Steps forward in targeted therapy of breast cancer

Phase Ib/II study of BKM120 in combination with trastuzumab

Phase I study of E3810 with expansion in $FGFR1$ amplified breast cancer

SAFIR trial – molecular screening

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Disclosure relevant to discussion

Nicholas Turner

Honoraria

Novartis
AstraZeneca
EOS
Background: PI3K-Akt pathway

PIK3CA mutated in ~30% HER2 amplified cancers

Baselga J The Oncologist 2011
HER2 (ERBB2) amplified breast cancer is dependent on PI3 kinase signalling

RNAi screening, 34 breast cancer cell lines

Brough et al Cancer Discovery 2012
Activation of PI3 kinase pathway induces resistance to HER2 targeting

Loss of PTEN

Mutation of PIK3CA

Eichhorn et al Cancer Res 2008
Background: PI3K-Akt pathway

PIK3CA mutated in ~30% HER2 amplified cancers
Phase I/II Study of Trastuzumab in Combination With Everolimus (RAD001) in Patients With HER2-Overexpressing Metastatic Breast Cancer Who Progressed on Trastuzumab-Based Therapy

Phuong K. Morrow, Gerburg M. Wulf, Joe Enssor, Daniel J. Booser, Julia A. Moore, Peter R. Flores, Yan Xiong, Siyuan Zhang, Ian E. Krop, Eric P. Winer, David W. Kindelberger, Jeanna Coviello, Aysegul A. Sahin, Rodolfo Nuñez, Gabriel N. Hortobagyi, Dihua Yu, and Francisco J. Esteva

47 patients resistant to trastuzumab

Treated with traztuzumab + mTOR inhibitors everolimus

15% (7/47) partial response
Ph Ib/II study of BKM120 plus trastuzumab in patients with trastuzumab-resistant HER2+ advanced breast cancer

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Trial summary

BKM120     Pan-PI3 kinase inhibitor in combination with trastuzumab

Trastuzumab resistant pre-treated disease
    median 2.5 prior lines of HER2 directed therapy

50 Patients (with another 3 who never received BKM120)

Combination generally well tolerated
Clinical efficacy of BKM120 plus trastuzumab

40% Progression as best response

Response rate 10%

Median exposure to drug 9 weeks
Benefit appears to be only a relatively small proportion of patients – but in those patients an impressive level of activity

Strongly suggests biomarkers to guide future development

Full analysis of PIK3CA mutations required
BKM120 and trastuzumab – who benefits?

Response rate comparable with that reported for everolimus-trastuzumab

Responders on BKM120 - trastuzumab - same subset (or not) that responds to everolimus-trastuzumab?

Bolero 1 and 3 pivotal trials awaiting reporting

HER2 amplified cell lines are specifically reliant on the alpha catalytic subunit (PIK3CA)

Could higher responses be achieved with alpha specific PI3K inhibitors?
Activation of FGFR signalling in cancer

Ligand independent signalling  Ligand dependent signalling  Angiogenesis

FGFR

Activating mutation  Translocation  Gene amplification  Altered splicing

Aberrant FGF

Turner and Grose Nat Rev Cancer 2009
**FGFR1 amplification in luminal B type breast cancer**

Amplification in Luminal B subtype

- Basal-like
- HER2+/ER-
- Luminal A
- Luminal B
- Normal Breast-like

Disease free survival

- No FGFR1 Amplification (n=280)
- FGFR1 Amplified (n=27)

*Turner et al Cancer Res 2010*

*El-Sheikh et al BCR 2007*
FGFR1 is amplified in squamous lung cancer

Weiss et al Science Trans Med 2011
Significant antitumor activity of E-3810, a novel FGFR and VEGFR inhibitor, in patients with FGFR1 amplified breast cancer

**Breast Cancer Patients**

**Best Overall Response**

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<thead>
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<th>FGF+</th>
<th>Antiangiogenic sensitive</th>
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<tbody>
<tr>
<td></td>
<td>Evaluable</td>
<td>PR</td>
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<td>Breast cancer</td>
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<tr>
<td>ER+/PR+, HER2-</td>
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<td>TPN</td>
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**Response rate**

*FGFR1* amplified 4/9 patients

11q amplified 3/3 patients

**Estimate of Median PFS ~5 months**
Discussion points

EOS3810 - highly efficacious

Tolerability profile

Is this just a simple story of oncogene addiction?
# Expansion Cohorts - Overall Safety

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<tr>
<th>Off for</th>
<th>FGF+</th>
<th>Antiangiogenic Sensitive</th>
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<tbody>
<tr>
<td>20 mg (n=3)</td>
<td>15 mg (n=15)</td>
<td>20 mg (n=10)</td>
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- **Reasons for interruption/dose decrease:** GI toxicity and asthenia (14 pts), proteinuria (10 pts), HTN (8 pts).
- **Other significant events:** LVEF decrease (2 pts), asymptomatic amylase-lipase increase (2 pts)

At 15mg Dose 47% (18/38) patients dose decrease in first 2 cycles

Side effects of VEGFR and multi-kinase inhibition

Further work on identifying a chronically tolerable dose/schedule
Why do 11q amplified patients respond?

11q amplicon CCND1, FGF3, FGF4, FGF19

3/3 patients respond to E-3810

But FGFs not frequently expressed from amplicon?

TCGA RNA Seq data
Phase II study of TKI258

VEGFR – FGFR inhibitor

Best % change from baseline

-100
-80
-60
-40
-20
0
20
40
60
80
100

FGF3 amplified
FGFR1 and/or FGFR2 amplified only
FGF pathway unamplified

Andre et al ASCO 2011
Target growth factor redundancy in angiogenesis

Bevacizumab

VEGF

FGF2, PDGFα, ANG, PLGF, SDF1α...

VEGFR

VEGFR

TKI

ERK

Angiogenesis

ERK

Angiogenesis
Target growth factor redundancy in angiogenesis

VEGFR

VEGF

FGFRs

FGF2

E3810

ERK

Angiogenesis
E3810 as an anti-angiogenic inhibitor

Thyroid cancers

Max percent change from baseline

FGF+ BC patients

PR
Is this just a simple story of oncogene addiction?

FGF2 is highly expressed in ER positive breast cancer stroma

Smith et al Ann Oncol 1999

FGF2 is expressed in an autocrine fashion by activated endothelium

Schweigerer et al Nature 1987

Is this a combined effect on angiogenesis and oncogene?
ARRAY CGH AND DNA SEQUENCING TO PERSONALIZE THERAPY FOR METASTATIC BREAST CANCER: A PROSPECTIVE NATIONAL TRIAL (UNICANCER SAFIR-01)

Personalized Medicine: To identify and target the right molecular pathway for each patient

Targeted therapy according to the genomic profile

Biopsy metastases

Whole genome profiling

Identification of the Genomic Alteration