Caratterizzazione genomica dei tumori e impatto terapeutico per i pazienti

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European Association of Urology – Research Foundation
Disclosures

Consulting or Advisory Role:

- **Company**: Roche, Bayer, Merck & Co. Inc., Astra Zeneca, Janssen, Astellas/Seattle Genetics, Clovis Oncology, BioClin Therapeutics, Foundation Medicine

Travel, Accommodations, Expenses:

- **Company**: Roche, Merck & Co. Inc., Janssen, PeerVoice

Research Funding (Institution):

- **Company**: Merck & Co. Inc., Astra Zeneca
Presentation agenda

- To highlight the role of immunotherapy as a “precision therapy” in GU cancers
  - The TMB/microsatellite instability feature and the frequency of germline mutations
- FGFR inhibitors: a success story and insights into therapeutic sequences
- Emerging molecular targets from routine clinical testing and clinical research
- Q&A
FoundationONE™ Assay: comprehensive genomic profiling

CLIA-certified, FDA-approved, CAP-accredited laboratory, NYS-approved

Sample requirements:
- Surface area ≥25 mm²
- Sample volume ≥1 mm³
- Tumor content ≥20%

Laboratory process:
- ≥50 ng dsDNA
- Library construction
- Hybridization capture
- Sequencing on Illumina HiSeq platform

Analytic methods:
- Customized computational biology algorithms
- Manual secondary review

Report curation:
- Clinically relevant GA
- FDA-approved therapies in patient tumor type
- FDA approved therapies in other tumor types
- Available clinical trials

Turnaround time ~14 days
Analytical Validation

- Demonstration of high accuracy and reproducibility required for clinical use

### Base Substitutions
(MAF 5-100%)
Sensitivity: >99.9%; PPV: >99.9%

### Insertions/Deletions
(1-40bp, MAF 10-100%)
Sensitivity: 98%; PPV: >99%

### Copy Number Alterations
(>20% tumor content, zero or ≥8 copies)
Sensitivity: >95%; PPV: >99%

### Gene Fusions
(>20% tumor content, select introns)
Sensitivity: >99%; PPV: >99%

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Frampton et al, *Nature Biotechnology* 2013

Controlled validation studies:

- Cell-line pools with known alterations:
  - 2056 subs
  - 227 indels
  - 310 CNAs
  - 32 fusions

Concordance studies with existing platforms on clinical samples:

- 118 subs/indels: Sequenom, PCR
- 185 CNAs: FISH, IHC
- 43 fusions: break-apart FISH
To highlight the role of immunotherapy as “precision therapy” in GU cancers
The therapeutic area of UBC has evolved rapidly following the 2016 approval of atezolizumab.

Five checkpoint inhibitors now approved for UC!

- Vinflunine (EU only)
- Atezolizumab (US/EU) (2L)
- Atezolizumab (US/EU) (1L) cisplatin-ineligible
- Nivolumab (US/EU) (2L)
- Durvalumab (US) (2L)
- Avelumab (US) (2L)
- Pembrolizumab (US/EU) (1L cisplatin-ineligible) (2L)

Timeline:
- 1990
- 2009
- MAY 2016
- FEB 2017
- APR 2017
- MAY 1, 2017
- MAY 9, 2017
- MAY 18, 2017

References:
1. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm501762.htm
2. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm539646.htm
5. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm557162.htm
6. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm559300.htm

1L, first-line; 2L, second-line; BCG, Bacillus Calmette–Guérin vaccine; UC, urothelial carcinoma.
Selection of Appropriate Genitourinary Cancers for Immunotherapy

- **Immunotherapy uses in genitourinary cancers**
  - FDA Approved Indications
    - Urothelial carcinoma
    - Clear cell renal cell carcinoma
  - Other potential approvals
    - High-grade castrate resistant prostate cancer with high tumor mutation burden
    - Platinum-resistant testicular germ cell tumors with high mutation burden

