Open Clinical Trials: What’s Out There Now
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Acquired Capabilities of Cancer

- Self-sufficiency in growth signals
- Insensitivity to anti-growth signals
- Evading apoptosis
- Sustained angiogenesis
- Tissue invasion & metastasis
- Limitless replicative potential

Hanahan and Weinberg, 2000
Clinical Trials

- When should I consider a clinical trial?
- How do I find the right clinical trial?
Early Local Therapy in Metastatic Breast Cancer

- Randomized, phase III trial of early local therapy for the intact, primary tumor in patients with metastatic breast cancer

- Eligibility:
  - Stage IV disease with intact primary
  - Patients are candidates for complete resection followed by radiation (if RT indicated)

ClinicalTrials.gov Identifier: NCT01242800
Early Local Therapy in Metastatic Breast Cancer

- Patients must have completed at least 16 weeks of optimal systemic therapy
- Patients must not have had disease progression since the start of systemic therapy
- Patients may register at any time from the time of diagnosis of stage IV breast cancer to the time when a maximum of 30 weeks of induction systemic therapy has been completed

ClinicalTrials.gov Identifier:NCT0124280000
Targeting Multiple Pathways in Metastatic Breast Cancer
By targeting both the survival and proliferation pathways, there is a synergistic effect on tumor cell death.

G1/S checkpoint alterations in breast cancer

Lapenna and Giordano, Nature Reviews, 2009
Phase 2 Design

**Part 1**

- **Randomization**
- ER+, HER2- BC
- PD 0332991 125 mg QD + Letrozole 2.5 mg QD
- Letrozole 2.5 mg QD

**Part 2**

- **Randomization**
- ER+, HER2- BC with CCND1 amp and/or loss of p16
- PD 0332991 125 mg QD + Letrozole 2.5 mg QD
- Letrozole 2.5 mg QD

**Stratification Factors**
- Disease Site (Visceral vs Bone only vs Other)
- Disease-Free Interval (>12 vs ≤12 mo from end of adjuvant to recurrence or de novo advanced disease)

N = 66

N = 99

* Schedule 3/1.
Conclusions

• The combination of PD 0332991 and letrozole compared with letrozole alone continues to show statistically significant improvement in median PFS in patients with ER+/HER2– breast cancer

• These results confirm the preclinical observations made with PD 0332991 in breast cancer models

• The combination is generally well tolerated, with uncomplicated neutropenia as the most frequent adverse event

• A randomized phase 3 study is planned to start in 2013
PD-0332991: An Oral CDK 4/6 inhibitor

- Randomized, phase III trial of PD-0332991 plus letrozole versus placebo plus letrozole for postmenopausal women with ER+, HER2- breast cancer who have not received prior therapy for advanced disease

ClinicalTrials.gov Identifier:NCT01740427
PD-0332991: Oral CDK 4/6 inhibitor

• Eligibility:
  – Loco/regionally recurrent or metastatic disease
  – Confirmed diagnosis of ER positive breast cancer
  – Postmenopausal
  – Measurable disease or bone-only disease
  – ECOG 0-2
  – Adequate organ and marrow function
  – Excludes HER2 positive disease
  – Excludes prior (neo)adjuvant treatment with letrozole or anastrozole with disease-free interval \( \leq \) 12 months from completion of treatment
  – Excludes prior treatment with any CDK 4/6 inhibitor

ClinicalTrials.gov Identifier:NCT01740427
UPCC 02111: A Phase I Trial of PD0332991 and Paclitaxel in Patients with Rb-Expressing Advanced Breast Cancer

ClinicalTrials.gov Identifier:NCT01320592
UPCC 02111: A Phase I Trial of PD0332991 and Paclitaxel in Patients with Rb-Expressing Advanced Breast Cancer

• Eligibility:
  – Must have histologically confirmed metastatic breast cancer
  – Any ER, PR or HER2 status is allowed
  – Tumor must express the Retinoblastoma (Rb) protein
  – Patients must have received < 2 prior cytotoxic regimens for metastatic breast cancer, not including cytotoxic regimens in the adjuvant setting
  – Prior taxane therapy in the adjuvant or metastatic setting is allowed
  – Patients with stable, treated CNS disease are eligible
  – Excludes patients with Diabetes Mellitus, Hypertension

