.g. alkylators?



Modified from Kennedy R et al. *J Nat Cancer Inst* 2004;96(22):1659-68.

Adjuvant Choices for TNBC? NCIC-CTG MA.5 Revisited

Biologic subtype	CEF		CMF		
	N	5-year OS	N	5-year OS	*p*-value
Luminal A	62	93%	71	90%	
Luminal NOS	36	94%	26	85%	
Luminal B	61	71%	65	71%	
Luminal B (HER2+)	21	71%	27	44%	<0.001
HER2+/ER-	20	55%	23	30%	
Core Basal	**35**	**51%**	**35**	**71%**	**<0.0001**
TNP Non-Basal	**9**	**65%**	**20**	**63%**	

- Intriguing, although retrospective and small

Cheang M et al. *Proc ASCO* 2009;Abstract 519.

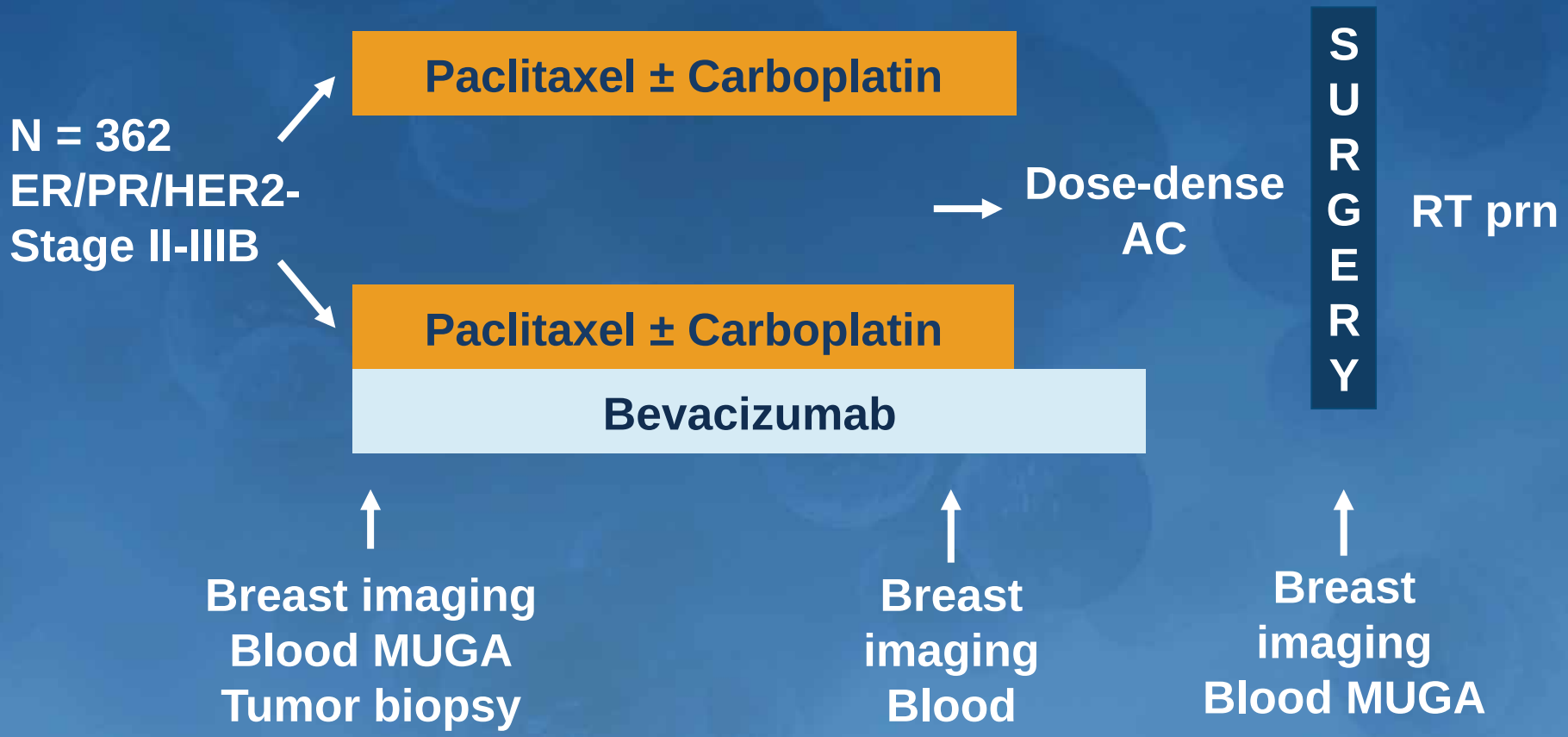
Platinum Sensitivity in BRCA1+/TNBC

Trial	Pop'n	Regimen	N	pCR
Byrski	BRCA1+	Non-platinum	90	14 (16%)
	BRCA1+	CDDP 75mg/m^2 x 4	12	10 (83%)
Silver	Sporadic TNBC	CDDP 75mg/m^2 x 4	28	6 (22%)
	BRCA1+	" "	2	2 (100%)

- Neoadjuvant trials:
  - Retrospective trial suggests exquisite sensitivity in BRCA1+
  - Prospective trial in TNBC less clear
- Metastatic TNBC:
  - BALI-1 control arm cisplatin only – 10% RR

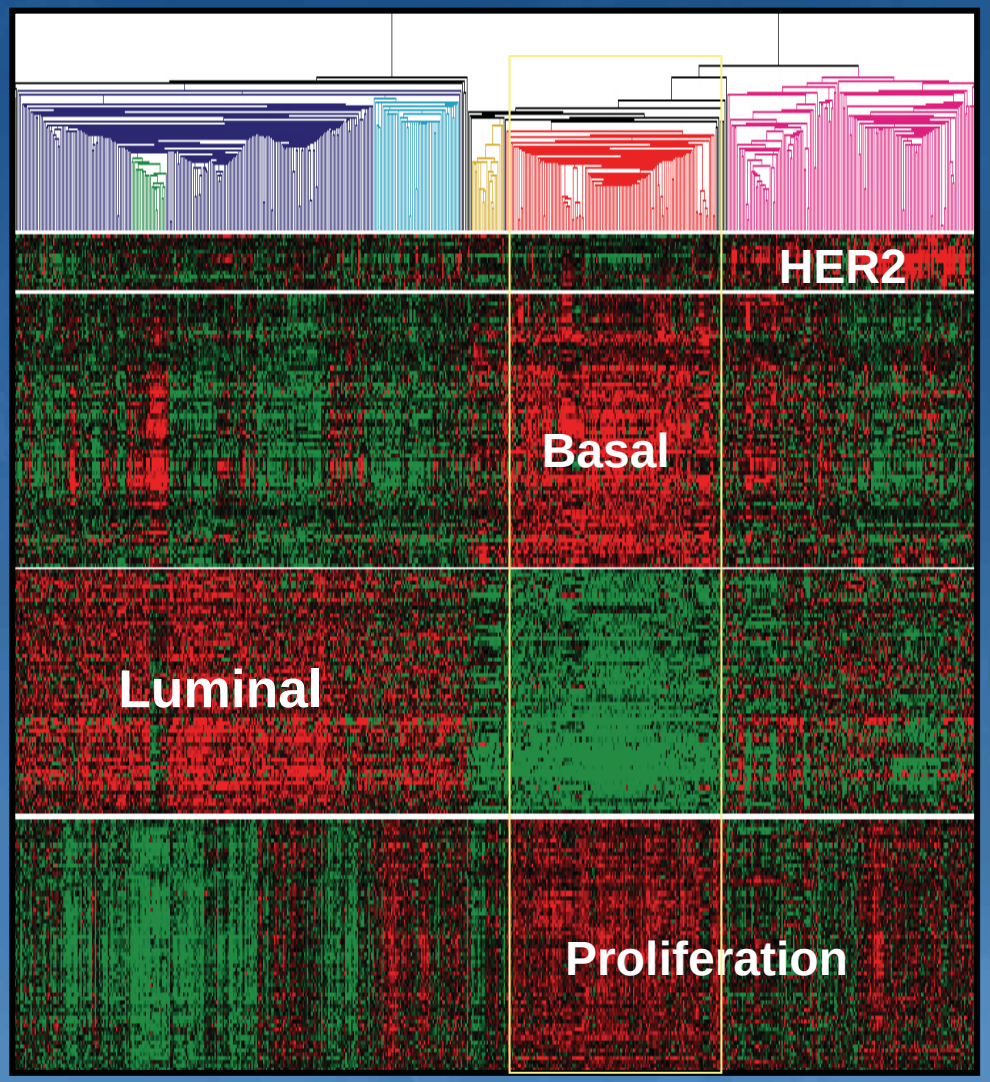
Byrski, *JCO* 2010; Silver *JCO* 2010: Baselga *ESMO* 2010; Isakoff SABCS 2010