- **Biomarkers predicting immunotherapy response in genitourinary cancers**
  - PD-L1 immunostaining
  - PD-L1 (CD-274) Gene Amplification
  - MSI status
  - Tumor Mutation Burden
  - γ-interferon signature
  - Emerging Single Gene Biomarkers
    - PBRM1 mutation status
    - STK11 mutation status
    - MDM2 amplification status
The proportion of tumour area occupied by PD-L1 expressing ICs of any intensity

<table>
<thead>
<tr>
<th>SCORING DEFINITION</th>
<th>ASSAY</th>
<th>USED IN CLINICAL TRIALS BY</th>
<th>CUT-OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>The proportion of tumour area occupied by PD-L1 expressing ICs of any intensity</td>
<td>SP142¹</td>
<td>Roche²</td>
<td>IC ≥5%</td>
</tr>
</tbody>
</table>

IC, tumour-infiltrating immune cells; PD-L1, programmed cell death ligand-1; UC, urothelial carcinoma

SCORING DEFINITION
The proportion of TCs with membrane staining for PD-L1 at any intensity above background staining

ASSAY USED IN CLINICAL TRIALS BY CUT-OFF

<table>
<thead>
<tr>
<th>Assay</th>
<th>TC ≥1%¹,²</th>
<th>TC ≥5%³</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-8¹</td>
<td>Bristol-Myers Squibb²</td>
<td></td>
</tr>
<tr>
<td>73-10³</td>
<td>Pfizer / Merck KGaA³</td>
<td></td>
</tr>
</tbody>
</table>

UC: BMS and Pfizer / Merck KGaA algorithms use TC score

• BMS, Bristol-Myers Squibb; IC, tumour-infiltrating immune cells; PD-L1, programmed cell death ligand-1; TC, tumour cells; UC, urothelial carcinoma
The percentage of PD-L1 expressing TCs and ICs relative to the total number of TCs (CPS)

CPS, combined positive score; IC, tumour-infiltrating immune cells; MSD, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co; PD-L1, programmed cell death ligand-1; TC, tumour cells; UC, urothelial carcinoma

SCORING DEFINITION

TC: proportion of TCs with membrane staining for PD-L1 at any intensity above background staining
IC: proportion of ICs with staining for PD-L1 at any intensity above background staining

ASSAY USED IN CLINICAL TRIALS BY AstraZeneca

<table>
<thead>
<tr>
<th>SP263</th>
<th>AstraZeneca</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC ≥25% OR IC ≥25%</td>
<td></td>
</tr>
</tbody>
</table>

UC: AstraZeneca algorithm uses TC and IC scores

- IC, tumour-infiltrating immune cells; PD-L1, programmed cell death ligand-1; TC, tumour cells; UC, urothelial carcinoma
### Summary of PD-L1 IHC assay scoring in UC

<table>
<thead>
<tr>
<th>Bristol-Myers Squibb, Pfizer / Merck KGaA&lt;sup&gt;1-3&lt;/sup&gt;</th>
<th>MSD/Merck USA&lt;sup&gt;4,5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TCs</strong></td>
<td><strong>TCs</strong></td>
</tr>
<tr>
<td><strong>ICs</strong></td>
<td><strong>ICs</strong></td>
</tr>
<tr>
<td>TC area with PD-L1 expression</td>
<td>TCs with PD-L1 expression + ICs with PD-L1 expression</td>
</tr>
<tr>
<td>Not scored</td>
<td>Total number of TCs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Roche&lt;sup&gt;6-8&lt;/sup&gt;</th>
<th>AstraZeneca&lt;sup&gt;9,10&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TCs</strong></td>
<td><strong>TCs</strong></td>
</tr>
<tr>
<td><strong>ICs</strong></td>
<td><strong>ICs</strong></td>
</tr>
<tr>
<td>Not scored</td>
<td>IC area with PD-L1 expression</td>
</tr>
<tr>
<td></td>
<td>Tumour area</td>
</tr>
</tbody>
</table>