ClinicalTrials.gov Identifier:NCT01320592
BKM120: A PI3K Inhibitor
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- BELLE-2: Phase III Study of BKM120/Placebo With Fulvestrant in Postmenopausal Patients With Hormone Receptor Positive HER2-negative Locally Advanced or Metastatic Breast Cancer Refractory to Aromatase Inhibitor [ClinicalTrials.gov Identifier: NCT01610284]
- BELLE-3: A Phase III Study of BKM120 With Fulvestrant in Patients With HR+, HER2-, AI Treated, Locally Advanced or Metastatic Breast Cancer Who Progressed on or After mTORi [ClinicalTrials.gov Identifier: NCT01633060]
- BELLE-4: A Randomized, Double-blind, Placebo Controlled, Phase II Study of BKM120 Plus Paclitaxel in Patients With HER2 Negative Inoperable Locally Advanced or Metastatic Breast Cancer, With or Without PI3K Pathway Activation [NCT01572727]
BELLE-2

**Inclusion Criteria:**
- Postmenopausal, locally advanced or metastatic breast cancer
- HER2-negative and hormone receptor-positive status
- A tumor sample must be shipped to a central designated laboratory for identification of biomarkers (PI3K activation status)
- Progression or recurrence of breast cancer while on or after aromatase inhibitor treatment
- Measurable disease or non-measurable disease bone lesions in the absence of measurable disease as per RECIST 1.1
- Adequate bone marrow and organ function defined by laboratory values

**Exclusion Criteria:**
- Previous treatment with PI3K inhibitors, AKT inhibitors, mTOR inhibitor or fulvestrant
- More than one prior chemotherapy line for metastatic disease
- Symptomatic brain metastases
BELLE-3

• Inclusion Criteria:
  – Postmenopausal women, locally advanced or metastatic
  – HER2 negative disease, and a known positive hormone receptor status
  – A tumor sample must be shipped to a central lab for identification of biomarkers (PI3K activation status) before randomization
  – Prior treatment with Ais
  – Evidence of progression to the combination of mTORi and endocrine therapy given as the last therapy prior to study entry
  – Adequate bone marrow and organ function

• Exclusion Criteria:
  – More than 1 prior chemotherapy given for locally advanced or metastatic disease
  – Previous treatment with PI3K inhibitors, AKT inhibitors or fulvestrant
  – Symptomatic CNS metastases
BKM120: A PI3K Inhibitor

- A Phase Ib/II, Open Label, Multi-center Study Evaluating the Safety and Efficacy of BKM120 in Combination With Trastuzumab in Patients With Relapsing HER2 Overexpressing Breast Cancer Who Have Previously Progressed on Trastuzumab [ClinicalTrials.gov Identifier: NCT01132664]

- A Phase II Trial of BKM120 in Patients With Triple Negative Metastatic Breast Cancer [ClinicalTrials.gov Identifier: NCT01629615]
Hedgehog Signaling Pathway

- LDE225 and LEQ506
- Smo
- Hh
- Ptc
- Sufu
- Gli

INCREASED APOPTOSIS
DECREASED PROLIFERATION
Dual-Targeted Therapy

- A Phase Ib, Multi-center, Open Label, Dose Escalation Study of Oral LDE225 in Combination With BKM 120 in Patients With Advanced Solid Tumors [ClinicalTrials.gov Identifier: NCT01576666]
A Phase Ib, Multi-center, Open Label, Dose Escalation Study of Oral LDE225 in Combination With BKM 120 in Patients With Advanced Solid Tumors

• Eligibility:
  – Male or female adult patients (> 18 years)
  – Patients with histologically/cytologically confirmed diagnosis of the following advanced tumors that have progressed despite standard therapy or that have no available established treatments: metastatic breast cancer, pancreatic adenocarcinoma, metastatic CRC or recurrent GBM will be included.
  – Provision of an archival tumor sample to a central designated laboratory for molecular profiling. The tumor material submitted for these analyses may have been obtained at any time during the course of the patient's disease.

ClinicalTrials.gov Identifier: NCT01576666
Growth factor receptors

GDC-0980
PI3K
PIP2
PIP3
PTEN
PDK1
mTORC2
mTORC1
S6K
S6
Protein synthesis and growth

Proliferation
Survival
Other Studies with PI3K Inhibitors

• A Phase II, Double-Blind, Placebo Controlled, Randomized Study of GDC-0941 or GDC-0980 With Fulvestrant Versus Fulvestrant in Advanced or Metastatic Breast Cancer in Patients Resistant to Aromatase Inhibitor Therapy [ClinicalTrials.gov Identifier:NCT01437566]

• A Phase II, Randomized Study of Paclitaxel With GDC-0941 Versus Paclitaxel With Placebo in Patients With Locally Recurrent or Metastatic Breast Cancer [ClinicalTrials.gov Identifier:NCT01740336]
Afatinib (BIBW 2992) in Metastatic Breast Cancer

