Precision medicine becomes reality for tumor type-agnostic therapy

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According to FDA spokesperson Stephanie Yao, “Much still needs to be learned, but as we further understand cancers, it is possible we could see a shift from approving drugs based on disease type to the molecular pathways that drive them.” Nov 2013
Tumor type-agnostic therapy

• Common tumors can have:
  • Molecular subtypes
  • Therapeutics to match

• Rare cancers can have driver mutations with therapeutics to match

• Rapidly evolving evidence for new driver and pathway mechanisms with potential therapeutics.

\(^a\) Pao and Hutchinson Nature Medicine 18: 349-351, 2012
\(^b\) Von Hoff et al. NEJM 361:1164-1172, 2009
\(^c\) TCGA Nature 497: 67-73, 2013; NEJM May 1\(^{st}\) 2013

Basal cell – PTCH mutation \(^b\)
A very robust analysis of the tumor’s biology and potential clinically actionable targets can be enabled by a Multi-platform, technology independent analysis (mutational, rearrangements, gene copy number, etc.)
Cancer is a dynamic reality: Intra-tumor heterogeneity & the development of therapeutic resistance

Forty five out of 160 breast cancer samples (28%) exhibited changes in hormone receptor status.

Fifteen percent of tumors change human epidermal growth-factor receptor 2, or HER2, status during the course of disease.

Since these changes can completely change the patient's clinical management... patients should undergo regular biopsies.
Strategies in the fight against Cancer

- Primary prevention (healthy life-style, drugs, surgery, etc.)
- Secondary prevention (screening programs)
- Increase in diagnostic accuracy (technology, molecular pathology)
- Cancer biology knowledge enhancement (basic, translational & clinical research)
- Treatment efficacy: (A) personalized treatments (B) well-trained multidisciplinary teams, (C) continuum of treatment
Applications of Liquid Biopsies (ctDNA)

• Early detection
• Assessment of molecular heterogeneity of overall disease
• Identification of genetic determinants for targeted therapy
• Evaluation of early treatment response
• Monitoring of minimal residual disease
• Assessment of evolution of resistance in real time
Liquid bx screening approach

With non-invasive prenatal testing, several groups incidentally detected copy number alterations (CNA) in cfDNA that could not be attributed to the maternal or fetal genomic constitution.

Clinical work-up lead to the diagnosis of several different types of cancer in asymptomatic pregnant women.

In addition to CNAs also structural variants (SV) and single nucleotide variants (SNV) can be evaluated.

Monitoring cancer evolution

Hypothesized Dynamics of Resistance

Vilar et al Nature 2012

Bettegowda et al, Sci Tran Med Feb 2014
Tumor type-agnostic therapy. Biomarkers of response in tumor biopsies

The development of cancer drugs that are “tissue agnostic.”

Pembrolizumab was approved in 2017 for MSI-high tumors regardless of site of origin. It had previously been approved for multiple tumors.

Other tentative Biomarkers for immune therapies:

- PD1/PD-L1 expression
- Tumor infiltrating lymphocytes (TIL)
  - A “pre-existent” adaptive T-cell response in the tumor microenvironment correlates with clinical response to checkpoint blockade
  - Inflamed tumors
- Tumor Mutation Burden (TMB)
**Conclusions**

- Nivolumab + ipilimumab provided durable clinical benefit in previously treated patients with dMMR/MSI-H mCRC
  - High ORR (55%) and durable responses (median DOR not reached)
  - Median PFS and OS not reached with median follow-up of 13 months; 85% of patients alive at 1 year
- Meaningful improvements in quality of life were observed
- Safety was manageable with a low rate of discontinuation due to TRAEs
- Indirect comparisons in CheckMate-142 suggest that nivolumab + ipilimumab provides improved clinical benefit relative to nivolumab monotherapy
- Nivolumab + ipilimumab represents a promising new treatment option for patients with previously treated dMMR/MSI-H mCRC
Emerging Biomarkers of Response to Immunotherapy in Liquid Bx

- **Tumor mutation burden (TMB)**
  - High TMB may predict response across most tumor types
  - Mutations may encode for neo-antigens… recognized by T-cells

- **Soluble PDL1**
  - Although PD-L1 expression appears to enrich for response in some disease settings, it has low negative & positive predictive value

- **Pre-existent tumor-antigen specific T-cell clones**
Neo-antigens as Biomarkers of Response to Immunotherapy in Liquid Bx

- Neoantigen load/signature related to clinical response (*Brown Gen Res 2014; Champiat Oncoimmunology 2014; Snyder NEJM 2014*)


- Neoantigen-specific T cells kill tumors *in vivo*
Tumor neo-epitopes & T-cell response

• Long-term PDAC survivors display an enhanced tumor-specific T cell response
• Increased T cell response and survival are associated with unique neo-epitope quality, not quantity
• Homology of tumor neo-epitopes with those from microbiota are associated with enhanced immune response and survival
• Persistent T-cell clones that cross react with both tumor and microbiota are displayed by long-term survivors
• Implications:
  • Selection of patients for immune treatments
  • Design of individualized peptide-based vaccines
Significant differences in diversity and composition of the gut microbiome was noted in responders (R) vs non-responders (NR) to anti PD-1.