*When ICs are >1% of the tumour area. When ICs =1% of the tumour area, normal scoring is believed to be beyond the limit of detection for the pathologist; in these circumstances a simplified method is used<sup>1</sup>.*

**IC**, tumour-infiltrating immune cells; **IHC**, immunohistochemistry; **MSD**, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co; **PD-L1**, programmed cell death ligand-1; **TC**, tumour cells; **UC**, urothelial carcinoma

There are differences in the populations selected by 22C3 (CPS 10%), SP142 (IC 5%) and SP263 (TC/IC 25%) algorithms.

Discordance explained by:
- Inclusion of TC in SP263 algorithm vs SP142 algorithm
- Lower TC cut off for 22C3 CPS algorithm vs SP263 algorithm
- Different denominators for IC scoring approach in all 3 cases

Caveat: In this sample cohort, only 6% of samples were classed as PD-L1 high by SP142 assay using IC 5% algorithm.
Lymphoepithelioma-like bladder UC: PD-L1 IHC sustained by *PD-L1/2* gene amplification

Case ID#31: T3N0 > pT0pN0

PD-L1 CPS: 95%

Beyond PD-L1: The Search for New Biomarkers—A Multiparameter Approach

Tumor foreignness
Neoantigen load
TMB, DDR and ctDNA

Tumor sensitivity to immune effectors
MHC expression/function
MHC polymorphisms/mutations
IFN-γ sensitivity
Gene expression

Absence of inhibitory tumor metabolism
LDH, glucose utilization
IDO1, tumor acidity

Absence of soluble inhibitors
IL-6 → CRP/ESR
CD73 → adenosine

Absence of checkpoints
PD-L1

General immune status
Lymphocyte count, TIM3, LAG3, TIGIT, CD27, Ki67, PD-1 + CD8

Microbiome
Low bactericides
High Faecalibacterium prausnitzii

Immune cell infiltration
Intratumoral T cells
Shared T-cell clones
B7-H3/CD276 macrophages
CCL5-attracting T cells
NK cells

Immune cell infiltration
CCL5-expressing BATF3 DCs

Spatial correlations


BATF3, basic leucine aipper ATF-like transcription factor 3; CCL5, chemokine (C-C motif) ligand 5; CCR5, C-C chemokine receptor type 5; CRP, C-reactive protein; DC, dendritic cell; ESR, erythrocyte sedimentation rate; IDO, indoleamine 2,3-dioxygenase; IL, interleukin; LAG3, lymphocyte-activation gene 3; LDH, lactate dehydrogenase; MHC, major histocompatibility complex; TIL, tumor infiltrating lymphocyte; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains.
Predictive Biomarkers: MSI Status

• FDA-approved as a companion biomarker for pembrolizumab for all solid tumors including GU cancers
• MSI-high status extremely uncommon in GU cancers (1-2% of cases)
• Virtually all MSI-High cancers are TMB high
MSI-High is a subset of high TMB specimens

(100,000 human cancer genomes)

~84% of MSI-H specimens are TMB-H...

....However only 14.5% of TMB-H specimens are MSI-H

Chalmers et al. Genome Medicine (2017);9:34
High MSI sensor score (MSK-IMPACT) is associated with increased mutation burden

High MSI sensor score is associated with Lynch Syndrome

Presented By Gopa Iyer at 2017 ASCO Annual Meeting
Tumor-Specific Mutations Have the Potential to Generate Neoantigens

Mutation Load Comparisons

FoundationONE and MSK-IMPACT next generation sequencing panels (both FDA-approved) can accurately impute mutation load.

