INTEGRATION OF GENOMICS INTO CLINICAL PRACTICE

Howard A Burris, III, MD
Chief Medical Officer, Sarah Cannon
BURNING QUESTIONS

• With the new immunotherapies, do I still need to molecularly profile my patient?
• Is it worth ordering a molecular profile to search for the rare mutation?
• Is it not simpler to just order a blood based test on my patients?
BIOMARKER SUCCESSES OF PRECISION MEDICINE

- Breast cancer: hormone receptor and HER2
- Ph+ leukemia: BCR-ABL
- Colorectal cancer: RAS pathway
- Melanoma: B-RAF
- Non-small cell lung cancer: EGFR and ALK
TRASTUZUMAB: THE FIRST HER-2 TARGETED THERAPY

Years From Randomization

<table>
<thead>
<tr>
<th>N</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC→T</td>
<td>1679</td>
</tr>
<tr>
<td>AC→TH</td>
<td>1672</td>
</tr>
</tbody>
</table>

HR=0.48, 2P=3x10^{-12}

AC→T: 87% 85%
AC→TH: 75% 67%
THE CHALLENGE OF PRECISION MEDICINE

PERSONALIZED MEDICINE ACCELERATES DRUG DEVELOPMENT

2001 – Imatinib is FDA approved for CML after 3 years of clinical testing

• On the basis of two phase 2 trials

2013 – Crizotinib is FDA approved for ALK+ NSCLC after 3 years of clinical testing

• On the basis of a highly positive phase 1 trial and confirmatory phase 2 trial

2014 – Ceritinib is approved for ALK+ NSCLC previously treated with crizotinib after less than 3 years of clinical testing

• On the basis of a phase 1 trial that enrolled 163 patients

2017 – Pembrolizumab is approved for adult and pediatric MSI-H or dMMR solid tumors that have progressed following prior treatment

• On the basis of 149 patients across 5 multi-cohort single arm trials
WHICH IS MORE HELPFUL?

February 2013

January 2014

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### Tumor Type: Breast Carcinoma (NOS)

**Patient Name:**

**Report Date:** 04 March 2016

**Tumor Type:** Breast carcinoma (NOS)

- **Date of Birth:** Not Given
- **Sex:** Female
- **Medical Facility:** Tennessee Oncology
- **Ordering Physician:** Burris, Howard
- **Tumor Site:** Liver
- **Additional Recipient:** Not Given
- **Medical Record #:** Not Given
- **Additional Medical Facility #:** 1021-060554 14
- **Pathologist:** Not Provided
- **Specimen ID:** 22 February 2016
- **Specimen Site:** Not Given
- **Date of Collection:** 15 February 2016
- **Specimen Type:** Breast

**ABOUT THE TEST:**

FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

**PATIENT RESULTS**

- **7 genomic alterations**
- **4 therapies associated with potential clinical benefit**
- **0 therapies associated with lack of response**
- **19 clinical trials**

**TUMOR TYPE: BREAST CARCINOMA (NOS)**

- **Genomic Alterations Identified**
  - **PARK2** duplication exon 7
  - **PI3K** amplification
  - **ERBB1** amplification
  - **ENKTY** amplification
  - **RBI** loss exons 2-17
  - **ZNF703** amplification

- **Additional Disease-relevant Genes with No Reportable Alterations Identified**
  - **ERBB2**

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*For a complete list of the genes assayed and performance specifications, please refer to the appendix.*
CHALLENGES OF MOLECULAR DIAGNOSTICS

• Determining what test to order and knowing which technology is needed for comprehensive tissue testing
• Interpretation of tests and what results might mean
• Determining when to rebiopsy
• Getting enough tissue and prioritizing use of tissue
• Cost
WHAT TEST DO I ORDER?
2018 MEDICARE PRICING

- Oncotype DX $3873
- Prosigna (Nanostring) $3099
- Foundation CDX $\sim3000
Routine single marker molecular tests such as IHC, PCR and FISH that have been used for decades and will continue to play an important role in cancer diagnosis.
A hot spot NGS panels can identify pre-specified mutations occurring in very limited areas of genes of interest and could fail to detect all classes of genomic alterations.

