Disruptive approaches to cancer therapy

Linda Vahdat
MIT Sloan EMBA 2014
Definitions:

• Troublesome, unruly, disorderly or undisciplined

• Innovative and groundbreaking
Cancer is complicated

Bob Weinberg’s “Hallmarks of Cancer”

Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge,
Targeted agents

- EGFR inhibitors
- Cyclin-dependent kinase inhibitors
- Immune activating anti-CTLA4 mAb
- Telomerase Inhibitors
- Selective anti-inflammatory drugs
- Inhibitors of VEGF signaling
- Inhibitors of HGF/c-Met

- Proapoptotic BH3 mimetics
- Aerobic glycolysis inhibitors
- Sustaining proliferative signaling
- Evading growth suppressors
- Deregulating cellular energetics
- Resisting cell death
- Enabling replicative immortality
- Avoiding immune destruction
- Tumor-promoting inflammation
- Genomic instability & mutation
- Inducing angiogenesis
- Activating invasion & metastasis

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Hot topic 2015

Checkpoint inhibitors
Checkpoint Inhibitors

PD-1 Pathway and Immune Surveillance

- PD-1 is expressed primarily on activated T cells\(^1\)
- Binding of PD-1 to its ligands PD-L1 and PD-L2 impairs T-cell function\(^1\)
- PD-L1 is expressed on tumor cells and macrophages\(^2\)
- \textbf{Tumors can co-opt the PD-1 pathway to evade immune surveillance}\(^2\)

Plenary talk on immuno-oncology drugs in metastatic melanoma

Melanoma patients

- Ipilumumab
- Nivolumab
- Ipilumumab + Nivolumab

<table>
<thead>
<tr>
<th>Drug</th>
<th>AVG time kept cancer under control (PFS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilumumab (Ipi)</td>
<td>2.9 months</td>
</tr>
<tr>
<td>Nivolumab (Nivo)</td>
<td>6.9 months</td>
</tr>
<tr>
<td>Ipi + Nivo</td>
<td>11.9 months</td>
</tr>
</tbody>
</table>

Wolchuk ASCO 2015
# Regimen Cost (80 kg patient)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cost of Nivolumab</th>
<th>Cost of Ipilimumab</th>
<th>Cost of Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo+ Ipi for 11.5 m</td>
<td>$144,408</td>
<td>$151,158</td>
<td>$295,566</td>
</tr>
<tr>
<td>Nivo for 6.9 m</td>
<td>$103,220</td>
<td>$0</td>
<td>$103,220</td>
</tr>
<tr>
<td>Ipilimumab for 2.9 m</td>
<td>$0</td>
<td>$158,252</td>
<td>$158,252</td>
</tr>
</tbody>
</table>
A thought experiment:

- 1,658,370 expected new cases of cancer in 2015 in the U.S., resulting in 589,430 deaths.  
  (CA Cancer J Clin 2015;65:5-29)

- Assume:
  - all deaths are ultimately due to metastatic disease
  - $295,000 worth of drugs given to each metastatic patient

- 589,430 patients/year x $295,000/patient = $173,881,850,000

$174 billion, just for drugs to treat patients with metastatic disease, for the first year only
Value $\neq$ Benefit

Value $\approx$ Benefit

Cost + Toxicity

Probably as *disruptive* a concept as checkpoint inhibitors in as a therapeutic strategy in cancer

Presented By Leonard Saltz at 2015 ASCO Annual Meeting
checkpoint inhibitors

• When they work, they work great
• Efficacy in: refractory Hodgkin's Disease and other Solid tumors including:
  – Melanoma
  – Bladder cancer
  – Lung cancer
  – Other GI tumors
  – Triple negative breast cancer
Immuno oncology is disruptive

• **Troublesome**, unruly, disorderly or undisciplined
• **Innovative** and **groundbreaking**
Research

Strategies to target the tumor microenvironment

Is this disruptive?
Definition:

- Cellular environment in which the tumor exists including surrounding blood vessels, immune cells, fibroblasts, signaling molecules and the extracellular matrix\(^1\)

\(^1\) Wikipedia, Picture: Journal of Cell Science 2012, 125, 5591–5596
Current strategy to target tumors