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<table>
<thead>
<tr>
<th>TMB Categories</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMB - High</td>
<td>greater than or equal to 20 mutations per megabase (~7% of specimens tested at Foundation Medicine are TMB-High)</td>
</tr>
<tr>
<td>TMB – Intermediate</td>
<td>between 6 and 19 mutations per megabase (~38% of specimens tested at Foundation Medicine are TMB-Intermediate)</td>
</tr>
<tr>
<td>TMB - Low</td>
<td>less than or equal to 5 mutations per megabase (~55% of specimens tested at Foundation Medicine are TMB-Low)</td>
</tr>
<tr>
<td>TMB – Unknown (cannot be determined)</td>
<td>A determination of TMB could not be made for this specimen due at least in part to low tumor content, high contamination rate, or poor exon coverage.</td>
</tr>
</tbody>
</table>
High TMB associated with ICPI OS in bladder cancer

Quartile-split TMB is associated with anti-PD-L1 OS in urothelial carcinoma
Patients with the highest TMB (Q4) had significantly longer OS vs those in Q1-Q3

Lack of correlation between PD-L1 IHC and TMB in UC treated with IO in different clinical stages

- PD-L1 IHC and TMB measure distinct biological features

Powles T, et al. GU-ASCO 2018

Necchi A, et al. ASCO 2018
Genomic Characterization of Testicular Germ Cell Tumors Relapsing After Chemotherapy

Andrea Necchi\(^a\), Gennady Bratslavsky\(^b\), Robert J. Corona\(^b\), Jon H. Chung\(^c\), Sherri Z. Millis\(^c\), Julia A. Elvin\(^c\), Jo-Anne Vergilio\(^c\), James Suh\(^c\), Shakti Ramkissoon\(^c\), Eric Severson\(^c\), Sugganth Daniel\(^c\), Jonathan K. Killian\(^c\), Siraj M. Ali\(^c\), Alexa B. Schrock\(^c\), Prasanth Reddy\(^c\), Vincent A. Miller\(^c\), Allison Welsh\(^c\), Laurie M. Gay\(^c\), Jeffrey S. Ross\(^b\)\(^c\)

| Main GA subgroups | Genes altered | Seminoma (n, %) | Nonseminoma (n, %) | p value
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no.</td>
<td></td>
<td>23</td>
<td>84</td>
<td>NS</td>
</tr>
<tr>
<td>RAS-RAF pathway</td>
<td>KRAS, NRAS, HRAS, BRAF</td>
<td>13 (56.5%)</td>
<td>44 (52.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>TP53 pathway</td>
<td>TP53, MDM2</td>
<td>1 (4.3%)</td>
<td>17 (20.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cell-cycle pathway</td>
<td>CCND1/2/3, CDK4/6, CDKN2A/B, RB1</td>
<td>12 (52.2%)</td>
<td>47 (56.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>RTK pathway</td>
<td>ERBB2, PDGFR, KIT, MET, FGFR1/2/3</td>
<td>6 (26.1%)</td>
<td>6 (7.1%)</td>
<td>0.02</td>
</tr>
<tr>
<td>PI3K pathway</td>
<td>PIK3CA, MTOR, PTEN, AKT1/2</td>
<td>6 (26.1%)</td>
<td>5 (6.0%)</td>
<td>0.02</td>
</tr>
<tr>
<td>DDR pathway</td>
<td>BRCA1/2, ATM, CHEK2, MUTYH</td>
<td>3 (13.0%)</td>
<td>11 (13.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean GA per tumor</td>
<td>2.9 (2.6)</td>
<td>4.0 (2.7)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Median GA per tumor (IQR)</td>
<td>2 (1–4.5)</td>
<td>3 (2–6)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Median GA per tumor (IQR)—testes</td>
<td>2 (1–2)</td>
<td>3 (2–5.5)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Median GA per tumor (IQR)—metastases</td>
<td>2.5 (1–6)</td>
<td>4 (1–6)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>MSI-high</td>
<td>0</td>
<td>1</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Median TMB (mut/Mb, range)</td>
<td>1.8 (0–6.3)</td>
<td>2.7 (0–23.4)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>TMB ≥10–20 mut/Mb</td>
<td>0</td>
<td>3 (3.5)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>TMB ≥20 mut/Mb</td>
<td>0</td>
<td>1 (1.2)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Predictive Biomarkers of response to immunotherapy in UC cancers: DDR-gene amplifications and response to IO – MSKCC cohort