Intergroup/CALGB-40603 Triple Negative Neoadjuvant Trial



www.clinicaltrials.gov, December 2010.

EGFR in Basal-Like Breast Cancer



The basal cluster includes CK 5, 17, EGFR, αB crystallin, c-kit, etc expression.

Molecular target?

54%+ by immunostains
Cell lines EGFR dependent

EGFR Inhibition in Stage IV Breast Cancer: US Oncology 225200

	Irinotecan + carboplatin	Irinotecan + carboplatin + cetuximab
Parent trial RR	31%	38%
TNBC RR (N = 62)	30%	49%
TNBC PFS	5.1m	4.7m

- Augmented response rate in TNBC, but no improvement in PFS

O'Shaughnessy J et al. *Proc SABCS* 2007;Abstract 308.

EGFR Inhibition in Triple Negative: TBCRC 001

Largely pretreated stage IV TNBC:

	Cetuximab	Cetuximab + carboplatin
N	31	**71**
Clinical benefit	10%	**31%**
Response rate	6%	**17%**
PFS	1.4 m	**2 m**

- Single agent EGFR – low RR, not pursued
- 16 patients allowed serial biopsy of a metastatic lesion
  → This is how we learn about drug effect and resistance

Carey L et al. *Proc ASCO* 2008;Abstract 1009.