* - mutation, short indels, some copy number alterations

A comprehensive genomic profiling approach is testing all of the known clinically relevant cancer genes for all classes of alterations.

* - all classes of alterations, including mutation, indels, copy number alterations, rearrangements
TISSUE BIOPSY VERSUS LIQUID BIOPSY

Tissue Biopsy
• Gold standard
• Invasive procedure
• Tissue accessibility
• Limited to biopsied tissue only
• Clinical complications
• Cost
• Time

Liquid Biopsy
• Non-invasive blood test
• “Summation” tumor heterogeneity
• Potential for periodic monitoring for response or resistance
• ? Cost
• ? Speed
SELF-REPORTED AND PHYSICIAN ASSESSED WILLINGNESS TO CONSIDER BIOMARKER TESTING

Ciardiello et al. The Oncologist 2016;21:292-300
IMPLICATIONS FOR THERAPY AND OUTCOME

Intertumour Heterogeneity

Intratumour Heterogeneity

Intercellular Heterogeneity

Burrell, Mcgranahan, Bartek and Swanton Nature 2013
A NEW BIOPSY MIGHT BE NEEDED BEFORE PROFILING...

- Patients’ tumors change over time depending on treatments and can acquire resistance mutations specific to their therapy.
- The molecular status of a historical sample may not reflect a patient’s current disease status

LIQUID BIOPSIES: “THE STETHOSCOPE FOR THE NEXT 200 YEARS”

Plasma vs. Serum

Mutations in tumor can also be found in the blood

ctDNA≠CTCs

Crowley et. al., Nature Reviews, 2013
2014

49 yo F diagnosed at age 36 (2004) with invasive breast cancer, ER +, PR +, Her2 normal.

- Initial treatment with neoadjuvant DD AC-T f/b bilateral mastectomies (T1, N1)
- Adjuvant tamoxifen x 5 years (2005-2010)
- In 2012, back pain led to a biopsy; recurrent ER / PR + breast cancer
- Tamoxifen, LHRH-I, XRT; then BSO, and anastrozole
- 11/2013, fulvestrant added
- 8/2014, initiated trial of fulvestrant, ribociclib (LEE), and PI3K-I (BYL)
- After 17 months, PD w/ new liver lesions, biopsies and sent for molecular profiling
IDENTIFYING NEW MUTATIONS

2016

Patient Name

Date of Birth

Sex

Medical Facility

Ordering Physician

Tumor Type

Tumor Status

Genomic Alterations Identified

- FGFR1
- PTEN
- ESR1
- AR
- TP53
- KRAS
- PIK3CA

Additional Disease-relevant Genes with No Reportable Alterations Identified

- CDH1
- TP73

14 Clinical Trials

2017

Patient Name

Date of Birth

Sex

Medical Facility

Ordering Physician

Tumor Type

Tumor Status

Genomic Alterations Identified

- FGFR1
- PTEN
- ESR1
- AR
- TP53
- KRAS
- PIK3CA

Additional Disease-relevant Genes with No Reportable Alterations Identified

- CDH1
- TP73

12 Clinical Trials

*For a complete list of the genes assayed and performance specifications, please refer to the appendix.
**VARIANTS OF UNKNOWN SIGNIFICANCE**

Note: One or more variants of unknown significance (VUS) were detected in this patient’s tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations make their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>P117Q</td>
</tr>
<tr>
<td>FGF1</td>
<td>S691F</td>
</tr>
<tr>
<td>KEL</td>
<td>D157Y,M156I</td>
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<tr>
<td>PIK3CB</td>
<td>L704V</td>
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<tr>
<td>SNCAIP</td>
<td>S46R</td>
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<tr>
<td>AR</td>
<td>E654*,L371M</td>
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<tr>
<td>FLT1</td>
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<td>KLHL6</td>
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<td>HGF</td>
<td>A532E</td>
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<td>NF1</td>
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<tr>
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<tr>
<td>SLIT2</td>
<td>G1150C,S33C</td>
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</tbody>
</table>
GENOSPACE: ENABLING THE CONVERGENCE OF CLINICAL RESEARCH AND CLINICAL CARE

