Precision Oncology in routine practice: the coming of age?

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The 50s to the 90s: embryogenesis

- 1952: photo of the helical shape of DNA
- 1953: Discovery of the double helix
- 1961: The code from DNA to protein
- 1977: The Sanger rapid DNA seq technique
- 1983: Huntington’s disease is mapped
- 1990: First evidence of the BRCA1 gene
2000s: the genome was decoded and technological advances accelerated...

The era of massively parallel sequencing or NGS

<table>
<thead>
<tr>
<th></th>
<th>Sanger sequencing</th>
<th>Massively parallel sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of input DNA</td>
<td>High to nanograms</td>
<td>Moderate to milligrams</td>
</tr>
<tr>
<td>Library amplification method</td>
<td>Retardation</td>
<td>PCR amplification</td>
</tr>
<tr>
<td>Sequencing reaction</td>
<td>Sanger chain termination</td>
<td>Sequencing by synthesis</td>
</tr>
<tr>
<td>Capture of signal</td>
<td>Fluorescence-based scanning</td>
<td>Sequencing by ligation</td>
</tr>
<tr>
<td>Read length</td>
<td>Moderate (1000 bp)</td>
<td>Short (100-500 bp)</td>
</tr>
<tr>
<td>Multiplexing capacity</td>
<td>Averaged across many copies of DNA</td>
<td>Averaged across many copies of DNA</td>
</tr>
<tr>
<td>Error rate</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cost per base called</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>
The Precision Oncology schema

The leap was too far (2010 -2015)…
Obstacles and Pitfalls in the clinic

- Physician education and standardized guidelines
- Technology, logistics and resources:
  - Biopsies
  - Genomics, epigenetics, transcriptomics, proteomics
  - Heterogeneity
  - Liquid biopsies
- Target prioritization and molecular advisory boards
- Genetic counselling
- Drug access and novel clinical trial designs
- Data sharing

Limitations of Targeted Gene Sequencing: transcriptomics

RNA-based Precision Medicine

Neuroendocrine small gut tumor:
NGS found no DNA alterations;
RNA matches revealed AKT2 and AKT3 overexpression.
The WINTHER CMC recommended an mTOR inhibitor.
Everolimus was started (May 2015).

Gene fusions are not detected using small panel TGS

Recurrent cancer-associated transcript fusions in 33 cancer types

Efficacy of laroctrectinib in TRK fusion cancers
Tissue-agnostic FDA approval

Intra-tumor heterogeneity: resistant and lethal clones in metastatic breast cancer

The advent and potential applications for liquid biopsies

Different techniques for liquid biopsies

**Candidate mutation**
- Mutation(s) are known or first identified in the primary tumor and then followed in plasma
- Higher sensitivity, feasible even when low disease burden
- Only few mutations can be tracked

**Unbiased**
- Direct plasma ctDNA detection without prior analysis of tumor
- Lower sensitivity, high disease burden required
- Genome-wide analysis

Digital PCR, targeted sequencing

Courtes F Rothé
A therapeutically targetable mutation was detected in tissue alone for 47 patients (20.5%), whereas the addition of plasma testing increased this number to 82 (35.8%).

Aggarwal C et al. JAMA Oncology 2018.
New partners involved in a molecular advisory board

- Pathologist
- Ethicist
- Early clinical trials expert
- Geneticist
- Medical oncologist
- Sequencing scientist
- Translational oncology expert
- Bio-informatician

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**LETTER**

doi:10.1038/nature10668

Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR

Aniruddh Prabhulal, Chong Sun, Sidong Huang, Federica Di Nicolantonio, Ramon Salazar, Davide Zecchin, Roderick L. Bojarsberger, Alberto Bardelli & René Bernards

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Target prioritization

- **Level 1**: FDA-recognized biomarker predictive of response to an FDA-approved drug in this indication
- **Level 2A**: Standard care biomarker predictive of response to an FDA-approved drug in this indication
- **Level 2B**: Standard care biomarker predictive of response to an FDA-approved drug in another indication, but not standard care for this indication
- **Level 3A**: Compelling clinical evidence supports the biomarker as being predictive of response to a drug in this indication, but neither biomarker nor drug are standard care
- **Level 3B**: Compelling clinical evidence supports the biomarker as being predictive of response to a drug in another indication, but neither biomarker nor drug are standard care
- **Level 4**: Compelling biological evidence supports the biomarker as being predictive of response to a drug, but neither biomarker nor drug are standard care
- **Level R1**: Standard care biomarker predictive of resistance to an FDA-approved drug in this indication

**ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)**

<table>
<thead>
<tr>
<th>Tier</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (I-A, I-B, I-C)</td>
<td>Targets ready for implementation in routine clinical decisions</td>
<td>HER2 in breast cancer, BRCA1/2 in ovarian and breast cancer, EGFR, ROS1/ALK in NSCLC</td>
</tr>
<tr>
<td>II (II-A, II-B)</td>
<td>Investigational targets likely to define patients who benefit from a targeted drug, but additional data needed</td>
<td>PTEN pathway (PIK3CA, AKT1)</td>
</tr>
<tr>
<td>III (III-A, III-B)</td>
<td>Clinical benefit previously demonstrated in other tumour type or for similar molecular targets</td>
<td>BRAF in non-melanoma cancers, PALB2 and other non-BRCA DNA repair mutations</td>
</tr>
<tr>
<td>IV (IVA, IVB)</td>
<td>Preclinical evidence of actionability</td>
<td>Hypothetical targets for future clinical testing</td>
</tr>
<tr>
<td>V</td>
<td>Evidence supporting co-targeting approaches</td>
<td>PIK3CA in ER+, HER2-breast cancer</td>
</tr>
<tr>
<td>X</td>
<td>Lack of evidence for actionability</td>
<td>NSCLC, non-small cell lung cancer</td>
</tr>
</tbody>
</table>

*J Clin Oncol 34, 2016 (suppl; abstr 11583)*

*ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)*

1893 patients were enrolled

245 patients (15 %) who were tested were subsequently treated...