EGFR Inhibition in Triple Negative: BALI-1

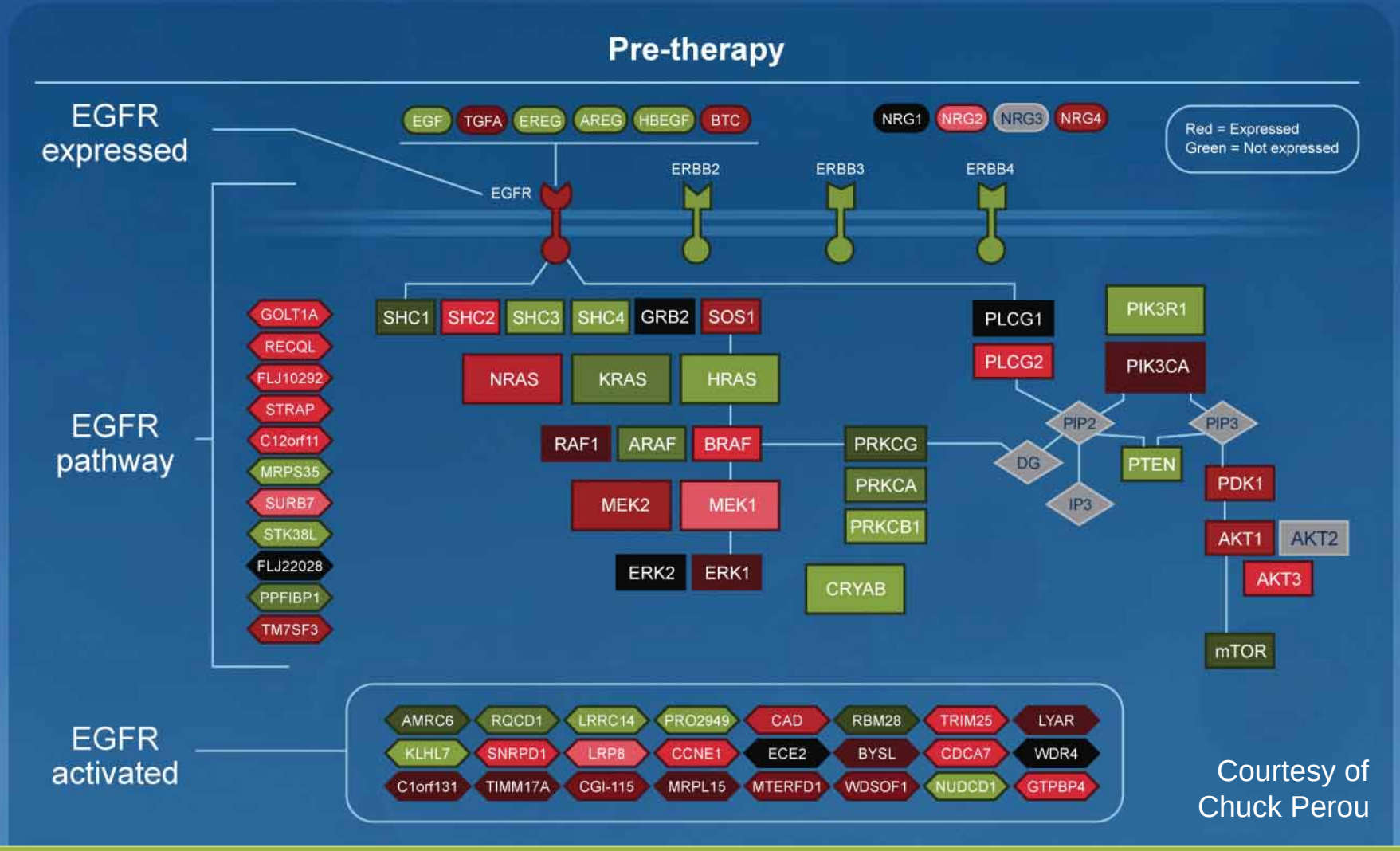
Largely 1st line stage IV:
CDDP 75 mg/m^2 q3wk x 6 cycles ± cetuximab (usual dose/schedule).
Crossover permitted.

	Cisplatin + Cetuximab	Cisplatin (CDDP)
N	115	71
Response Rate (1˚ endpt)	20% (13-28%)	10% (4-21%)
PFS (radiographic)	3.7m (2.8-4.3)	1.5m (1.4-2.8)

- Did not meet RR endpoint (OR 2.9)
- RR doubled, PFS 1.5m → 3.7m
- But poor outcome regardless. Is this active enough?

Baselga J et al. *Proc ESMO* 2010;Abstract 2740.