Teo MY, et al. J Clin Oncol 2018
Emerging Single Gene Predictive Biomarkers of ICPI Response

Markers of Efficacy
- **BRAF** mutation
- **MET** Exon 14 splice site mutation
- **PBRM1** mutation

Markers of Resistance
- **STK11 (LKB1)**
- **JAK1/2**

Markers of Hyper-Progression
- **MDM2** amplification

Sharma et al., Cell 2017
**PBRM1** Mutation and Clinical Benefit from ICPI in ccRCC

Metastatic clear cell renal cell carcinoma to bone in a 70 year old Caucasian man. Comprehensive genomic profiling revealed an inactivating splice site 528+1G>C mutation in \textit{PBRM1} and an inactivating N141fs*3 mutation in the \textit{VHL} gene. The tumor was MSI stable and the TMB was 4 mutation/Mb. In addition, IHC staining for PD-L1 was negative (inset). PBRM1 protein loss or mutation is correlated with late tumor stage, low differentiation grade, and/or poor patient prognosis in ccRCC. In ccRCC, \textit{PBRM1} alterations are generally observed to be uniformly detected in ccRCC with \textit{VHL} inactivating mutations as seen in this case. \textit{PBRM1} mutations in ccRCC, in contrast with mesotheliomas, appear to be mutually exclusive with \textit{BAP1} alterations.
**PBRM1 Mutation Frequencies and Co-Altered Genes**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Frequency of PRMB1 Genomic Alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear Cell RCC</td>
<td>41%</td>
</tr>
<tr>
<td>Papillary RCC</td>
<td>23%</td>
</tr>
<tr>
<td>Peritoneal Mesothelioma</td>
<td>19%</td>
</tr>
<tr>
<td>Intra-hepatic Cholangiocarcinoma</td>
<td>9%</td>
</tr>
<tr>
<td>Extra-hepatic Cholangiocarcinoma</td>
<td>7%</td>
</tr>
<tr>
<td>Pleural Mesothelioma</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3%</td>
</tr>
<tr>
<td>Non-small Cell Lung Cancer</td>
<td>2%</td>
</tr>
<tr>
<td>Breast Carcinoma</td>
<td>2%</td>
</tr>
<tr>
<td>Colorectal Carcinoma</td>
<td>1%</td>
</tr>
</tbody>
</table>

Bratslavsky et al. ASCO 2018
STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma

Inactivation of STK11 (or its protein product, LKB1) by mutational or nonmutational mechanisms is associated with an inert or “cold” tumor immune microenvironment, with reduced density of infiltrating cytotoxic CD8+ T lymphocytes.

STK11 alterations enriched in TMB HIGH, PD-L1 LOW tumors

STK11-mutant NSCLCs may do worse on immunotherapies

Bonferroni P = 3.23*10^{-12}

HR = 2.59;  P = 0.0314

This observation is now confirmed by other groups and while provocative, requires validation in additional cohorts

Bladder cancer
FGFR inhibitors – a success story; insights into therapeutic sequences
Foundation Medicine Cohort (n=295)

- There were 75% male and 25% female patients with a mean age of 66 years.
- 295/295 (100%) of UC were high grade and 295/295 (100%) of UC were advanced stage (III and IV).
- 294/295 (99.7%) UC featured at least 1 genomic alteration (GA) on comprehensive profiling with a mean of 6.4 GA/UC.
- 61% SUB + INDEL
- 37% CNA
- 2% fusions.
275 (93%) UC had at least 1 clinically relevant GA (CRGA) involving 75 individual genes with a mean of 2.6 CRGA/UC

The most common clinically CRGAs were:

- CDKN2A (34%)
- FGFR3 (21%)
- PIK3CA (20%)

FGFR3 GA were of diverse type and included 10% fusions.