Large-scale clinical-genomic data aggregation

Clinical Decision Support

Discovery & Trial Recruitment

WISDOM

Data

Action

Insight
COMPONENTS OF OMICS CLEARINGHOUSE (GENOMICS ANALYTICS)

HCA SYSTEMS
- HCA SYSTEMS (MT, EPIC, ECW)
  Server Based
- BMT SOLUTION
  Server Based
- RAD ONC - EHR
  Server Based
- CANCER REGISTRY
  Server Based
- CANCER NAVIGATION
  Server Based

NATURAL LANGUAGE PROCESSING
Server Based

MOLECULAR PROFILING LABS
- CARIS
- FOUNDATION MEDICINE
- GUARDANT PATHGROUP

AFFILIATED MEDICAL ONCOLOGIST EMRS
- VARIAN
  Aria MO
- ELEKTA
  Mosaic MO
- ALTOS
  OncoFMR
Molecular Tumor Board (aka: Molecular Cancer Conference)

- **Purpose:** To solely review molecular profiling data and provide guidance and education on:
  - Potential suitability of patients to clinical trial options
  - Potential suitability of patients to targeted therapies
  - Potential contraindications
  - Potential germline considerations

- **What we do not do**
  - We do not take into consideration other clinical parameters that might otherwise influence patient eligibility for target therapies/clinical trials
  - We do not track slot availability of studies
  - We do not practice medicine – we give scientific rationale for why (or why not) a patient might be appropriate for specific study/therapy

MOLECULAR CANCER CONFERENCES

- We are performing Molecular Cancer Conferences in:
  - 8 Tennessee Oncology (TO) facilities in Middle Tennessee and Chattanooga
  - 3 Florida Cancer Specialists regions

- We receive an average of >5 physician requests per week for *ad hoc* patient molecular reviews
  - These cases are coming from physicians at all strategic site locations

- Two abstracts describing Sarah Cannon’s Molecular Cancer Conferences were submitted to ASCO (1 accepted for online publication and 1 accepted as a poster)

Since May 2017, the Personalized Medicine team has reviewed > 600 patients’ molecular reports for Molecular Cancer Conferences or for *ad hoc* requests
Molecular profiling has increased since the inception of the Molecular Cancer Conferences.

**TO-Chattanooga Molecular Profile Ordering Trends**

P < 0.0001

Over 18% of patients discussed at MCCs went on a clinical trial, and the majority of MCC patients went on targeted therapies.
EXAMPLE CASE METASTATIC MELANOMA

• 70 yo male diagnosed June 2017 stage IV cutaneous melanoma (T4a, N3, M1c)
• September 2017 single dose XRT L frontal lesion
• September 2017 – November 2017: received nivolumab at VICC with progressive disease on scans
• November 2017 single dose radiation to pons lesion
• December 2017 referral to Sarah Cannon; molecular profiling ordered
• RM 463 (dual ERK inhibitor) initiated January 22, 2018; currently Cycle 5; neck nodes improved on scans with no new lesions; mild rash, nausea, fatigue, and decreased appetite.
FoundationOne from skin biopsy was performed 01/13/2018

- All mutations found by Guardant were found by FoundationOne. FoundationOne found numerous other mutations
- TMB-High (75 Muts/Mb)
  - Emerging data are supporting a positive correlation between increased TMB and response to immune checkpoint inhibitors (BMS)
  - Numerous early-phase immunotherapy options
  - MEL55 – Atezo + Cobi vs Pembro in advanced, previously untreated BRAFwt melanoma
- With high TMB, we are hesitant to discuss targeting a specific mutation as inhibition on any one target will likely be usurped by other co-occurring mutations/pathways. However, mutations converging on the same pathway may be advantageous to target.
  - NRAS Q61L lies within a GTP-binding region of the Nras protein (UniProt.org). Q61L results decreased Nras GTPase activity, leading to increased activation of downstream pathway signaling, and is transforming in cell culture (PMID: 19492075, PMID: 21993244).
  - MAP2K2 F57C has been characterized to be activating and has also been identified in patients with cardio-facio-cutaneous (CFC) syndrome which is characterized by activating alterations in the RAS/RAF/MEK/ERK pathway.
  - Both FGFR2 mutations have been documented in COSMIC, but have unknown functional significance (as is true with all other VUSs found by FMI). There is known functional involvement of FGFRs in Melanoma.
  - Since NRAS, MEK2, and FGFR2 are all mutated, a signaling pathway inhibition strategy might be more strategic than targeting any one alone.
    - REFMAL463 – Dual ERK inhibitor