TBCRC 001: Treatment Effect in Serial Biopsies



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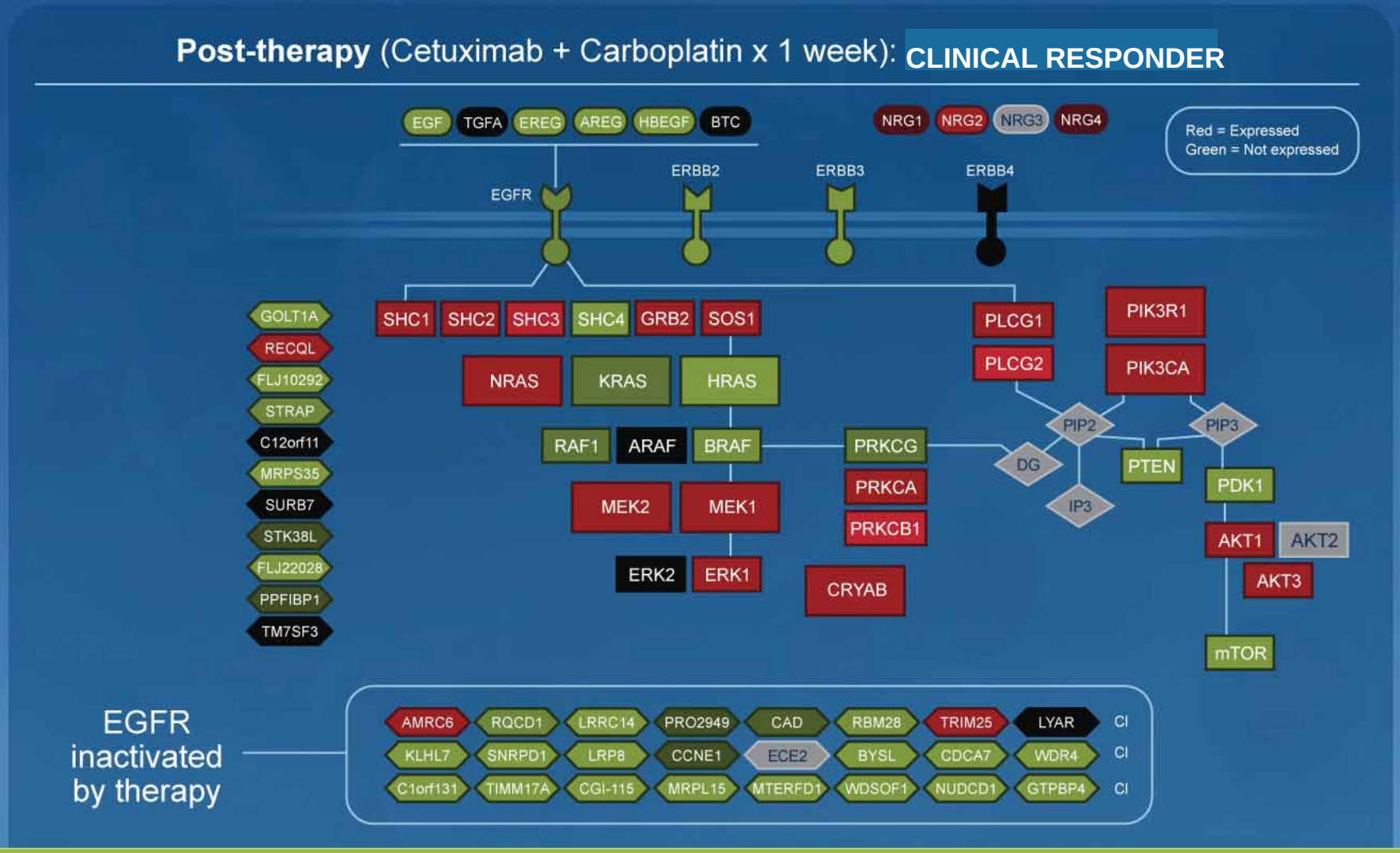
TBCRC 001: Treatment Effect in Serial Biopsies (cont)



