

Rational development of targeted therapies: ErbB receptors in IBC and potential candidates for chordoma

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DUMC



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TGF α
EGF
EPR
HG-EGF
BTC
AR

NRG/HRG1
NRG/HRG2

NRG1
NRG2
HB-EGF
BTC

ErbB2-ErbB2

ErbB1-ErbB2

ErbB2-ErbB3

ErbB2-ErbB4



ErbB2 homodimers primarily activate MAPK signaling

Activates MAPK and PI3K-Akt proliferation and survival signals

Most potent activator of PI3K-Akt survival signaling

ErbB4 involved in breast differentiation

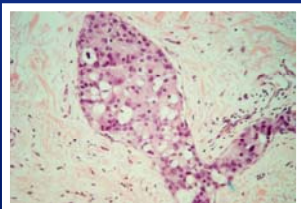


IBC Background

Diagnosis

Clinical: rapidly progressive diffuse erythema; edema >2/3 breast; peau d'orange; induration; tenderness.

Histopathology: AJCC T4d designation of IBC based on 1971 criteria including dermal-lymphatic invasion (DLI); However, DLI occurs in NIBC and IBC can occur without DLI



Prognosis

Most aggressive form of breast cancer

35% with metastatic disease at the time of initial diagnosis

Worse survival compared with NIBC (3 yr survival is 40%)

Demographics

Incidence: 1-6% in U.S. (10% in African Americans); 30% in Tunisia

younger age group (<50 yrs old at diagnosis: 34% versus 24% in IBC and NIBC, respectively)

Tendency towards ErbB2 overexpression (reported frequency 30-58%)

Spector et al. ASCO 2006; Abstract 502



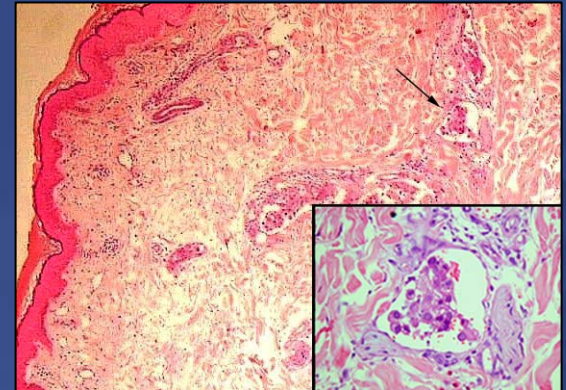
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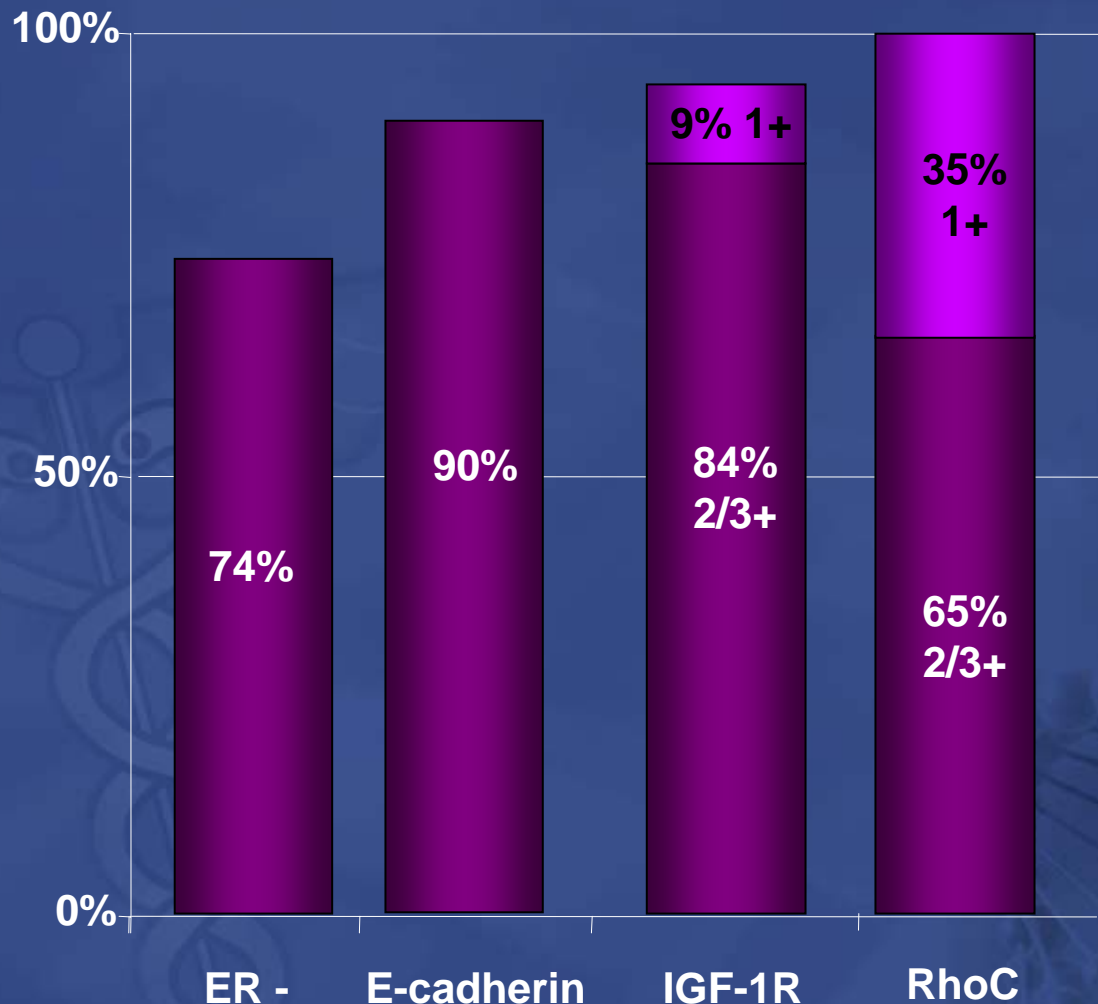
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Molecular Biology