There was a higher abundance of chlostridiales in R and of bacteroidales in NR.

Diversity (p=0.009, HR=7.67) and abundance of specific bacteria in R (p=0.007, HR=3.88) was associated with improved PFS

Dubin K et al. Nar Comun 2016
Wargo J et al. ASCO 2017
Immune therapy & liquid bx

- Immune therapy responders have durable responses, greater than those with Chemo plus biologics.
- Cold tumors need a previous step to become hot (vaccines, RT..)
- Blood keeps the information of past encounters of immune cells with different antigens (microbial, tumor….)
- We are learning how to interpret results from liquid biopsies, T-cell responses to tumor antigens, response rates & duration, to novel immune treatment modalities.
- Promising future but significant challenges ahead, like dealing with big data sets.
Another FDA approved tissue-agnostic drug

On November 27, 2018, by the FDA approved larotrectinib, the first drug fully approved independent of the tumor site of origin. It is a new paradigm in the development of cancer drugs that are “tissue agnostic.”

Larotrectinib was found to selectively inhibit the neurotropic receptor tyrosine kinase - NTRK - fusion proteins and demonstrated a 75 percent overall response rate across different types of solid tumors.

NTRK fusion occurs in < 1% of people with cancer, although in the study leading to FDA approval, the RR to larotrectinib was over 75%.
We have three different genes: NTRK1, 2, and 3. NTRK1 fusions are found in tumours like colorectal cancer or glioblastoma. NTRK2 fusions are more frequently found in lung adenocarcinoma or at the neck in squamous cell carcinoma, and NTRK3 fusions are a hallmark of secretory breast carcinoma, congenital mesoblastic nephroma, or congenital fibrosarcoma. Altogether, you can see that we have very different types of tumours and very different proportions of tumours with NTRK gene fusions. For all those type of tumours, using TRK inhibitors has proven to save lives.

tumor type-agnostic therapy

<table>
<thead>
<tr>
<th>Gene</th>
<th>Normal Physiological Role</th>
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</thead>
<tbody>
<tr>
<td>NTRK1</td>
<td>Pain, thermoregulation</td>
</tr>
<tr>
<td>NTRK2</td>
<td>Movement, memory, mood, appetite, bodyweight</td>
</tr>
<tr>
<td>NTRK3</td>
<td>Proprioception</td>
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</tbody>
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Activity of TRK Fusion Protein

- Fusion of Genes
  - Uncontrolled overexpression of receptor
  - Uncontrolled activation of kinase
  - Oncogenic driver, continuous proliferation

Addressing Resistance to First-Generation TRK Inhibitors: Emerging Agents

- TPX-0005
  - Phase 1/2
  - Target fusions: NTRK1, ALK, NTRK3, ROS1
- LOXO-195
  - Phase 1/2
  - Target fusions: NTRK1, NTRK2, NTRK3

Second-generation TRK inhibitors in development

Rare cancer (NTRK is pathognomonic)
- IHC, FISH
  - If screening is routinely performed (e.g., NSCLC):
    - Add NTRK fusion to RNA-based NGS panel

Common cancer (NTRK is rare)
- If screening is not routinely performed (e.g., CRC):
  - IHC
  - If positive, use NGS-RNA, add NTRK fusion

TRK inhibitors have demonstrated quick onset of action and durable responses

Activity of TRK inhibitors was observed regardless of age and tumour type

Identification of tumours for NTRK fusions will be key to optimising treatment
Translational research

Basic Research     Translational Research     Clinical Research

Bidirectionality
Cancer is a dynamic & complex disease

There are interlinked cellular signalling pathways in mCRC

Multidisciplinary approach & precision treatment strategies for cancer patient management

- Right patient
- Right tumor profile
- Right drugs
- Right sequence

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- Increased efficacy
- Improved safety
- Increased cost-efficacy
¡¡¡ Ata a próxima !!!

¡¡¡ Muchas gracias !!!

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