Guardant test performed 12/26/2017
# MyPathway: Study Design

## MyPathway Study
*Unique master protocol with multiple basket studies*

<table>
<thead>
<tr>
<th>Molecular alteration</th>
<th>HER2 overexpression, amplification, or activating mutation</th>
<th>BRAF-activating mutation (V600E and others)</th>
<th>SMO-activating mutation, PTCH-1 loss-of-function mutation</th>
<th>EGFR-activating mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment(s)</td>
<td>Trastuzumab + pertuzumab</td>
<td>Vemurafenib</td>
<td>Vismodegib</td>
<td>Erlotinib</td>
</tr>
</tbody>
</table>
MY PATHWAY BASKET TRIAL PRELIMINARY RESULTS

HER2 Colorectal 38% ORR

HER2 Bladder 33% ORR

HER2 Biliary 29% ORR

BRAF NSCLC 43% ORR

Hainsworth et al. J Clin Oncol January 10, 2018 (epub)
EXAMPLE COLORECTAL CANCER MCC CASE REVIEW

- Reduced sensitivity report – consider re-testing
  - Trust the results provided, realize that there may be alterations that were not detected because of reduced sensitivity
- ERBB2 amplification - 31 copies
  - PRO02 – trastuzumab/Pertuzumab colon cohort is performing well
  - MY PATHWAY HER2-Amplified/overexpressed crc: trastuzumab/pertuzumab (n=34)
• 53 yo male diagnosed with metastatic colon cancer Jun 2016
• First line: FOLFOX/Avastin/cancer stemness inhibitor June 2016 – Feb 2017
• Second line: FOLFIRI/Avastin Mar 2017 – Jul 2017
• Third line: Trastuzumab/pertuzumab Aug 2017 – present (NGS testing Dec 2016: ERBB2 amplification - 31 copies)
59 yo male diagnosed squamous cell carcinoma R vocal cord 02/2013.

Initial treatment---radiation.
First recurrence—surgical resection.
Second recurrence---radiation.
Third recurrence---chemotherapy.
Disease progression---immunotherapy.

Guardant testing demonstrated two ERBB2 point mutations classified as variants of unknown significance. Molecular Tumor Conference Committee determined one of the mutations lies in the ligand binding domain and is predicted to be pathogenic.

PRO 10 afatinib (HER2 TKI) 08/2017 – present.
The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers

Hyman DM,1 Laetsch TW,2 Kummar S,3 DuBois SG,4 Farago AF,5 Pappo AS,6 Demetri GD,7 El-Deiry WS,8 Lassen UN,9 Dowlati A,10 Brose MS,11 Boni V,12 Turpin B,13 Nagasubramanian R,14 Cruickshank S,15 Cox MC,15 Ku NC,15 Hawkins DS,16 Hong DS,17 Drilon AE1

1Memorial Sloan Kettering Cancer Center, New York, NY; 2University of Texas Southwestern, Dallas, TX; 3Stanford University School of Medicine, Palo Alto, CA; 4Dana-Farber Cancer Institute/Boston Children’s Cancer and Blood Disorders Center, Boston, MA; 5Massachusetts General Hospital, Boston, MA; 6St. Jude Children’s Research Hospital, Memphis, TN; 7Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; 8Fox Chase Cancer Center, Philadelphia, PA; 9Rigshospitalet, Copenhagen, Denmark; 10UH Cleveland Medical Center, Cleveland, OH; 11Department of Otorhinolaryngology: Head and Neck Surgery, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; 12START Madrid CIIOC, Hospital HM Universitario Sanchinarro, Madrid, Spain; 13Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 14Nemour’s Children’s Hospital, Orlando, FL; 15Loxo Oncology, Inc., San Francisco, CA; 16Seattle Children’s Hospital, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA; 17The University of Texas MD Anderson Cancer Center, Houston, TX

