2017 Cancer Center Business Summit

Transforming the Business of Oncology through Science and Technology
Oncology Office of the Future

Moderator:
Erich Mounce, M.S.H.S., Chief Executive Officer
West Cancer Center

Panelists:
Robert Green, M.D., M.S.C.E, Senior Vice President
Clinical Oncology, Flatiron Health

Keith Cowling, Director of Product Management
Flatiron Health

Mohan Giridharadas, Founder & C.E.O.
LeanTaaS

John Lee, M.D., Cancer Center Director
Chan Soon-Shiong Institute of Molecular Medicine

Edward Stepanski, Ph.D, C.O.O., Professor of Medicine, UTHSC
Vector Oncology,
Oncology Office of the Future

Robert Green, M.D., M.S.C.E
Senior Vice President Clinical Oncology
Flatiron Health

Keith Cowling
Director of Product Management
Flatiron Health
To serve cancer patients and our customers by dramatically improving treatment and accelerating research.
Evolution of the EHR

- **Paper Charts**
  - flowsheets, not much better than paper

- **EHRs**
  - better design, more efficient
  - no change in care

- **Improved EHRs**
- **Future State**
  - 10x more efficient
  - improved patient care
Oncology Office of the Future

Mohan Giridharadadas

Founder & CEO, LeanTaaS
Introduction to LeanTaaS

**BACKGROUND:**
Silicon Valley software company with world-class IP in lean, data science and optimization applied to healthcare.

**MISSION:**
Use Lean and Predictive Analytics to:
1) Increase Patient Access
2) Reduce Wait Times
3) Lower Cost

**FOR INFUSION CENTERS:**
- Enable 10-15% additional treatments each week
- Reduce wait times by 30-50% during the mid-day peak
- Reduce nursing overtime by 40-60%

**Commercially Available**

Partial list of customers include:
- Stanford Health Care
- UCH Health
- Memorial Sloan Kettering
- UCSF
- MD Anderson
- Cleveland Clinic
- New York Presbyterian
- Wake Forest
- Sutter Health
- Emory Healthcare
- Miami Baptist
- USC Keck
- ...

2017 Cancer Center Business Summit
Cancer Centers Face 3 Operational Problems

#1: Each patient has a unique journey through the Cancer Center
Cancer Centers Face 3 Operational Problems (continued)

#2: Patients are forced to endure long waits at each step

Waiting Time | Waiting Time | Waiting Time
---|---|---
See the Oncologist | Get lab work done | Undergo infusion treatment

Value Added Time

Non-Value Added Time

Waiting Time | Waiting Time | Waiting Time

LeanTaaS

2017 Cancer Center Business Summit
Cancer Centers Face 3 Operational Problems (continued)

#3: “Rush-hour effect” on some steps causes a ripple effect downstream resulting in further delays

Labs peak in the morning

Infusion peaks at mid-day
Synchronize the Demand and Supply Patterns

**Demand**
- Analyze the resource (people and assets) utilization patterns
- Optimal staff ramp-up schedule and asset allocation model

**Data Science Algorithms**
- Sophisticated Forecasting Models
- Resource rules and constraints

**Supply**
- Forecast the daily demand volume, mix and timing based on historical demand data
- Level loaded demand profile that optimizes the duration and sequence of appointments

**LeanTaaS**

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Requires Sophisticated Data Science to Execute

1. PREDICT
   Predict demand patterns (volume, mix, timing) using sophisticated mathematical and geometric models

2. OPTIMIZE
   Generate optimal templates through lean principles and constraint-based optimization algorithms that flatten the workload

3. SIMULATE
   Validate the resilience of the templates to the inevitable variances that will occur

4. DEPLOY
   Translate the optimal templates into appointment slots that are monitored daily

5. LEARN
   Use machine learning to tweak the coefficients of the forecasting models in order to continuously improve the accuracy of the forecasts
Process Improvement is Not Enough

If the appointments for a given day were not assembled using rigorous mathematical optimization, process improvement efforts simply CANNOT capture the full opportunity.
Applying the Approach to Infusion Centers