# Foundation Medicine Cohort (n=295)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Substitution</th>
<th>Truncation</th>
<th>Amplification</th>
<th>Deletion</th>
<th>Fusion/Rearrangement</th>
<th>Total count</th>
<th>% of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR3</td>
<td>53</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>63</td>
<td>21.4%</td>
</tr>
</tbody>
</table>

Phase 2 Erdafinitib in FGFR – Altered mUC

- Pan-FGFR (1-4) activity
- Study evaluated multiple dose/schedules – 8 mg QD (N=99)
- Centrally selected for FGFR fusions or mutations

Siefker-Radtke et al J Clin Oncol 36, 2018 (suppl; abstr 4503)
Foundation Medicine Cohort (n=295)

- 66F with stage IV disease
- FGFR3-TACC3 fusion as well as CDKN2A/B loss, MDM2 amplification and the MLL2 G5467fs*20 mutation seen
- 21.4% of the UC in this study harbored alterations of FGFR3 including base substitutions (83%), amplifications (2%) and fusions (11%)

Enrichment of FGFR3-TACC3 Fusions in Patients With Bladder Cancer Who Are Young, Asian, or Have Never Smoked – combined DFCI and TCGA cohorts

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>FGFR3-TACC3 Fusion</th>
<th>Total</th>
<th>FGFR3-TACC3 Fusion</th>
<th>Total</th>
<th>FGFR3-TACC3 Fusion</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Total</td>
<td>Yes</td>
<td>No</td>
<td>Total</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>3 (12)</td>
<td>22 (88)</td>
<td>25</td>
<td>1 (13)</td>
<td>7 (87)</td>
<td>8</td>
</tr>
<tr>
<td>51-65</td>
<td>2 (1)</td>
<td>135 (99)</td>
<td>137</td>
<td>5 (5)</td>
<td>90 (95)</td>
<td>95</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>5 (2)</td>
<td>245 (98)</td>
<td>250</td>
<td>1 (0)</td>
<td>252 (100)</td>
<td>253</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>402</td>
<td>412</td>
<td>7</td>
<td>349</td>
<td>356</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>6 (14)</td>
<td>38 (86)</td>
<td>44</td>
<td>0 (0)</td>
<td>3 (100)</td>
<td>3</td>
</tr>
<tr>
<td>African American</td>
<td>1 (4)</td>
<td>22 (96)</td>
<td>23</td>
<td>0 (0)</td>
<td>5 (100)</td>
<td>5</td>
</tr>
<tr>
<td>White</td>
<td>3 (1)</td>
<td>324 (99)</td>
<td>327</td>
<td>7 (2)</td>
<td>332 (98)</td>
<td>339</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>384</td>
<td>394</td>
<td>7</td>
<td>340</td>
<td>347</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>8 (7)</td>
<td>103 (93)</td>
<td>111</td>
<td>3 (4)</td>
<td>81 (96)</td>
<td>84</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>2 (1)</td>
<td>286 (99)</td>
<td>288</td>
<td>4 (2)</td>
<td>257 (98)</td>
<td>261</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>389</td>
<td>399</td>
<td>7</td>
<td>338</td>
<td>345</td>
</tr>
</tbody>
</table>

Nassar AH, et al. JCO Precis Oncol 2018
Strategies for taking genomic profiling into the clinic
Pembrolizumab > Radical Cystectomy in MIBC (PURE-01 study)
• The proportion of pre-therapy versus shared versus post-therapy genomic alterations (FoundationONE assay) in 14 patients with paired tumor tissue samples

Necchi A, et al. ASCO 2018, ESMO 2018
Patient journey and therapeutic options across the clinical stages

MIBC/1L metastatic
- Neoadjuvant/Adjuvant/1L Cisplatin-base chemo first

Cis-ineligible/treated pts, FGFR-mutation/fusion+ tumor
pan-FGFR inhibitor-first?

