Cross-Institutional Implementation of Cancer Genome Sequencing for Personalized Oncology

Lessons From the MASTER Program of the German Cancer Consortium

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Integrating Genomics Into Personalized Healthcare

Brussels | February 12, 2019
Large-scale sequencing projects have completed exomes/genomes from >50,000 cases representing >80 cancer types. Most common (present at >5% frequency per tumor type) cancer drivers are defined. Majority of cancer genes mutated at frequencies of <5% within any given histologic tumor subtype.

**Gene mountains and hills**
*Wood et al. Science 2007*

**Long tail of actionable cancer gene alterations**
*Lawrence et al. Nature 2013*
• 1,500-5,000 NTRK fusion-positive cancers in the US annually
• Constitutively active receptor tyrosine kinases
• Small-molecule inhibitors
  • Larotrectinib
  • Entrectinib

• Pooled analysis of 3 larotrectinib basket trials
• 55 NTRK fusion-positive patients (pediatric, adult)
• Overall response rate: 75%
  • Complete: 13%
  • Partial: 62%
• Efficacy across age groups and histologies
• Median response duration not reached (median follow-up: 9.4 months)

Drilon et al. N Engl J Med 2018
**Sensitivity**

- Overall mutational load and neoantigen burden
  
  *Rizvi et al. Science 2015*

- Neoantigen intratumoral heterogeneity
  
  *McGranahan et al. Science 2016*

- Immunogenic insertion/deletion mutations
  
  *Turajlic et al. Lancet Oncol 2017*

- PDL1 amplification and/or overexpression
  

- Structural rearrangements of **PDL1/2**
  
  *Steidl et al. Nature 2011*

- Disruption of **PDL1** 3’ untranslated region
  
  *Kataoka et al. Nature 2016*

- Loss-of-function PBRM1 mutations
  
  *Miao et al. Science 2018*

- T-cell-inflamed gene expression profile
  
  *Cristescu et al. Science 2018*

**Resistance**

- Inactivating JAK family member and B2M mutations
  

- MDM2/4 amplification
  

- PTEN loss
  
  *Peng et al. Cancer Discov 2016*

- Inactivating STK11 mutations
  
  *Skoulidis et al. Cancer Discov 2018*
Comprehensive Molecular Profiling

Molecular diversity and genetic taxonomy of cancer

Individual, “private” patterns of molecular lesions

Actionability of molecular lesions

Comprehensive molecular stratification approaches that are able to capture the entire spectrum of
- Rare driver mutations
- Complex, multifactorial biomarkers
- Newly emerging diagnostic, prognostic, and predictive parameters
Molecularly Aided Stratification for Tumor Eradication Research

**Molecular diversity and genetic taxonomy of cancer**

**Individual, “private” patterns of molecular lesions**

**Actionability of molecular lesions**

- Young adults with advanced-stage cancer
- Patients with rare tumors
- Fast-track exome and RNA sequencing
-~ 100 external partners

**Start:** 06/2013

**MASTER Registry Trial**

- Feasibility
- Diagnostic information
- Therapeutic opportunities

**Molecularly stratified clinical trials**

**Since 10/2016:**
Genome sequencing (60x)

*Horak et al. Int J Cancer 2017*
Joint DKTK activity since March 2016

- Institutional Review Board approval
- Internet-based clinical data repository
- Access to sequencing data
- DKTK MASTER Molecular Tumor Board
  - Semiweekly videoconference
- DKTK MASTER Scientific Board
  - Monthly videoconference

Joint publications

- Lier, Penzel, Heining et al. JCO Precis Oncol 2018
- Heining, Horak, Uhrig et al. Cancer Discov 2018
- Perera-Bel et al. Genome Med 2018
- Terziev et al. Eur J Haematol 2018
- Chudasama, Mughal, Sanders, Hübschmann et al. Nat Commun 2018
- Ugurel et al. Eur J Cancer 2017
- Czink et al. Cold Spring Harb Mol Case Stud 2017
- Chudasama et al. Clin Cancer Res 2017
- Czink et al. Z Gastroenterol 2016
- Kordes, Röring, Heining et al. Leukemia 2016
January 30, 2019
Molecular tumor board
Management recommendation (Level 1-4)
Genomics-guided clinical management
Disease control rate (CR, PR, SD)
Progression-free survival ratio >1.3

1,382 patients
~80%
~35%
~40%
~45% (MOSCATO 01: 33%)
Clinical evaluation of rare germline variants in 220 tumor predisposition genes

- Pathogenic variants (ACMG Class 5) in 23 tumor predisposition genes (BRCA1/2, PALB2, ATM, NF1, MEN1, RB1, APC, SDHB, PTEN, CDH1, MSH2, etc.) in 11% of cases
- Carrier status for autosomal recessive disorders (Fanconi anemia, Bloom syndrome, xeroderma pigmentosum, etc.) in 4% of cases
- Implications for patients and family members (genetic counseling, predictive diagnostics, surveillance, prevention)
- Entry points for targeted therapies in individual patients (e.g. PARP inhibition in patients with pathogenic BRCA1/2 or PALB2 mutations)
Reevaluation of clinical diagnosis in ~5% of cases