- Features of IBC:
 - High proliferative index
 - ER and PR negative (66%)
 - Mutant p53 (30-60%)
 - ErbB2 overexpression (40-60%)
 - Higher intra-tumor microvessel density (MVD)
 - Additional signaling pathways →
 - E-cadherin (intercellular adhesion protein)
 - MUC1
 - RhoC oncoprotein w/ concomitant upregulation of VEGF
 - Loss of LIBC (*lost in inflammatory breast cancer*) tumor suppressor gene; IGFBPr9



Molecular Profile of Patients on EGF103009 (N=58)



Baseline Characteristics/ Demographics

Median age, years (range)	53 (32-79)
Stage of disease	79% Stage IV 21% Stage IIIB
Median prior chemotherapy regimens (range)	4.5 (0-21)
–Prior anthracycline	98%
–Prior anthracycline/taxane	78%
–Prior anthracycline + taxane or navelbine	86%
–Patients in Cohort A treated with trastuzumab (in countries where trastuzumab is available)	75% (15/20)
Evidence of dermal lymphatic invasion	75%
Sites of enrollment	71% N.America/EU/Israel 29% Tunisia

*based on data from 49 patients; efficacy/safety data from 47 patients





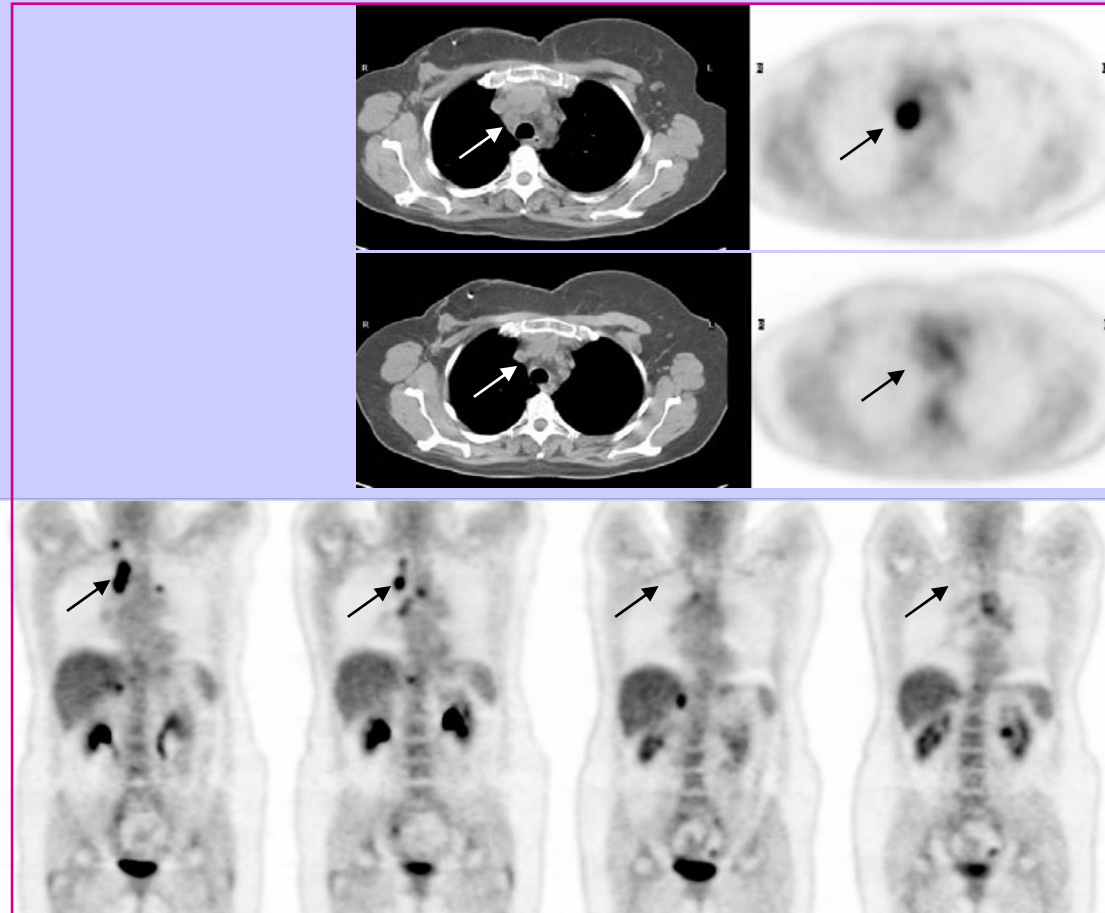
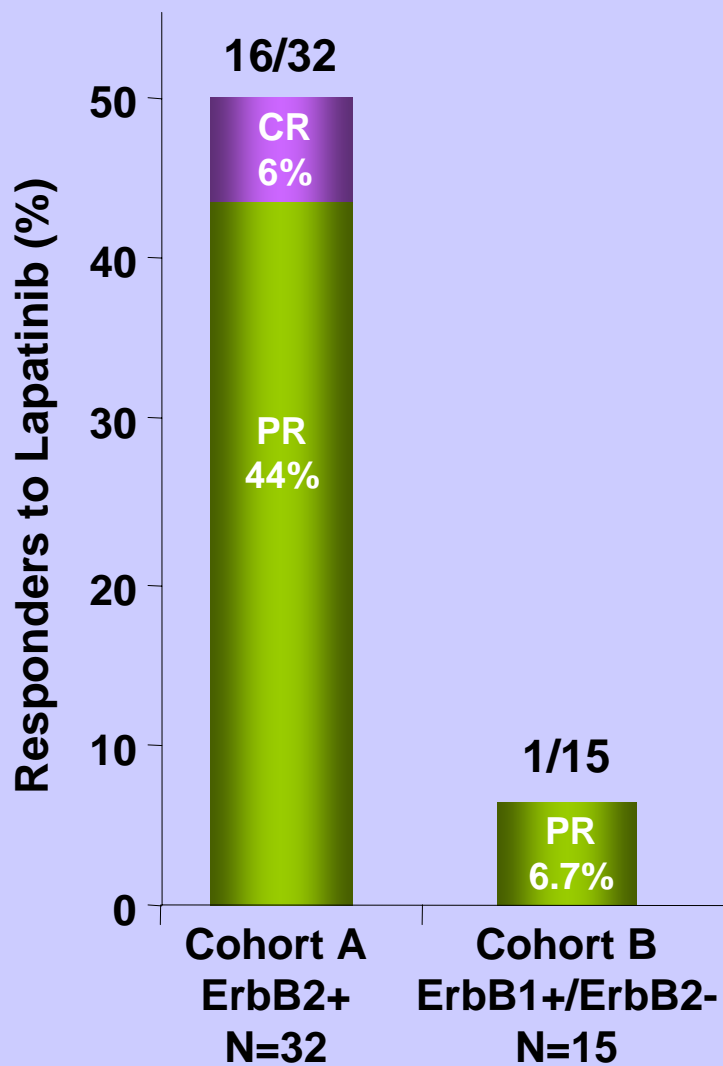
Pre-treatment