Duration of the appointment

- Short
- Medium
- Long
- Very long/Complex

Even workload throughout the day allows for more predictable schedules

Unlock capacity to help deal with unexpected delays and add-ons
iQueue has been deployed at 50 infusion centers
End Vision is an Air Traffic Control Approach

- Ambulatory Surgical Centers
- Inpatient Beds
- Operating Rooms
- Pharmacy Labs Imaging
- Infusion Clinics
- Primary and Specialty Clinics
- Emergency Room
- Radiation Oncology
Oncology Office of the Future

John Lee, M.D.
Cancer Center Director
Chan Soon-Shiong Institute of Molecular Medicine
Over 60 Molecules in Development

Next Gen Abraxane

Chemotherapy / Radiation

MDSC

T-Reg

Macrophage

Checkpoint Inhibitor

GPS Cancer

Consolidation Phase

Killer T-Cell

Dendritic Cell

Fusion Protein

B-Cell

Memory T-Cell

Cytokine Stimulator

Natural Killer

Induction Phase

Transplantation Phase

Cancer Breakthroughs 2020: QUILT Trial
What is GPS Cancer: Genomic Proteomic Spectrometry

Comprehensive Molecular Profiling Targeted Proteogenomic Test is performed in a CAP-accredited and CLIA-certified laboratory.

**GPS Paradigm**
- Tumor
- Normal
- FFPE

**GPS Contraster**
- Whole Genome DNA
  - 3 Billion Base Pairs
  - ~20,000 Genes

**GPS Proteomics**
- Quantitative Proteomics
  - By Mass Spectrometry

A Universal Decision Support For All Cancer Drug Therapy
Identifying the cancer immuno-biology and actionable target

- Cancer Immuno-Biology
- Personalized Immunotherapy
- Chemo Resistance Biomarker
- Actionable Peptide Target
- Therapeutic Agent
- Chemotherapy
GPS Cancer: Transforming Cancer Care and Fulfilling an Unmet Need

GPS Proteomics (Quantitative Proteins)

- Personalized Chemotherapy
- Personalized mAbs
- Personalized Checkpoints
- Personalized Targeted Therapy

GPS Paradigm Algorithm* (Expression & Activity Pathways)

- Inflamed or Cold Tumor
- Expressed Actionable Targets
- Chemo Sensitive Clusters
- Neoepliotpe Discovery
- Predictive Modeling

GPS Contrastor Algorithm* (Tumor/Normal)

- Polyclonality
- Heterogeneity
- Microsatellite Instability (MSI)
- Loss of heterozygosity (LOH)
- Resistant Clones
- Provenance
- Virome
- Environmental Exposure

* See Selected References Attached
GPS Cancer™: Enable utilization of lower cost chemotherapy with knowledge of quantitative proteomic chemo-resistance or chemo-sensitivity biomarkers before treatment begins.

Addressing the Question:
“Doctor, what information do you have from my tumor tissue that will help inform you that the treatment you are about to prescribe has a probability of being effective?”

GPS Guided Breast Cancer Treatment
- Doxorubicin
- Paclitaxel
- Oxaliplatin
- Cetuximab, Panitumumab
- Irinotecan
- Trastuzumab, Pertuzumab
- Gemcitabine

GPS Guided Colon Cancer Treatment
- Oxaliplatin
- Cetuximab, Panitumumab
- Irinotecan
- Trastuzumab, Pertuzumab
- Gemcitabine

GPS Guided Lung Cancer Treatment
- Oxaliplatin
- Cetuximab, Panitumumab
- Irinotecan
- Trastuzumab, Pertuzumab
- Gemcitabine
Results of the ITACA-S trial showing no clinical difference when choosing between chemotherapy agents in the treatment of gastric cancer in the absence of molecular intelligence
Patients predicted to be resistant to docetaxel by quantitative proteomics suffer worse outcomes if (mis)treated with docetaxel vs 5-FU.