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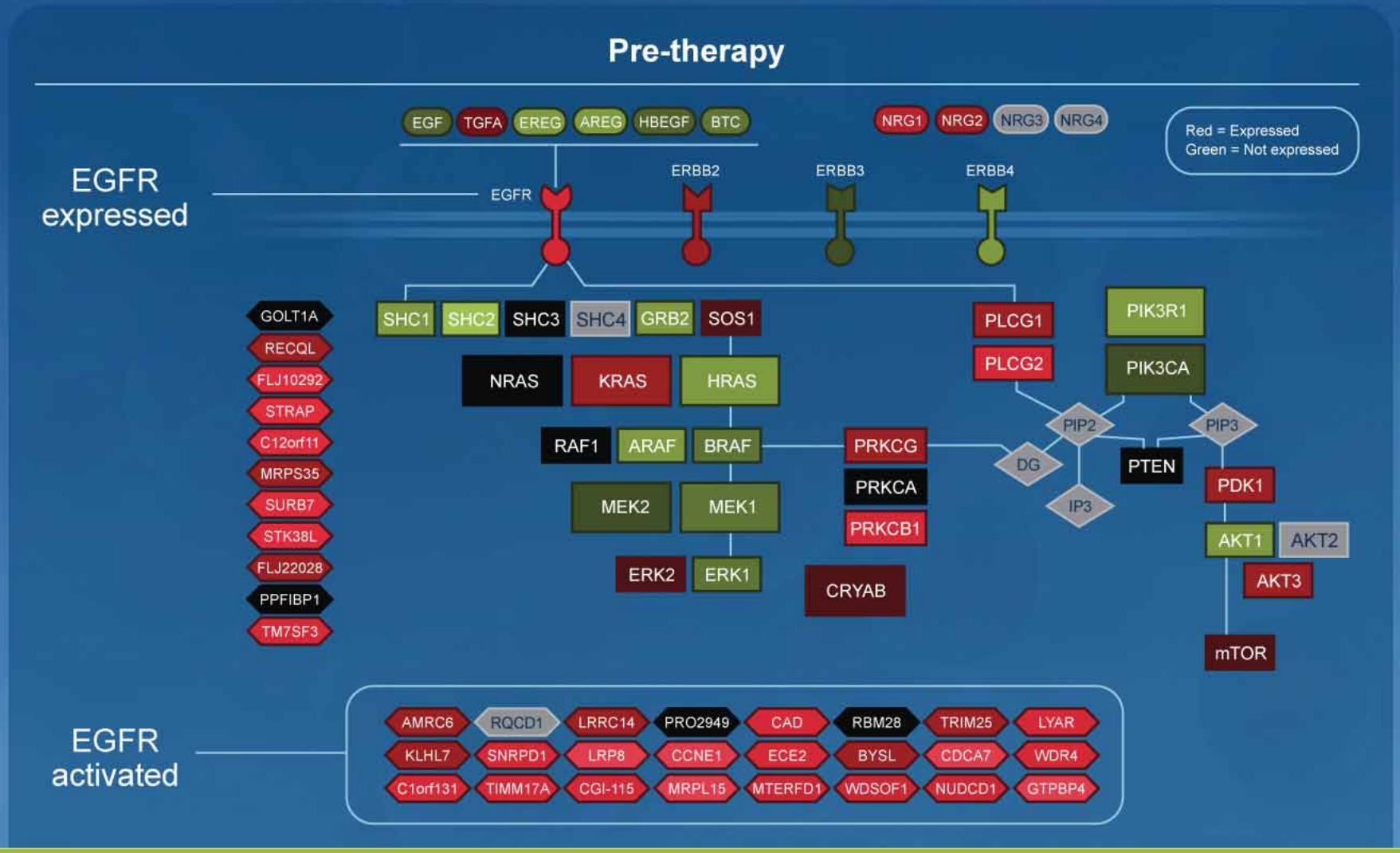
Non-Response in an EGFR-Activated Tumor