Presented By David Hyman at 2017 ASCO Annual Meeting
TRK fusions found in diverse cancer histologies

Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

Presented By David Hyman at 2017 ASCO Annual Meeting
Diversity of cancers treated - 17 unique types

- Peripheral nerve sheath tumor: 4%
- Sarcoma, NOS: 4%
- Myopericytoma: 4%
- Cholangiocarcinoma: 4%
- Spindle cell sarcoma: 5%
- GIST: 5%
- Melanoma: 7%
- Lung: 7%
- Colon: 7%
- Pancreatic myofibromatosis: 2%
- Breast: 2%
- Appendix: 2%
- Inflammatory myofibroblastic kidney tumor: 2%
- Salivary gland: 22%
- Infantile fibrosarcoma (IFS): 13%
- Thyroid: 9%
Efficacy regardless of tumor type

*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy. **Pathologic CR.

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

Presented By David Hyman at 2017 ASCO Annual Meeting
Duration of larotrectinib therapy

93% of responding patients and 75% of all patients remain on treatment or underwent surgery with curative intent.

Presented By David Hyman at 2017 ASCO Annual Meeting
SQSTM1-NTRK1 lung cancer patient

Baseline

Cycle 4

45F NSCLC & paraneoplastic hypertrophic osteoarthropathy

Prior therapy: platinum/pemetrexed

Larotrectinib ongoing in month 8, resolution of paraneoplastic symptoms
ETV6-NTRK3 secretory breast cancer patient

Baseline  Day 6  Day 20

14F, prior therapy: 4 lines of chemotherapy and repeated resections
Treated with larotrectinib under expanded access
**MULTIPLE MUTATIONS!!!**

<table>
<thead>
<tr>
<th>PATIENT RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>37 genomic findings</td>
</tr>
<tr>
<td>19 therapies associated with potential clinical benefit</td>
</tr>
<tr>
<td>0 therapies associated with lack of response</td>
</tr>
<tr>
<td>34 clinical trials</td>
</tr>
</tbody>
</table>

**TUMOR TYPE: SKIN SQUAMOUS CELL CARCINOMA (SCC)**

Genomic Alterations identified

- ALK D1123N
- BRCAl2 S1271*
- FGFR1 G315E
- KIT D419N
- ABL2 E660K
- ARID2 Q1575*
- ATR R2001*
- ATRX G2406*
- BCO2 S1371L
- DCKR1 R1895*
- EPHA4 R136*
- EPN45 E632K
- ERBB4 M631K
- FAT1 R1098*
- GATA1 R305*
- INPP4B E609*
- KDM6A Q129*
- KMT2C (MLL3) Q318* — subclonal*
- LRPL6 splice site B51-1G-A
- LYN G256R
- MAGI2 E776*, E929K, N1048S*26
- ML2 C1765*15
- NOTCH1 G1049*
- PDK4PA E985K
- PRRG2 R552C, R844Q
- POLE P1601S
- RB1 splice site 1960G>T>C
- SLIT2 G1650*
- SPTBN1 A414G*, splice site 10510-1G>C
- TPS1 R1116H, V1060I

**Additional Findings**

- Microsatellite status: MS-Stable
- Tumor Mutational Burden: TMB-High; 494 Muts/Mb
Tumor Mutation Burden: Leading Immunotherapy to the Era of Precision Medicine?