Cis-ineligible/treated pts, FGFR wild-type tumors
ICI first option (IO combo?)

ICI progression, FGFR wild-type
Ramucirumab-docetaxel first¹
Continue ICI
Salvage chemo

---

FGFR: fibroblas growth-factor receptor; ICI: immune checkpoint inhibitors; IO: immune-oncology; MIBC: muscle-invasive bladder cancer

Strategies for taking genomic profiling into the clinic

S1500 (N=180)

Detailed analyses of: MET mutation, MET amplification

Primary Endpoint:
- Progression-free survival

Secondary Endpoints:
- Overall survival
- Response rate
- Adverse events
- Exploratory evaluation of:
  - MET mutational status
  - MET expression

P.I.: SK Pal; NCT02761057
A Phase II Trial of Risk Enabled Therapy After Initiating Neoadjuvant Chemotherapy for Bladder Cancer (RETAIIN BLADDER) NCT02710734

Major Inclusion Criteria:

- cT2-T3 N0M0
- ECOG 0-1
- Urothelial Predominant Histology
- MFS is defined as the absence of a recurrence of urothelial carcinoma that is >cN1 (more than one clinically suspicious pelvic lymph node) or surgically unresectable local recurrence (eg, cT4a) or M1 disease.

Primary Endpoint: Metastasis-free survival (MFS) at 2 years. Non-inferiority design with a 14% margin between risk-adapted design (MFS=78%) and standard-of-care (MFS=64%). Sample size=70 with an 82% power. Type I error=0.045
BISCAY: open-label, randomised, multi-drug, biomarker-directed, multicentre, multi-arm Phase 1b study in patients with muscle-invasive bladder cancer who have progressed on prior treatment

A Phase 1b umbrella* study and the first multi-drug study combining immunotherapy and small molecule agents in metastatic bladder cancer

1. Objective is to explore predictive value of common molecular aberrations in MIBC
2. Assign patients to a cohort with the best chance of benefit
3. Primary endpoint is ORR
4. Ensure that all patients have the option to receive immunotherapy
5. Signal search within each cohort and make early decisions based on the benefit-risk
6. Carry out further collaborative translational science work
7. Option for additional cohorts to be added to the overall study based on translational science evidence
8. Steer the study in direction of where the science is leading
9. Can enable rapid deployment to earlier stages

*STUDY OPEN in UK, US, France, Spain, Canada centres
Exceptional response to olaparib in BRCA2-altered urothelial carcinoma after PD-L1 inhibitor and chemotherapy failure

**Previous treatments:**
Atezolizumab > MVAC > Vinflunine

**Off-label therapy:**
Oct 2017 > Sept 2018
Olaparib 400 mg bid

**PARP inhibitor trials in UC:**
- RUCAPARIB (unselected pts); NCT03375307 and NCT03397394
- OLAPARIB (enriched population); NCT03375307 and NCT03448718
- OLAPARIB + DURVALUMAB (enriched population); BISCAY trial, NCT02546661
- OLAPARIB + DURVALUMAB (CDDP-ineligible pts); BAYOU trial, NCT 02516241

See Chung JH, et al. Pan-cancer assessment of BRCA1/2 genomic alterations (GAs) by comprehensive genomic profiling (CGP) of tissue and circulating tumor DNA (ctDNA). ESMO 2018

Somatic vs Germline DDR gene alterations in UC, RCC and PCa

Frequency and distribution of pathogenic germline mutations in 176 patients with UC

Germline mutations were observed in 57.8% of BRCA2-mutated cases, 25.0% of BRCA1-mutated cases, 35.8% of ATM-mutated cases, 80.0% of CHEK2-mutated cases, 52.2% of FANCA-mutated cases, 42.3% of MSH2-mutated cases, 20.0% of MSH6-mutated cases, 25.0% of MLH1-mutated cases, and 44.4% of PMS2-mutated cases. Germline/somatic status was determined computationally² for short variant mutations in each of the DNA repair genes.