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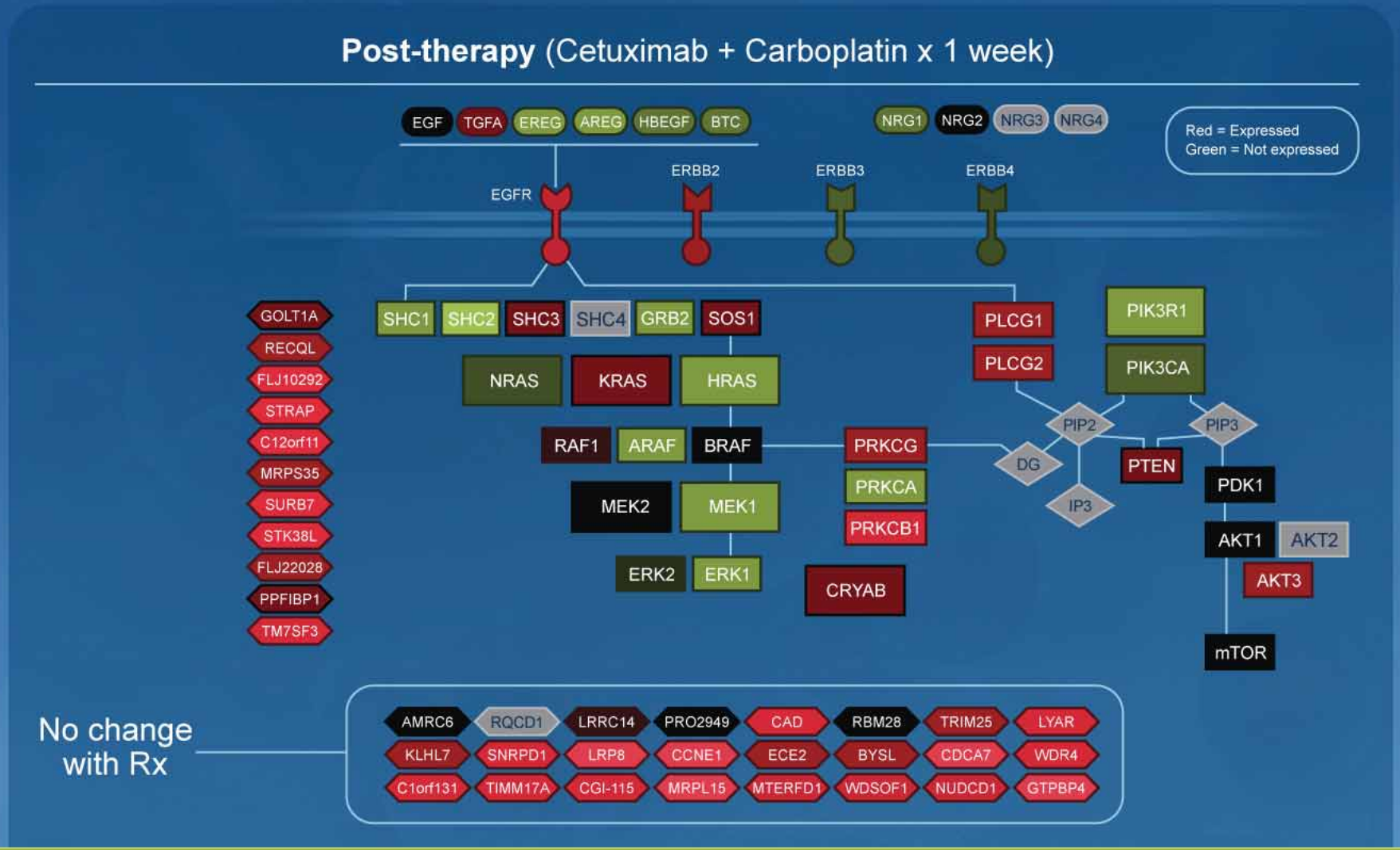
Non-Response in an EGFR-Activated Tumor (cont)



Carey L et al. *Proc ASCO* 2008;Abstract 1009.

Summary

- Triple-negative disease has aggressive behavior
  - High proliferation may make it chemosensitive
  - Duration of response typically short
- Preclinical rationale for DNA damaging cytotoxic agents
  - Validity of approach awaits clinical trials
- EGFR is a natural target in basal-like breast cancer
  - Preclinical data consistent
  - Clinical data – activity but not enough
  - Better selection? Single biologic may not suffice.
- Tissue-based studies are key to solving these riddles!