Conor E. Steuer and Suresh S. Ramalingam, Winship Cancer Institute of Emory University, Atlanta, GA

See accompanying article doi:https://doi.org/10.1200/JCO.2017.75.3384
CORRELATION BETWEEN TMB AND RESPONSE RATE TO PD-1 INHIBITION

Yarchoan et al. NEJM 2017;377;25:2500-2501

FONE (1.1 MB) DERIVED TMB PREDICTS CIT RESPONSE IN THREE INDICATIONS

Melanoma (n = 65)  NSCLC (n = 464)  Urothelial carcinoma (n = 94)

PFS

OS

DB Johnson et al., Cancer Immunol Research, 2017

M Kowanetz et al., Annals of Oncology, 2017

Balar AV et al., Lancet, 2017
Nivolumab + Ipilimumab vs Platinum-Doublet Chemotherapy as First-line Treatment for Advanced Non-Small Cell Lung Cancer: Initial Results From CheckMate 227

Matthew D. Hellmann,1 Tudor-Eliade Ciuleanu,2 Adam Pluzanski,3 Jong Seok Lee,4 Gregory A. Otterson,5 Clarisse Audigier-Valette,6 Elisa Minenza,7 Helena Linardou,8 Sjaak Burgers,9 Pamela Salman,10 Hossein Borghaei,11 Suresh S. Ramalingam,12 Julie Brahmer,13 Martin Reck,14 Kenneth J. O’Byrne,15 William J. Geese,16 George Green,16 Han Chang,16 Joseph Szustakowski,16 Prabhu Bhagavatheeswaran,16 Diane Healey,16 Yali Fu,16 Faith Nathan,16 Luis Paz-Ares17

1Memorial Sloan Kettering Cancer Center Hospital, New York, NY, USA; 2Prof. Dr. Ion Chiricuta Institute of Oncology and Universitatea de Medicina si Farmacie Iuliu Hatieganu, Cluj-napoca, Romania; 3Centrum Onkologii–Instytut im. Marii Skłodowskiej-Curie, Warsaw, Poland; 4Seoul National University Bundang Hospital, Seoul, South Korea; 5The Ohio State University, Columbus, OH, USA; 6Hôpital Sainte Musse, Toulon, France; 7Ospedale Santa Maria della Misericordia, Perugia, Italy; 8First Department of Oncology, Metropolitan Hospital, Athens, Greece; 9Antoni Van Leeuwenhoek Ziekenhuis, Amsterdam, the Netherlands; 10Fundación Arturo López Pérez, Santiago, Chile; 11Fox Chase Cancer Center, Philadelphia, PA, USA; 12Winship Cancer Institute, Emory University, Atlanta, GA, USA; 13Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; 14LungenClinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; 15Princess Alexandra Hospital, Brisbane, QLD, Australia; 16Bristol-Myers Squibb, Princeton, NJ, USA; 17Hospital Universitario 12 de Octubre, Centro Nacional de Investigaciones Oncológicas, Universidad Complutense, & CiberOnc, Madrid, Spain
Co-primary Endpoint: PFS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>Nivo + ipi (n = 139)</th>
<th>Chemo (n = 160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS,\textsuperscript{b} mo</td>
<td>7.2</td>
<td>5.4</td>
</tr>
<tr>
<td>HR\textsuperscript{c}</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>97.5% CI</td>
<td>0.41, 0.81</td>
<td></td>
</tr>
<tr>
<td>\textit{P}</td>
<td>0.0002</td>
<td></td>
</tr>
</tbody>
</table>

- In patients with TMB <10 mut/Mb treated with nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)\textsuperscript{d}

\textsuperscript{a}Per blinded independent central review (BICR); median (range) of follow-up in the co-primary analysis population was 13.6 mo (0.4, 25.1) for nivo + ipi and 13.2 mo (0.2, 26.0) for chemo;
\textsuperscript{b}95% CI: nivo + ipi (5.5, 13.2 mo), chemo (4.4, 5.8 mo); \textsuperscript{c}95% CI: 0.43, 0.77 mo; \textsuperscript{d}The \textit{P}-value for the treatment interaction was 0.0018
CheckMate 227: Nivo + Ipi in 1L NSCLC With High TMB (≥10 mut/Mb)