<table>
<thead>
<tr>
<th>TUBB3 (amol/ug)</th>
<th>Docetaxel + Cisplatin (OS days)</th>
<th>5-FU + LV (OS days)</th>
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<tbody>
<tr>
<td>&gt; 700</td>
<td>801</td>
<td>1991</td>
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<tr>
<td>&lt; 700</td>
<td>1556</td>
<td>1227</td>
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</table>
GPS Cancer: Guided Cancer Therapy Predictive of Efficacy and Resistance

2014-2016 Case Study: Metastatic Uterine Cancer

<table>
<thead>
<tr>
<th>Standard of Care Treatment Options</th>
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<tbody>
<tr>
<td>Paclitaxel</td>
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</tbody>
</table>

Quantitative Proteomics (GPS Cancer)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Analyte</th>
<th>DNA</th>
<th>RNA</th>
<th>Quant Protein (amol/ug)</th>
<th>Efficacy Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab MK-3475</td>
<td>PD-L1, MSI</td>
<td>No MSI</td>
<td>No PD-L1</td>
<td>&lt; 100</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>TUBβ3</td>
<td>Intact</td>
<td>Expressed</td>
<td>&lt; 100</td>
<td>&lt; 850</td>
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<tr>
<td>Trastuzumab</td>
<td>HER2</td>
<td>Amplified</td>
<td>Amplified</td>
<td>4,995</td>
<td>&gt; 740</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>TOPO2A</td>
<td>Intact</td>
<td>Expressed</td>
<td>472</td>
<td>&gt; 1,530</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>FRα</td>
<td>Intact</td>
<td>Expressed</td>
<td>10,500</td>
<td>&gt; 1,510</td>
</tr>
</tbody>
</table>

Green: Likely to respond; Red: Unlikely to respond

A Universal Decision Support For All Cancer Drug Therapy

GPS Cancer
Cancer MoonShot 2020
QUILT Schema

QUILT – QUantum Integrative Lifelong Trial

- Diagnosis and/or Progression
  - Biopsy with GPS Cancer

- GPS Cancer
  - Molecular Tumor Board

- GPS Guided
  - Approved Therapies
    - FDA approved product with a known target

- GPS Guided
  - Investigational Therapies

- Novel Novel Immunotherapy
  - Combinations

- Toxicity
- No Response

- Progression
  - Biopsy with GPS Cancer

- Continue Rx
  - Follow Until Progression

- Response
Next Generation Abraxane

Developed Nano-Immune Conjugate (NIC) technology consisting of a nab-cytotoxic drug coated with mABs as a platform for antibody directed chemotherapy delivery.

Technology developed at Mayo Clinic based on observations around the interaction of antibodies with albumin.

**Flexible platform technology**
- Customizable targeting, payload, PK/PD characteristics
- Can use existing and/or novel agents

**Initial products pursued**
- 1st compound AB160 (Abraxane + Avastin) in phase 1 clinical testing
- 2nd compound AR160 (Abraxane + Rituxan) to enter clinic late 2016
- 3rd compound ABC160 (Abraxane + Avastin + Cisplatin) to enter clinic 2017
In vivo model

A375 human Melanoma (VEGF+)

Size of ~ 750mm³

Single IV treatment on day 0 (and 1)

Saline
ABX
BEV
BEV+ABX
AB160 (complex)
Fluorescent analysis of tumor accumulation of alexafluor 750 labeled nanoparticles: (A) Mice received IV injections of equal amounts of either labeled Abraxane, Abraxane coated with non-specific antibodies (AB IgG), or Abraxane coated with Rituximab (AR160). Regions of interest (ROI) 2, 3, and 4 track tumor accumulation based on a fluorescence threshold, ROI 1, 5, and 6 serve as background references. Taken 24 hours post injection. (B) Average fluorescence per unit of tumor area of mice in all three treatment groups, to give gross tumor delivery. *(P<0.05).
In vivo model: AB160

Day 7 tumor size

Survival

Complex = AB160

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Targeted nanoparticle therapy for advanced melanoma: Nab-paclitaxel/bevacizumab complex (AB16007)

Phase 1 clinical trial
IND# 116769
Prior to discussing protocol entry with the patient, call the MCCC Registration Office (507-284-2753) for dose level and to insure that a place on the protocol is open to the patient.