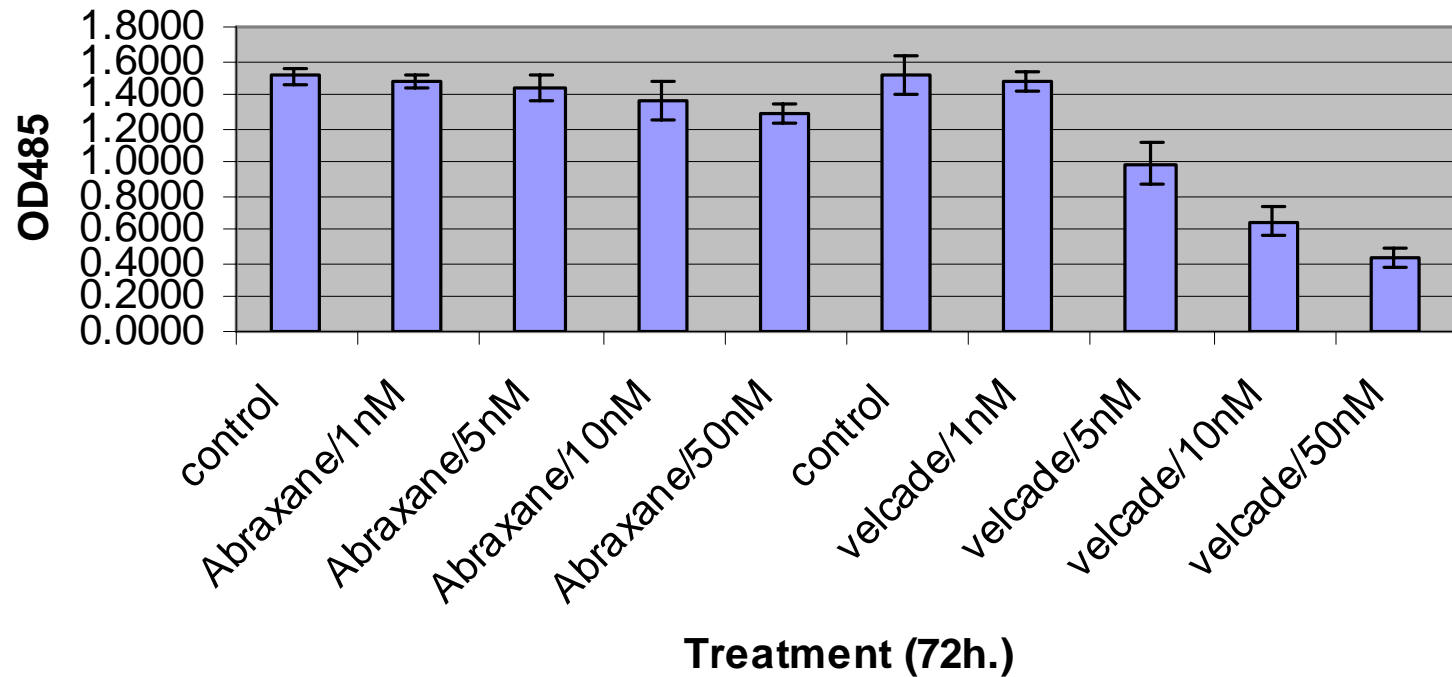
On therapy



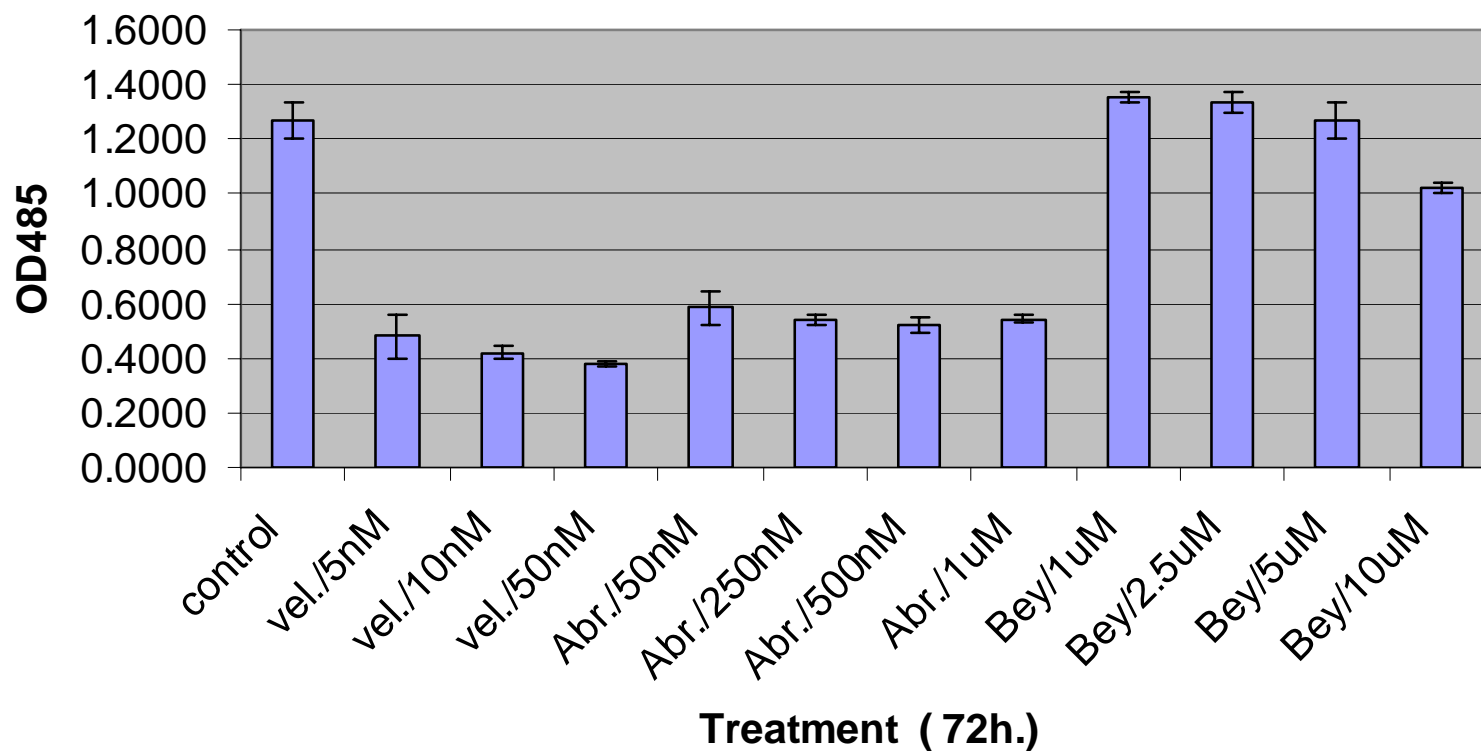
Overall Response Rate to Lapatinib Monotherapy



UCH1 Chordoma Cell Line (041607)