Target clonal abnormalities
Proposed strategy by WCMC group to target tumors

Primary tumor

- Normal cell
- Founder clone
- Subclones with individual genotypes

Pull out the infrastructure needed to spread
Pulling out infrastructure is like “having no gas in the tank” (or electricity in the battery)

Biotech CEO
Altering the Tumor Microenvironment: A Phase II Study of Copper-depletion using Tetrathiomolybdate in Patients with Breast Cancer at High Risk for Recurrence

E Nackos, N Kornhauser, A Willis, M Ward, T Cigler, A Moore, E Andreopoulou, N Chan, V Fitzpatrick, M Cobham, S Schneider, A Wiener, JD Warren, A Rubinchik, S Lee, M Lane, V Mittal, Linda Vahdat
Breast cancer relapse and metastasis

- Most common cancer in women worldwide \(^1\)
- Twenty to 50% relapse risk in early-stage breast cancer patients \(^2\)
- Metastasis responsible for 90% of breast cancer deaths \(^1\)

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Research question

Why can a breast cancer tumor be dormant and occult for years and then recur?
Models of tumor progression

In preclinical models:
- Contribution of BM derived cells to tumor neovasculature\(^1\)
- VEGFR1\(^+\) HPCs bookmark metastases (pre-metastatic niche)\(^2\)
- VEGFR2\(^+\) EPCs control the angiogenic switch in mouse lung metastases\(^3\)

In patients with breast cancer:
- VEGFR2\(^+\) EPCs, VEGFR1\(^+\) HPCs in breast cancer patients\(^4\):
  - Higher level with increasing stage
  - Quantitative change associated with response to therapy

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\(^1\) Lyden et al. Nat Med. 2001 Nov;7(11):1194-201;
\(^2\) Kaplan et al. Nature. 2005 Dec 8;438(7069):820-7;
\(^4\) Naik et al, Breast Cancer Res Treat 2008; Jan; 107(1): 133-8,
\(^5\) Bertolini F et al. Nat Cancer Rev. 2006 Nov 6; 835-845;

Defined as\(^5\): HPCs: CD45\(^+\), CD34\(^+\), VEGFR1\(^+\) and EPCs: CD45\(^\text{dim}\), CD133\(^+\), VEGFR2\(^+\)
Preclinical models of metastatic progression

Bone Marrow Niche

Primary Tumor Niche

VEGFR1+ hematopoietic progenitor cells (HPC)

VEGF
bFGF
PDGF

+ others

Distant Site

Premetastatic Niche

Avascular Micrometastases

Preclinical models of metastatic progression

VEGFR2+ endothelial progenitor cells (EPC)

Primary Tumor Niche

VEGF, bFGF, PDGF, + others

Bone Marrow Niche

Distant Site

Premetastatic Niche

VEGF, bFGF, PDGF, + others

Avascular Micrometastases

Angiogenic switch

Vascular Macrometastasis

Can we impact these BM derived progenitor cells (microenvironment) in a high risk for relapse BC population?

TM study
( phase II study of tetrathiomolybdate in BC pts at high risk of relapse)
Copper as a therapeutic target in the tumor microenvironment

Copper

- Many copper dependent enzymes and biologic processes are relevant in cancer
  - Required cofactor for activators of angiogenesis (bFGF, VEGF, NF-κB)\(^1,2,3\)
  - Superoxide dismutase and lysyl oxidase
  - Affects RAS-MAPK signalling
- Migration and invasion of endothelial cells \(^4\)
- Memo (Cu dependent redox enzyme) supports migration in TNBC \(^5\)
- Drives BRAF signalling by enhancing MEK1 phosphorylation of ERK1/2 through a Cu-MEK1 interaction

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Copper depletion with tetrathiomolybdate

- Inactivates copper chaperones and decreases incorporation into copper-containing enzymes\(^1\)

- Mouse models of cancer show tumor regression\(^2,3,4\)

- Phase I/II trials in overt disease with stable disease as best response\(^5,6,7\)

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TM treatment prevents breast cancer metastases in a preclinical model

Her2/neu transgenic mice that develop lung metastases by day 205, treated with TM vs. water for 180 days