- **LUX-Breast 1**: Phase III trial of vinorelbine plus afatinib vs vinorelbine plus Herceptin in patients with metastatic breast cancer after progression on Herceptin treatment.
- **LUX-Breast 2**: An open label, phase II trial of afatinib in patients with metastatic HER2-overexpressing breast cancer progressing after HER2-targeted treatment in the neoadjuvant and/or adjuvant treatment setting.
Afatinib (BIBW 2992) in Metastatic Breast Cancer

• **Inclusion criteria:**
  – Histologically confirmed diagnosis of HER2-overexpression breast cancer
  – Must have progressed on one prior trastuzumab treatment
  – No more than one prior trastuzumab based therapy regimen (either adjuvant or first-line)
  – Must have received anthracycline and/or taxane based chemotherapy for adjuvant treatment of breast cancer or first-line treatment of metastatic breast cancer
  – Must have (archived) tumor tissue sample available for central re-assessment of HER2-status
  – At least one measurable lesion according to RECIST 1.1
  – ECOG score of 0 or 1

• **Exclusion criteria:**
  – Prior treatment with EGFR/HER2-targeted small molecules or antibodies other than trastuzumab
  – Prior treatment with vinorelbine
  – Known pre-existing interstitial lung disease
  – Active brain metastases

*ClinicalTrials.gov Identifier:NCT01125566*
Ruxolitinib: JAK Inhibition
Ruxolitinib: JAK Inhibition

• A phase II trial of the JAK inhibitor, ruxolitinib, in combination with exemestane for patients with ER+ advanced breast cancer
  – ClinicalTrials.gov Identifier: NCT01594216
A phase II trial of the JAK inhibitor ruxolitinib in combination with exemestane for patients with ER+ advanced breast cancer

- **Inclusion Criteria:**
  - Histologically-confirmed metastatic breast cancer
  - Estrogen-receptor positivity on either the primary breast tumor or a metastatic biopsy
  - Postmenopausal status
  - Prior therapy for the current malignancy: Patient must have 1) relapsed within 2 years of completing adjuvant hormonal therapy with a non-steroidal aromatase inhibitor, OR 2) progressed on a non-steroidal aromatase inhibitor in the metastatic setting. There is no limit to prior chemotherapy or hormonal regimens for this malignancy

*ClinicalTrials.gov Identifier: NCT01594216*
HER3 Inhibitor: LJM716

• Phase 1 study of LJM716 Combined with trastuzumab in patients with HER2 over-expressing metastatic breast cancer

ClinicalTrials.gov Identifier: NCT01602406
Phase 1 study of LJM716 Combined with trastuzumab in patients with HER2 over-expressing metastatic breast cancer

• **Inclusion Criteria:**
  – Patients with confirmed HER-2 positive, metastatic or non-operable locally advanced breast or gastric cancer
  – Metastatic breast cancer patients must have received a minimum of 1 and a maximum of 3 prior anti HER2 based regimens with documented progression on the most recent regimen which must contain trastuzumab or lapatinib
  – Patients must have at least one prior trastuzumab-containing regimen

• **Exclusion Criteria:**
  – Patients with Central Nervous System (CNS) metastasis which are: symptomatic or require treatment for symptom control and/or growing
  – Prior treatment with any anti-HER3 (Human Epidermal growth factor Receptor 3) treatment
  – Impaired cardiac function

*ClinicalTrials.gov Identifier:NCT01602406*
Chaperones stabilize client proteins; chaperone inhibitors lead to client protein degradation

Hsp90 binds to client → Activated client; cell survival, proliferation

Ganetespib prevents Hsp90 binding to client → Inactive client, degraded through proteasome

ALK, AKT, BCR-ABL, BRAF, CDK4, CHK1, EGFR, FLT3, HER2, HIF1a, KIT, MET, PDGFRα, CRAF, SRC, VEGFR, AR, ER ...

Inactive client, degraded through proteasome
Hsp90 Inhibitor

• An Open Label Multicenter Phase 2 Window of Opportunity Study Evaluating Ganetespib (STA-9090) Monotherapy in Women With Previously Untreated Metastatic HER2 Positive or Triple Negative Breast Cancer
  – Pathologically confirmed diagnosis of invasive breast cancer
  – Documented HER2 and hormonal receptor status per protocol.
  – ECOG Performance status 0-1
  – Measurable disease per RECIST (1.1)

ClinicalTrials.gov Identifier NCT0167745