... on 277 therapeutic clinical trials...

... including 84 patients (5 %) on 89 genotype-matched trials.

Very few alteration – drug couples using WES...
Common cancers are now rare

Garraway LA, J Clin Oncol 2013;31:1806-1814

Novel clinical trial designs

West HJ. JAMA Oncol 2017.
What about Precision Immunotherapy?
- Mismatch repair deficiency and tumor mutational burden
- Identifying hyperprogressors
- Personalized vaccines

Prediction response: PDL1 to Mismatch Repair (MMR) Deficiency and Tumor Mutational Burden (TMB)


Atezolizumab PFS benefit in bTMB subgroups validated in the OAK study

- The bTMB ≥16 population accounted for 27% of the BEP (N = 158)
- PFS benefit with atezolizumab versus docetaxel was observed in the bTMB ≥16 subgroup
- No prognostic effect was observed: patients with bTMB ≥16 did not have improved PFS compared with patients with bTMB <16 in the docetaxel arm

Interaction P = 0.036

The concept of « hyperprogression »

36 year-old TNBC patient

21 days after 1 cycle of pembrolizumab
### Findings

<table>
<thead>
<tr>
<th>Age – Sex</th>
<th>Disease</th>
<th>TMB (Mut/Mb)</th>
<th>Checkpoint Inhibitor</th>
<th>NGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 – Male</td>
<td>NSCLC</td>
<td>6.30</td>
<td>Nivolumab</td>
<td>CCDN1, CKD4, FGFR2, FGFR4, MDM2, FGFR3, ERBB2</td>
</tr>
<tr>
<td>60 – Male</td>
<td>Esophageal Adeno</td>
<td>12.00</td>
<td>Pembrolizumab</td>
<td>CCDN2, FGFR, FGFR2, FGFR3, FGFR4</td>
</tr>
<tr>
<td>77 – Male</td>
<td>Esophageal SCC</td>
<td>7.20</td>
<td>Pembrolizumab</td>
<td>EPHA3, MDM4, CHEK2, EP300, NOTCH1, SPOP, TP53</td>
</tr>
<tr>
<td>59 – Male</td>
<td>Lung adenocarcinoma (neuropathologies)</td>
<td>4.50</td>
<td>Nivolumab</td>
<td>CCND1, FGFR2, FGFR3, FGFR4, KRAS, NF2L2, TP53</td>
</tr>
<tr>
<td>29 – Female</td>
<td>Duodenal Carcinoma</td>
<td>40.50</td>
<td>Nivolumab</td>
<td>KRAS, ATM, MSH6, SMARCBL1, APC, CDKN2A, CREBBP, CTCF, LRPIB, PIK3R1, TP53</td>
</tr>
</tbody>
</table>

3 months prior to ICI  
Prior to ICI  
3 months Post-ICI

Singavi A et al. ESMO 2017.

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**LETTERS**

Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer

William Zachoval, Yarden Czernichow, Marc Martel, Ho Kui Yong, Che-Che Loo, PM Chan, Anna Perminov, Michelle Laparot, Thomas Habermacher, Todd Poborch, Bernd Habermacher, L. Hu, Katja Brandt-Ambros, Robert K. Somerville, Paul A. Richardson, Stephan A. Reschlag, Yvonne J. Schöffski and Dennis A. Nadkarni

Immunotherapies often elicit responses in the tumor microenvironment, which are a result of an immune response to recognition of neoantigens derived from somatic mutations. While tumor dormancy is often observed in the setting of an effective immune response, upcoming studies have illustrated that some tumors can achieve durable remission following treatment with checkpoint inhibitors. Here, we present a case of breast cancer with extensive liver metastases, which regressed following treatment with pembrolizumab. The patient presented with metastatic breast cancer in 2014. After treatment with chemotherapy, the patient developed extensive liver metastases. Pembrolizumab was initiated in 2015, and the patient showed a partial response with an increase in activity of tumor markers. However, there was minimal clearance of liver metastases. A second-line treatment with atezolizumab was initiated, and the patient experienced a complete response, with normalization of tumor markers and a radiologic complete remission. The patient was subsequently treated with a third-line treatment with nivolumab, and the liver metastases continued to decrease, leading to a complete radiologic remission. This case highlights the potential for immune recognition of somatic mutations to lead to durable regression in metastatic breast cancer.
So what do I do in my clinic?

AURORA: Aiming to Understand the Molecular Aberrations in Metastatic Breast Cancer

Integrate molecular imaging as a predictive biomarker

- HER2-PET
- FES-PET
- PARP1-PET

- Makvandi M et al. J Clin Invest 2018
Data Sharing

Take home messages

- Use large and “comprehensive” panels: point mutations, CNVs, gene fusions, DNA damage response genes, mutational burden (solid or liquid)

- Prioritize targets within a molecular tumor board using published level of evidence scales

- Favor inclusion in clinical trials and try to avoid off-label therapy

- Share your data
Let’s interact… @aftimosp

Clinical trial referrals: trials.ijbctcu@bordet.be