**Agent | Dose | Route | Days | ReRx**
---|---|---|---|---
nanoAB assigned at time of registration | IV over 60 minutes (only 1st dose; subsequent doses infused over 30 minutes) | 1, 8 and 15 | Every 28 days*

*One treatment cycle = 28 days +/-3 days*

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dose (ABX)</th>
<th>Dose (BEV)</th>
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<tbody>
<tr>
<td>-2</td>
<td>75mg/m2</td>
<td>30mg/m2</td>
</tr>
<tr>
<td>-1</td>
<td>100mg/m2</td>
<td>40mg/m2</td>
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<tr>
<td>1*</td>
<td>125mg/m2</td>
<td>50mg/m2</td>
</tr>
<tr>
<td>2</td>
<td>150mg/m2</td>
<td>60mg/m2</td>
</tr>
<tr>
<td>3</td>
<td>175mg/m2</td>
<td>70mg/m2</td>
</tr>
</tbody>
</table>

CONFIDENTIAL
Clinical: Abraxane & Bevacizumab in Late Stage Melanoma

* Interim analysis of the first four patients. Two of four patients remain in PFS.
A Living Killing Machine: NK Cell Innate Immune Protector

1. Adhesion & Targeting Receptors
   Targets and binds to tumor cell & tumor cell matrix, and viral infected cells

2. Activation Receptors
   Triggers release of killing mechanism

3. Release of Chemokines
   Attracts killer T-Cells

4. Release of Cytokines
   Induces apoptosis

5. Release of Perforin & Granzyme
   Direct cell killing & targeted killing

6. Antibody Mediated Killing
   Binds to Antibodies
   Activates cell death (ADCC)

Innate CARs

Autologous Natural Killer Cell (NK Cell)

NKG2
NKG2D
CD16
NKp30, 44, 46
LFA-1
CD2
CD69
CD94
2B4
CD2

Targeted Killing

Friday, February 24, 2017 Confidential – Do Not Distribute
Study Objectives

Primary: 4-month PFS rate

Secondary: ORR, TTP, OS; safety, exploratory molecular analysis (panomics)

Study Timelines

Open 2015, preliminary data 2017
10/2014
First consultation at UW, Seattle

12/2014
After RT plus IFN plus Imiquimod

04/2015
anti-PD-1 after 12 weeks of pembrolizumab
Pembrolizumab discontinued due to progressive disease

07/2015
Received neutron RT to scalp and B/L neck tumors.

01/2015
Recurrent MCC nodules on scalp in RT fields. Started anti-PD-1 (pembrolizumab) for unresectable MCC

03/2016
Enrolled on aNK trial Baseline Day 01
First Infusion on 03/15/2016

03/14/2016
Enrolled on aNK trial
Baseline Day 01
First Infusion on 03/15/2016

03/30/2016
Day 14

06/21/2016
4 Months Later
No New Lesions
Since 03/2016

NantKwest Results of Merkel Cell Carcinoma

Cancer MoonShot 2020
haNK: high affinity CD16 expression for enhanced ADCC activity
Lysis of Human Carcinoma Cells with High Avidity NK (haNK) Cells via ADCC with IgG1 MAbs

Lung cancer: Cetuximab

Breast cancer: Trastuzumab and Pertuzumab
haNK: high affinity CD16 expression for enhanced ADCC activity
taNK Program
Target Associated Cell Killing
Safety of ErbB2/HER2-specific therapeutics based on FRP5

Application of an FRP5-based antibody-toxin in cancer patients

- Treatment of patients with ErbB2-positive malignancies by local injection or systemic infusion of an FRP5-based antibody-toxin did not result in on-target/off-tumor activities (Azemar et al. 2003; von Minckwitz et al. 2005)
Induction of secondary anti-glioma immune responses by adoptive therapy with NK-92/5.28.z cells