**ORR and DOR in Patients With High TMB (≥10 mut/Mb)**

**ORR (TMB ≥10 mut/Mb)**

- **Nivo + ipi (n = 63):**
  - CR: 45.3%
  - PR: 26.9%
  - ORR: 72.2%

- **Chemo (n = 43):**
  - CR: 41.7%
  - PR: 26.3%
  - ORR: 68.0%

**DOR (TMB ≥10 mut/Mb)**

- **Nivo + ipi (n = 63):**
  - ≥1-y DOR = 68%

- **Chemo (n = 43):**
  - ≥1-y DOR = 25%

- Median time to response was 2.7 months with nivolumab + ipilimumab and 1.5 months with chemotherapy

**Per BICR; ORR in patients with TMB <10 mut/Mb was 24.6% in nivo + ipi arm and 25.9% in chemo arm**
CheckMate 227: Nivo + Ipi in 1L NSCLC With High TMB (≥10 mut/Mb)

Preliminary Overall Survival With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)

- Database lock: March 15, 2018; minimum follow-up: 14.2 months; 53% of patients were censored
- In the chemotherapy arm, 31.3% received subsequent immunotherapy (38.3% among those with disease progressionc)

<table>
<thead>
<tr>
<th></th>
<th>Nivo + ipi (n = 139)</th>
<th>Chemo (n = 160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, b mo</td>
<td>23.0</td>
<td>16.4</td>
</tr>
<tr>
<td>HR</td>
<td>0.79</td>
<td>0.56, 1.10</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[a\]In the first 1.5 months, 8 deaths occurred in the nivo + ipi arm (4 due to disease progression; 1 patient never treated [respiratory sepsis]; 2 due to AEs unrelated to study drug per investigator [thromboembolism, septic shock]; 1 due to myocarditis related to study drug), and 2 deaths occurred in the chemo arm (1 due to disease progression; 1 due to multiple brain infarctions related to carboplatin); \[b\]95% CI: nivo + ipi (16.5 mo, NR), chemo (12.6 mo, NR); \[c\]Per investigator

* OS (%)a
  - Nivo + ipi: 1-y OS = 67%
  - Chemo: 1-y OS = 58%

* No. at risk
  - Nivo + ipi: 139, 120, 112, 98, 90, 71, 44, 16, 5, 0, 0
  - Chemo: 160, 148, 129, 104, 90, 75, 45, 23, 9, 1, 0

* Months
MSI-HIGH SPECIMENS ARE A SUBSET OF HIGH TMB SPECIMENS (N=46, 465)

MSI-High specimens are a subset of high TMB specimens (n=46,465)

- The majority of MSI-H specimens (~84%) are TMB-H, but not the reverse
  - Only 14.5% of TMB-H specimens are also MSI-H
FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This is the FDA’s first tissue/site-agnostic approval.

The approval was based on data from 149 patients with MSI-H or dMMR cancers enrolled across five uncontrolled, multi-cohort, multi-center, single-arm clinical trials. Ninety patients had colorectal cancer and 59 patients were diagnosed with one of 14 other cancer types. Patients received either pembrolizumab, 200 mg every 3 weeks, or pembrolizumab, 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity, or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or associated with a decline in performance status. A maximum of 24 months of treatment was administered.

The major efficacy outcome measures were objective response rate (ORR) assessed by blinded independent central radiologists’ review according to RECIST 1.1, and response duration. ORR was 39.6% (95% CI: 31.7, 47.9). Responses lasted six months or more for 78% percent of those who responded to pembrolizumab. There were 11 complete responses and 48 partial responses. ORR was similar irrespective of whether patients were diagnosed with CRC (36%) or a different cancer type (46% across the 14 other cancer types).
Objective response: 53%

Complete response: 21%

Disease control rate: 77%

Median PFS and OS not yet reached (median follow up 12.5 months)

*Le et al. Science 2017 July 28;357 (6349): 409-413*
Approximately 60,000 people per year (4% of all cancers)
NIVOLUMAB/IPILUMUMAB IN DMMR/MSI-H COLORECTAL CANCER

ORR 55%
DCR ≥ 12
weeks 80%

Nivolumab monotherapy ORR 32%
Pembrolizumab monotherapy ORR 36%

Overman et al. ePub J Clin Oncol January 20, 2018
OlympiAD: Phase III trial of olaparib monotherapy versus chemotherapy for patients with HER2-negative metastatic breast cancer and a germline BRCA mutation