P<0.0005
Phase 2 study of TM

Open-label, single-arm phase II trial

**Breast cancer at high risk of relapse and NED**

- Stage III and IV NED breast cancer
- Stage II triple negative breast cancer

**No Evidence of disease (NED)**
- Physical exam
- Labs: CBC, CMP, tumor markers
- Imaging: CT scan with bone scan or PET/CT

**Local and systemic therapy:**
- Completion of standard therapy

**Daily oral TM**
For 2 years to achieve Cp target $\leq 17$ mg/dL

**Primary endpoint:**
- VEGFR2+ EPCs
**Secondary endpoints:**
- PFS
- VEGFR1+ HPCs
- Adverse events
- Circulating markers of angiogenesis

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High Risk

- Stage III and IV NED breast cancer
- Stage II triple negative breast cancer
Phase 2 study of TM

Breast cancer at high risk of relapse and NED

Daily oral TM
For 2 years to achieve Cp target ≤ 17 mg/dL

Primary endpoint:
- VEGFR2+ EPCs
Secondary endpoints:
- PFS
- VEGFR1+ HPCs
- Adverse events
- Circulating markers of angiogenesis over time

Once every 4 weeks (1 cycle)
- Physical exam
- CBC, CMP, tumor markers
- Ceruloplasmin (Cp) level
- Flow cytometry for BMD progenitors and other research blood (banked)

Once every six months
- CT with BS or PET/CT

CBC= complete blood count; CMP= comprehensive metabolic panel; BMD= bone marrow derived progenitor cells
Phase 2 study of TM

Breast cancer at high risk of relapse and NED

Daily oral TM For 2 years to achieve Cp target ≤ 17 mg/dL

Primary endpoint: - VEGFR2+ EPCs
Secondary endpoints: - PFS - VEGFR1+ HPCs - Adverse events - Circulating markers of angiogenesis over time

Statistical Analysis

- Intent-to-treat population
  - All patients who received at least two doses TM
- Stratification by copper depletion and molecular subtype
- Other outcomes: toxicity attributable to TM, time to progression of disease
Demographics

<table>
<thead>
<tr>
<th>Selected demographic variables</th>
<th>No. of patients (75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, (range)</td>
<td>51 years (29-66)</td>
</tr>
<tr>
<td>AJCC Stage at Study entry, n (%)</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>41 (55)</td>
</tr>
<tr>
<td>Stage 4 NED</td>
<td>30 (40)</td>
</tr>
<tr>
<td>Median tumor size in Stage 2/3 adjuvant pts, cm (range)</td>
<td>2.3 (1.2-7)</td>
</tr>
<tr>
<td>Median no. of positive lymph nodes in Stage 2/3 adjuvant pts, n (range)</td>
<td>6 (1-42)</td>
</tr>
<tr>
<td>Sites of Stage 4 disease, n</td>
<td></td>
</tr>
<tr>
<td>• Chest wall/liver</td>
<td>13/4</td>
</tr>
<tr>
<td>• Brain/bone only</td>
<td>2/3</td>
</tr>
<tr>
<td>Luminal A or B/Her2neu/TNBC (%)</td>
<td>40/12/48</td>
</tr>
<tr>
<td>Prior Adjuvant Therapy (%)</td>
<td></td>
</tr>
<tr>
<td>• Anthraclycline +/- taxane-based</td>
<td>80</td>
</tr>
<tr>
<td>• Trastuzumab-based</td>
<td>14</td>
</tr>
<tr>
<td>• Non anthraclyline-based</td>
<td>7</td>
</tr>
<tr>
<td>• Concurrent hormonal therapy</td>
<td>51</td>
</tr>
<tr>
<td>• Prior hormonal therapy</td>
<td>15</td>
</tr>
</tbody>
</table>

Enrollment by Stage

- Stage 2: 5%
- Stage 3: 55%
- Stage 4: 40%

TNBC vs Non-TNBC Patients

- Non-TNBC: 52%
- TNBC: 48%
TM reduces ceruloplasmin (Cp)

We can easily copper deplete patients and target Cp sustained over time
Copper depletion by molecular subtype

Copper depletion is most effective in triple negative BC

$\text{p < 0.001}$
VEGFR2 +EPCs decreased only in copper depleted patients

These are the cells that “flip” the angiogenic switch
LOXL2 is decreased only in copper depleted patients over time.