Immunocompetent C57BL/6 mice carrying intracranial syngeneic GL261/ErbB2 glioma grafts

Cancer Breakthrough 2020: The QUILT Trial 2016 – 2020

Entering the Tumor Microenvironment
- Transcytosis (Gp60 & FcRn)
- Enhance Vascular Permeability (PEP)
- Tumor Necrosis Targeting (TNT)

The Path to the Cancer Vaccine: QUILT Trial
Entering the Era of Clinical Genomics & Proteomics to Deliver Neoepitope Immunotherapy for N=1 (Patient’s Own Control)

Off-the-Shelf Natural Killer Cells
- Low Dose Chemotherapy
- Low Dose Radiation
- Endocrine Deprivation
- Small-Molecule Inhibitors
- Monoclonal Antibody
- Fusion Proteins
- Checkpoint Inhibitors

Fusion Proteins, Cytokine, Chemokine, Checkpoints

T-Reg, MDSC, M2

Multi-Clonal Cancer Cells

Surviving Cell Fraction
Immunogenic Modulated Cell Under Stress

Heterogeneous Resistant Tumor Clone

INNATE IMMUNOTHERAPY
- Tumor Microenvironment Targeting & Immunomodulation
- Natural Killer (NK) Cell
  - NKG2D
  - aNK
  - taNK
  - Immunogenic Cell Death
  - Direct Cell to Cell Contact

ADAPTIVE IMMUNOTHERAPY
- B-Cell
  - Immature Dendritic Cell
  - Antibodies to Tumor Associated Antigens
  - Neoantigens

- Cancer Vaccine
  - Adenovirus & Yeast Vectors

- Killer T-cell
  - Checkpoints Cytokines & Fusion Proteins (Fc)

- Checkpoint Inhibitor
  - Cytokine Stimulator

Cancer MoonShot 2020
Better Treatment Outcomes with Innovative IT Solutions

Edward Stepanski, PhD
COO, Vector Oncology
Professor of Medicine, UTHSC
Digital Health Technology Improves Patient Outcomes

- Automated collection of patient reported outcomes at point of care and as part of mobile health strategies is being done now, and will become routine
- These data are archived in the EMR, and from there trigger pop-ups and alerts
Improving Outcomes While Containing Costs

• Poor outcomes in cancer care
  – Decreased treatment efficacy
  – Decreased quality of life

• Contributing Factors
  – Non-adherence to treatment
  – Early treatment discontinuation
  – Hospitalization
  – Untreated depression, other psychiatric morbidity
  – Toxicity leading to dose reductions, dose delays

• Patient engagement strategies can address these topics
Systematic Evaluation of Common Symptoms Improves Key Outcomes*

• 766 patients with advanced cancer receiving chemotherapy were randomized to usual care vs routine symptom monitoring
• The symptom monitoring group showed these statistically significant changes:
  – Improved QoL
  – Decreased hospitalization rates
  – Decreased ER visit rates
  – Increased one-year survival

Patient Reported Symptoms Can Drive Digital Education and Treatment Approaches

• Current applications:
  – Increasing treatment adherence
  – Symptom monitoring; self-triage and provider-based triage
  – Education
  – Delivery of evidence-based treatments

• Future applications:
  – CBT for anxiety
  – Implementing automated interventions based on risk stratification tiers
  – Scheduling software that order Uber for patients needing transportation to their radiation oncology treatments
Providing State of the Art Non-pharmacological Treatment for Insomnia Through a Digital Portal

The key components of ‘Sleepio’, digital Cognitive-Behavioral Treatment for insomnia

- Sleep tracking via daily sleep diary or connected wearable
- Weekly sessions of Cognitive Behavioral Therapy with The Prof
- Tools and techniques to help you back to sleep
- Access to Sleepio community and library of resources
Summary

• IT-driven patient engagement strategies will power cost-effective solutions to improve treatment outcomes
• These strategies will include patient monitoring, patient education, triage, and referral to on-line treatments
• Mobile health utilizing connectivity to patients through Smartphones will become integrated into ‘usual care’ models