Mark Robson,1 Seock-Ah Im,2 Elzbieta Senkus,3 Binghe Xu,4 Susan M Domchek,5 Norikazu Masuda,6 Suzette Delalorge,7 Wei Li,8 Nadine Tung,9 Anne Armstrong,10 Wenting Wu,11 Carsten Goessl,11 Sarah Runswick,12 Pierfranco Conte13

1Memorial Sloan Kettering Cancer Center, New York, USA; 2Seoul National University Hospital, Seoul, Korea; 3Medical University of Gdańsk, Gdańsk, Poland; 4Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; 5Basser Center, University of Pennsylvania, Philadelphia, USA; 6National Hospital Organization, Osaka National Hospital, Osaka, Japan; 7Institut Gustave Roussy, Villejuif, France; 8The First Hospital of Jilin University, Changchun, China; 9Beth Israel Deaconess Medical Center, Dana-Farber Harvard Cancer Center, Boston, USA; 10Christie Hospital NHS Foundation Trust, Manchester, UK; 11AstraZeneca, Gaithersburg, USA; 12AstraZeneca, Macclesfield, UK; 13University of Padova and Istituto Oncologico Veneto IRCCS, Padova, Italy

ClinicalTrials.gov identifier: NCT02000622. This study was sponsored by AstraZeneca
OlympiAD study design

- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious gBRCAm
- Prior anthracycline and taxane
- ≤2 prior chemotherapy lines in metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If prior platinum use
  - No evidence of progression during treatment in the advanced setting
  - ≥12 months since (neo)adjuvant treatment

Primary endpoint:
- Progression-free survival (RECIST 1.1, BICR)

Secondary endpoints:
- Time to second progression or death
- Overall survival
- Objective response rate
- Safety and tolerability
  - Global HRQoL (EORTC-QLQ-C30)

Olaparib
300 mg tablets bd
2:1 randomization
Chemotherapy treatment of physician’s choice (TPC)
- Capecitabine
- Eribulin
- Vinorelbine

BICR, blinded independent central review; ER, estrogen receptor; HRQoL, health-related quality of life; PR, progesterone receptor; RECIST, response evaluation criteria in solid tumors; TNBC, triple negative breast cancer.
Primary endpoint: progression-free survival by BICR

Progression/deaths, n (%)  
Median PFS, months

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<thead>
<tr>
<th></th>
<th>Olaparib 300 mg bd</th>
<th>Chemotherapy TPC</th>
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<tbody>
<tr>
<td>163 (79.5)</td>
<td>7.0</td>
<td>4.2</td>
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<tr>
<td>71 (73.2)</td>
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<tr>
<td>HR 0.58</td>
<td>95% CI 0.43 to 0.80; P=0.0009</td>
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DDR ALTERATIONS ASSOCIATED WITH RESPONSE TO PD1/PDL1 IN UROTHELIAL CARCINOMA

Teo MY et al. J Clin Oncol
https://doi.org/10.1200/JCO.2017.75.7740
CONCLUSIONS

• Incorporating the complete molecular profile will provide much more information and give us better insights.

• While the rare mutation can be a source of frustration, the impact of targeted therapy in these patients can be profound.

• Basket trials are a source of great learning -- future trials, biology of subtypes, areas of opportunity.

• Participation in a basket trial is far more impactful than the anecdotal, compassionate use story we hear too often.

• Tumor mutation burden (TMB) may help identify patients who will respond to treatment with immunotherapy.
Enhancing Cure Rates Through Precision Medicine

...with adjuvant therapy

HER2+ Breast – Node+

Disease-free survival

98.1
94.9
92.0

H+P 89.9
98.2
93.7
90.2
H 86.7

0 6 12 18 24 30 36 42 48

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52

Disease-free survival

RAF+MEK

Placebo

BRAF^{V600} Melanoma – Stage III

...with neo-adjuvant therapy

2 year old with ETV6-NTRK3 sarcoma - Pre-op larotrectinib → limb-sparing surgery
(4 neo-adjuvant pts on Phase 1)

THANK YOU