BIOMARKERS FOR IMMUNE CHECKPOINT INHIBITOR THERAPIES

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Zhongwu is a principal Scientist and team lead for bioinformatics and data science at AstraZeneca's Research and Early Development, Oncology R&D, in Boston. He is responsible in managing bioinformatics support for discovery and clinical projects to identify patient stratification biomarkers using validated clinical assays, understand drug MOA and resistance mechanisms. He also developed a widely adopted NGS variant caller, VarDict, and the analytical pipeline to identify actionable genomic biomarkers from patient samples. Finally, he was part of the team at Celera Genomics that decoded human genome.

Explain a bit more about your current work.

I work at AstraZeneca as a team lead in the Boston site bioinformatics team, of about 10 people. We are supporting projects from early stage, including target discovery all the way to late stage clinical development, even in some of the project's lifecycle management. The main focus is applying the genomics data, especially the patient's genomics data, using next generation sequencing either A) to identify clinically measurable biomarkers that can stratify patients or B) in the clinical trial design.

Are you currently combining multiple immunotherapy strategies in your work? If so, what combination strategies and what are the advantages?

At the moment, AstraZeneca has the PD-L1 Inhibitor, durvalumab for immunotherapy, and the PARP inhibitor olaparib, that have been approved by FDA. There are some hypotheses about these two compounds; we are especially interested in applying the PARP inhibitor that can induce immune response and convert a cold tumour into a hot tumour. The PARP inhibitor can induce DNA damage, theoretically generating more neoantigens, which will sensitise the tumour to the immuno-oncology therapies.

What are the challenges of determining the suitable biomarkers for immune checkpoint inhibitor therapies?

That is quite broad, but a good question. Many biomarkers have been brought forward. This includes the PD-L1 expression, TMB as a biomarker, the tumour infiltration lymphocyte and HLA typing. As all the literature and other data says, none of them tell the full story. I always like comparing it to the story of the four blind people trying to describe an elephant, none of them are wrong, but none of them are right. It is just not a complete picture.

It is very unlikely that we will find a biomarker like EGFR mutation for the EGFR inhibitors for the immuno-oncology therapy. I think we must look at the holistic view. I don't think a single trial will be powerful enough to do that. Therefore, we will have to combine different trials, maybe from different companies and healthcare systems. Machine learning and AI can play a big role in that. All the stakeholders in the pharmaceutical companies and even the health insurance companies must have people that can really take initiative, so they have a chance to find a good biomarker for the immunotherapy. This will clearly benefit

How can human mutation burden be utilised to predict patient response?

I think a tumour mutation burden is a biomarker for immunotherapies, however, I think the underlying tumour mutation burden is the neoantigen. Tumour mutation burden is just a surrogate. The current challenges are that there are so many different panels and technologies out there, people are using different filtering and cutoff that makes clinical adaption difficult., There is a need to harmonize TMB measurement.

The Friends of Cancer Research has an initiative to hold a consortium that includes many diagnostic companies and pharmaceutical companies, including AstraZeneca, to try to harmonise the TMB calculation. Once all of the different tests are harmonised, I think TMB will be another biomarker for immunotherapy.

What are the top three takeaways of your presentation?

I am going to talk about HRR mutation as a potential biomarker for the combination of PARP inhibitor and immunotherapy. The three takeaways are; firstly, that we know BRCA is a good biomarker for PARP inhibitor, but there are a significant number of somatic BRCA cases across the tumour types. The second takeaway is, beyond BRCA1 and BRCA2, there are other genes that are involved in the homologous recombination pathway, and their mutations correlate with the genome stability, as well as the tumour mutation burden. Thirdly, they always show higher tumour mutation burden, and this is supporting evidence that HRR mutation can potentially be a biomarker for combination of the PARP inhibitor and IO therapy.