- Close interaction with pathology essential

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mutation(s)</th>
<th>Differential Diagnosis</th>
<th>Potential Clinical Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovial sarcoma</td>
<td>FUS-CREB3L2</td>
<td>LGFMS</td>
<td>→ Surgery</td>
</tr>
<tr>
<td>Hidradenocarcinoma</td>
<td>SS18-SSX2</td>
<td>Synovial sarcoma</td>
<td>→ Doxorubicin/ifosfamide</td>
</tr>
<tr>
<td>Neuroendocrine carcinoma</td>
<td>EWSR1-WT1</td>
<td>DSRCT</td>
<td>→ EWING 2008</td>
</tr>
<tr>
<td>Carcinoma of unknown primary site</td>
<td>RP3-388E23.2-NFIB FGFR2-WAC IDH1 p.R132H EWSR1-WT1 NUTM1-NSD3</td>
<td>ACC CCC CCC DSRCT NUT midline carcinoma</td>
<td>→ Vorinostat* ☞ FGFR inhibitor ☞ IDH1 inhibitor ☞ EWING 2008 ☞ BET inhibitor</td>
</tr>
<tr>
<td>Thymic carcinoma</td>
<td>NUTM1-BRD3</td>
<td>NUT midline carcinoma</td>
<td>→ BET inhibitor</td>
</tr>
<tr>
<td>Urothelial carcinoma</td>
<td>NUTM1-BRD4</td>
<td>NUT midline carcinoma</td>
<td>→ BET inhibitor</td>
</tr>
</tbody>
</table>

*Not approved for this indication in Germany
Various NRG1 fusions in KRAS wildtype pancreatic adenocarcinoma

- EGF-like domain retained in all cases
- Transforming activity in vitro and in vivo

**Wildtype KRAS and gene fusion affecting kinase signaling pathways in 4 of 17 young adults with pancreatic adenocarcinoma**

*Heining, Horak, Uhrig et al. Cancer Discov 2018*
Response to ERBB-directed therapy in patients with NRG1-rearranged pancreatic adenocarcinoma

- Afatinib (pan-ERRB blockade)
- Erlotinib/pertuzumab (EGFR blockade and dimerization inhibition)

NRG-ERBB signaling axis
- Receptors: EGFR, ERBB2-4
- Ligands: NRG1-4

Heining, Horak, Uhrig et al. Cancer Discov 2018
Defective repair of DNA double-strand breaks via homologous recombination (HR) in >90% of patients with advanced-stage leiomyosarcoma

Somatic and germline alterations of individual HR genes

Extensive genomic instability
- HR deficiency score
- Large-scale state transitions
- Telomeric allelic imbalance

Enrichment of Alexandrov-COSMIC mutational signature AC3

Clinical actionability (i.e. sensitivity to PARP inhibition) currently unknown

Chudasama, Mughal, Sanders, Hübschmann et al. Nat Commun 2018
Strategies for Clinical Translation

NCT/DKTK MASTER
Biology-driven patient stratification

Therapeutic activity of pathway-targeted interventions

Individual-case basis
Clinical trials of genomics-guided treatments
Existing stratified trials
85% of all hotspot mutations affect <5% of any cancer type in which they are found

Clinical trials of genomics-guided treatments

Novel precision medicine trial designs

**Umbrella trial**
- 1 type of cancer
- Different genetic mutations (○○○)
- Test drug 1
- Test drug 2
- Test drug 3

**Basket trial**
- Multiple types of cancer
- 1 common genetic mutation (●)
- Test drug

*West et al. JAMA Oncol 2017*
Eligibility

- Advanced-stage cancer
- Prior standard treatment
- Actionable molecular alteration, as determined by analysis within NCT/DKTK MASTER

Basket Trials Linked to NCT/DKTK MASTER

- SoraTram: Sorafenib/trametinib in cancers with non-V600 BRAF mutations
  - NCT PMO-1604
- Afatinib in NRG1-rearranged cancers
  - NCT PMO-1601
- Palbociclib in CDKN2A/B-deficient chordoma
  - NCT PMO-1603
- Trabectedin/olaparib in DNA repair-deficient cancers
  - Cancer Core Europe Basket of Baskets
    - Atezolizumab in defined patient subsets
**Eligibility**
- Advanced-stage cancer
- Prior standard treatment
- Defective DNA repair via homologous recombination, as determined by molecular analysis within MASTER

**Exclusion Criteria**
- Prior treatment with PARP inhibitor
- ECOG Performance Status >1

**ClinicalTrials.gov Identifier**
- NCT03127215

**Treatment Schedule**
- Trabectedin 1.1 mg/m² on day 1
- Olaparib 150 mg twice daily on days 2-21

DKTK, AIO, and GISG investigators
Molecular profiling based on whole-exome/genome and RNA sequencing in a multi-institutional clinical setting

- Is feasible
- Provides relevant diagnostic information
- Creates therapeutic opportunities
- Complements and advances routine molecular diagnostics
- Needs to be evaluated within controlled clinical trials of genomics-guided therapies
- Should be integrated with additional layers of patient characterization
  - Proteomics
  - Epigenomics
  - Immune profiling
  - Functional profiling
  - Multiparameter imaging
- Should be extended to additional treatment modalities
  - Radiotherapy
  - Surgery
Thank you for the attention!

www.nct-heidelberg.de/tmo
www.nct-heidelberg.de/master