Prospective comprehensive genomic profiling of 3,476 primary and metastatic prostate tumors¹


Carlo MI, et al. J Clin Oncol 36, 2018 (suppl; abstr 1516)
Carlo MI, et al. JAMA Oncol. 2018 Sep 1;4(9):1228-1235
Broadening the View of Germline Mutations in GU cancers

• NGS has revolutionized precision oncology, with paired somatic and germline DNA variant analysis becoming more powerful and more widely accessible for clinical application
• A significant portion of patients have been incidentally found to have pathogenic or likely pathogenic germline mutations
• Many of these patients do not meet current clinical criteria for germline testing
• Thus, mutations in genes that are potentially associated with a patient’s cancer treatment and care, as well as cancer risk and prevention for the patient’s family members, are going undiscovered
# ABOUT THE TEST:

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

# PATIENT RESULTS

- 6 genomic alterations
- 5 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 5% clinical trials

# TUMOR TYPE: KIDNEY RENAL PAPILLARY CARCINOMA

Genomic Alterations Identified:
- BRAF amplification
- MET amplification
- CDKN2A/B loss
- KEL amplification
- MA012 rearrangement exon 7

# THERAPEUTIC IMPLICATIONS

<table>
<thead>
<tr>
<th>Genomic Alterations Detected</th>
<th>FDA Approved Therapies (by patient's tumor type)</th>
<th>FDA Approved Therapies (by another tissue type)</th>
<th>Potential Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF amplification</td>
<td>Sorafenib</td>
<td>Regorafenib</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td>MET amplification</td>
<td>None</td>
<td>Cabozantinib</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td>CDKN2A/B loss</td>
<td>None</td>
<td>Crizotinib</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td>KEL amplification</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>MA012 rearrangement exon 7</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient nor are they ranked in order of level of evidence for this patient's tumor type.*

Confidential – Do Not Distribute
A 60 year old female post neo-adjuvant cisplatin and gemcitabine with cystectomy showing advanced UC.

After tumor progression, CGP revealed alterations in NF2 Y153*1 (minor allele frequency [MAF]: 7%), ATM V2119fs*8 (MAF: 8%), ATR splice site 7349+2T>C (MAF: 44%), and TP53 R280K (MAF: 6%).

Given preclinical work suggesting NF2 loss may be associated with sensitivity to MTOR inhibitors, the patient was started on everolimus and paclitaxel using a dosing regimen currently being examined in a phase II study in urothelial carcinoma (everolimus at 10 mg oral daily and paclitaxel at 80 mg/m² intravenous weekly).

Imaging over 11 months of therapy with this regimen has demonstrated continued regression of the vaginal cuff lesion and disappearance of the previously noted iliac adenopathy.
Kidney Cancer

Genomic Characterization of Sarcomatoid Dedifferentiated Alterations


Platinum Priority – Kidney Cancer

Characterization of Clinical Cases of Advanced Papillary Renal Cell Carcinoma


Responses to Alectinib in ALK-rearranged Papillary Renal Cell Carcinoma


Comprehensive Genomic Profiling of Renal Cell Carcinoma at Initial Diagnosis and Putative Local Recurrence


Germ cell tumors - the most frequently reported genomic alterations in the two histologic subgroups

Clinical case of refractory testicular seminoma with outstanding response to FMI-based everolimus therapy

Patient-centric vision Vs. Patient-engaged vision in personalized medicine

New figures are joining multidisciplinary discussions and clinical trials planning
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