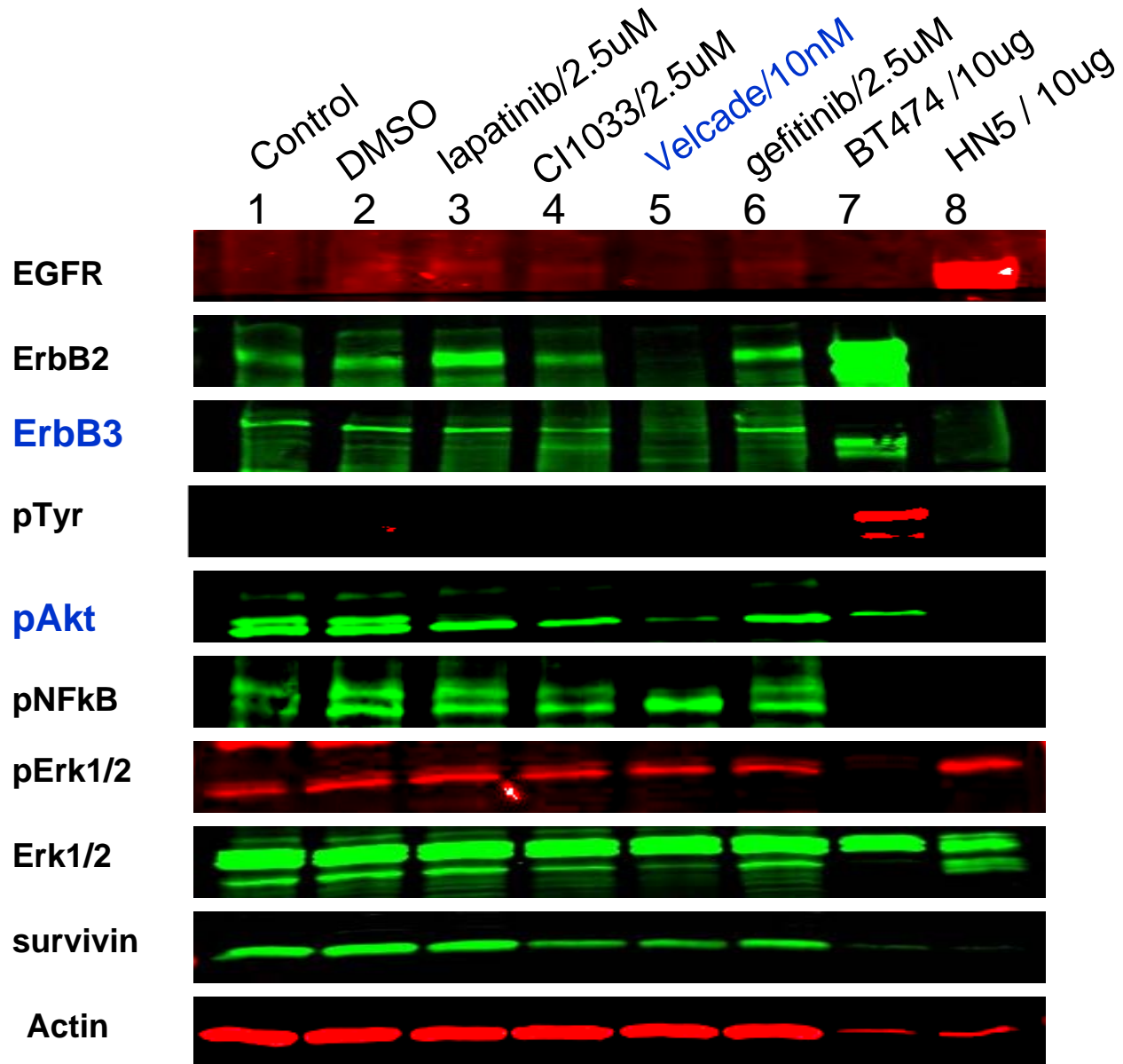


Proliferation assay in CCL3 cells (042707)



UCH-1

021207 WB 50ug/each 72h.



Summary

- Chordoma
 - ErbB receptors are expressed (? functional relevance to growth/survival)
 - PI3K-Akt pathway might represent a good/tractable target
 - Identify upstream regulators of Akt signaling (e.g., RTKs)
 - bortezomib and paclitaxel albumin-bound particles



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