This heavily copper dependent enzyme is responsible for creating a hospitable environment for tumors.
### Number of cycles complicated by adverse events (total cycles = 2021)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>279 (13.8)</td>
<td>1 (0.0005)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>396 (19.6)</td>
<td>65 (3.2)</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>1 (0.0005)</td>
<td>1 (0.0005)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>417 (20.6)</td>
<td>41 (2.0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>39 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfur Burps</td>
<td>646 (32.0)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>67 (3.3)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1 (0.0005)</td>
<td>0</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>322 (15.9)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>17 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>282 (14.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

Grade 3 or 4 adverse events < 6%
Progression free survival (PFS)

Median follow-up: 4.9 years

(1 cycle = 4 weeks)
PFS for adjuvant and stage 4 NED patients

Adjuvant (Stage 2 and 3)

Stage 4 NED

(1 cycle = 4 weeks)
PFS by molecular subtype and TNBC

PFS by molecular subtype (n=75)

- Triple Negative
- Her2-positive
- Luminal

PFS of triple negative patients by stage (n=36)

- Stage 2: 100%, n=4
- Stage 3: 88%, n=16
- Stage 4 NED: 71%, n=16

(1 cycle = 4 weeks)
Overall survival

Median follow-up: 4.9 years

(1 cycle = 4 weeks)
Context

Following slides courtesy of Mark Moasser MD from UCSF. 
*Discussant at ASCO Tumor Biology Session June 2, 2015*
Proposal tests against microscopic residual disease

Is prolonged copper depletion tolerable and feasible? Is there a signal of efficacy that warrants more rigorous study?

- surgery
- chemo
- XRT

stage 2/3
stage 4-NED

recurrence

copper depletion therapy x 2 years

tumor burden

time

sub-clinical disease
Nackos et al; #11008; Altering the tumor microenvironment: A phase II study of copper depletion using tetrathiomolybdate (TM) in patients (pts) with breast cancer (BC) at high risk for recurrence.

PFS of triple negative patients by stage (n=36)

- Stage 2: 100%, n=4
- Stage 3: 88%, n=16
- Stage 4: 71%, n=16


C

ITT

Progression-Free Survival (probability)

- GC: HR, 0.79 (95% CI, 0.65 to 0.98)
- GCI: Median PFS, GC/GCI: 4.1/5.1 months

Log-rank P = .0271

Time (months)

0 2 4 6 8 10 12 14 16

Nackos et al; #11008; Altering the tumor microenvironment: A phase II study of copper depletion using tetrathiomolybdate (TM) in patients (pts) with breast cancer (BC) at high risk for recurrence.

PFS of triple negative patients by stage (n=36)

- Stage 2: 100%, n=4
- Stage 3: 88%, n=16
- Stage 4 NED: 71%, n=16

Phase 3 gem/cis vs gem/taxol
Patients with stage 4 TNBC
n = 240

Nackos et al; #11008; Altering the tumor microenvironment: A phase II study of copper depletion using tetrathiomolybdate (TM) in patients (pts) with breast cancer (BC) at high risk for recurrence.
Nackos et al; #11008; Altering the tumor microenvironment: A phase II study of copper depletion using tetrathiomolybdate (TM) in patients (pts) with breast cancer (BC) at high risk for recurrence.

CALGB 9344; adjuvant AC/T chemotherapy patients with node-positive breast cancer n = 1500 subset with TNBC

Nackos et al; #11008; Altering the tumor microenvironment: A phase II study of copper depletion using tetrathiomolybdate (TM) in patients (pts) with breast cancer (BC) at high risk for recurrence.

Follow-up post-chemo observational study
patients with stage 1-3 TNBC
n = 269

Ovcaricek et al, Radio Oncol 2011; 45: 46-52.
Conclusions

• TM is safe and well tolerated
• Copper depletion affects processes in the microenvironment known to promote tumor metastases
• Tumor recurrence after 2 years is a rare event
• Phase 3 trial in the works for node + TNBC
Is this disruptive?

I hope so.....

.....stay tuned

The END
Questions?