Background

Cancer immunotherapy such as anti-CTLA4 and anti-PD-1/PD-L1 has shown great promise as treatments for many types of cancer, but only about 20-40% of patients respond to checkpoint inhibitor immunotherapy.

Methods

Over 1,000 cancer patients from more than 70 hospitals across 20 provinces in China were recruited into the project. Majority (78%) of these patients are with 4 major tumor types, which are lung, gastric, colorectal, and breast cancer.

The whole exome of tumor specimen and case-matched normal samples sequencing was performed through the clinical whole exome sequencing (CWES) and globally available treatment options. The treatment implementation and the outcome of each patient have been followed.

Results

Similar to TCGA cohort, the top 3 high TMB tumor types are lung, esophagus and colorectal cancer. Chinese hepatocellular carcinoma (HCC) patients showed higher TMB than the TCGA cohort (Median: 106 vs. 65 NSM), which might be due to different etiologies.

For lung adenocarcinoma (LUAD), patients with EGFR-mutant status had significantly lower TMB (Median: 74 vs. 113 NSM) compared with patients with EGFR wild-type (P=0.0039). This may help to explain why in EGFR-mutant advanced NSCLC, immune checkpoint inhibitors do not improve OS over that with docetaxel.

For Colorectal cancer (CRC), increased TMB is significantly associated with MMR-mutant (P<0.0001). MMR-mutant patients tumors on average have 15 fold more NSM (Median: 1567 vs. 106) than intact MMR patients.

The whole exome of tumor specimen and case-matched normal samples sequencing was performed through the clinical whole exome sequencing (CWES) and globally available treatment options. The treatment implementation and the outcome of each patient have been followed.

Figure 1. Constitution of 1,168 patients recruited into Clinical Whole Exome Sequencing and clinical interpretation by GenomiCare Cancer Hope™ Project from October 2015 to March 2016

No. of patients

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>No. of patients</th>
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<tbody>
<tr>
<td>Lung</td>
<td>384</td>
</tr>
<tr>
<td>Gastric</td>
<td>160</td>
</tr>
<tr>
<td>Colorectal</td>
<td>119</td>
</tr>
<tr>
<td>Breast</td>
<td>88</td>
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Figure 2. Analysis of 1,168 Chinese patients’ tumor genomes reveals the landscape of TMB and the relationship of TMB and EGFR/MMR mutations

(a) The landscape of tumor mutation burden

(b) Mutation Burden in Adeno-NSCLC with/without EGFR mutation

(c) Mutation Burden in CRC with/without MMR mutation

Figure 3. Correlation between somatic MSI and TMB identified by CWES

(a) MSI percentage distribution in all samples

(b) Mutation Burden in each MSI grade

<table>
<thead>
<tr>
<th>MSI classification</th>
<th>% of samples</th>
</tr>
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<tbody>
<tr>
<td>MSS</td>
<td>63%</td>
</tr>
<tr>
<td>MSI-low</td>
<td>33%</td>
</tr>
<tr>
<td>MSI-high</td>
<td>4%</td>
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Patients in the MSS, MSI-low, and MSI-high groups had 0-1%, 1-3.5%, and ≥3.5% of unstable microsatellite sites, respectively.

High TMB has been shown to be significantly associated with MSI-low and MSI-high (Median 90, 408, 1945 per tumor for MSS, MSI-low, and MSI-high group, respectively).

Figure 4. CWES analysis of PD-L1 amplification across 8 major tumor types

(a) PD-L1 amplification frequency across 8 major tumor types

(b) The overlap distributions of TMB, MMR, PD-L1 AMP and MSI

PD-L1 amplification most frequently occurred in lung squamous (14.3% VS 9.8% TCGA), HER2-positive breast cancer (8.5% VS 6.8% TCGA with unknown HER2 status) and sarcoma (6.0% VS 9.4% TCGA).

In 1,168 Chinese cancer patients, 22.2% TMB-high was overlapped with MMR mutant and MSI high. Almost all patients with MSI high (92.3%) harbored elevated TMB except 2 cases. 75% patients with MMR mutant harbored high TMB, only 34.6% PD-L1 amplification patients are high TMB.

Figure 5. A case of acquired resistance PD-1/PD-L1 blockade

(a) Primary lung large cell carcinoma CNV profile

(b) Acquired somatic co-deletion of CDKN2A and IFNA family

The patient was confirmed large cell carcinoma of lung (Stage IV) in Jun, 2014. He was heavily treated with multi-line radiotherapy and chemotherapy until May 2015. Next, CWES was performed and high TMB was found. Intravenous anti-PD-1 therapy (pembrolizumab) was utilized every 3 weeks. The patient achieved a best response of PR and disease remained stable for 17 months until Dec. 2016. A second biopsy CWES identified CDKN2A/INFA family co-deletion in acquired resistant tumor.

While the precise CDKN2A and IFNA family functions in resistance to PD-1 blockade are not clear yet, it has been shown that expression of IFNs-α promoting inflammatory response can be stimulated by radiation and chemotherapy, and lack of sensitivity to IFN signalling is associated with naturally acquired resistance.

Conclusions

TMB, MMR, MSI, and PD-L1 AMP represent frequent genetic alterations across many cancers, in particular, MMR and MSI are associated with higher mutational loads.

Our CWES analysis and limited clinical follow-up observations suggested that about 40% Chinese cancer patients had at least one of the 4 potential immunotherapy predictive biomarker mutations.

Our findings may reveal of CDKN2A and IFNA family deletion in NSCLC as a determinant of immune checkpoint therapy.

Abstract # 11605

Comprehensive analysis of potential immunotherapy genomic biomarkers by profiling paired tumor/normal exome of 1,000 Chinese cancer patients

Guan Wang1, Chun Dai1, Cheng Chen1, Xiaoan Xu2, Junwang Wei1, Angela Wu1, Jingping Wang2, Qiang Xu1

GenomiCare Biotechnology (Shanghai) Co., Ltd., 5F, Building 2, No. 111 Xiangke Road, Shanghai, China 201210; 2) Division of Surgical Oncology, Brigham and Women’s Hospital, Department of Surgery, Harvard Medical School, Boston, Massachusetts, USA

References


GenomiCare Biotechnology. Utilizing clinical genomics to bring actual benefits to Chinese cancer patients.