Poster 3577

A first assessment of CD8-PET/CT with 89-Zr-Crefmirlimab as predictive biomarker for response to standard of care immunotherapy in patients with solid tumors.

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Background

- CD8-PET (immunoPET) is a novel bioimaging allowing for the in vivo visualization of the CD8+ cells population in humans.
- AZ engaged with ImaginAb (IAB), Takeda and Pfizer in a pre-competitive consortium to gain early access to IAB's Ph2a clinical trial data and evaluate.
- Several aspects of CD8-PET are presented here including CD8-PET's ability to predict patient response to Standard of Care(SOC) Immuno-Oncology Treatment (IOT).
- In parallel IAB's technology is implemented in several AZ studies, allowing for an evaluation of the operative aspects of CD8-PET's implementation in clinical trials.

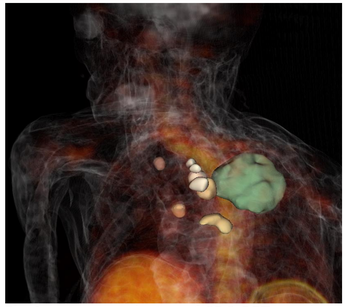

Fig.1 artistic rendering of CD8-PET uptake measurement values overlayed with 3D annotation of lesions.

Materials and methods

- ImaginAb's Ph2a BOT study recruited patients with advanced solid metastatic tumour undergoing SOC-IOT with or without previous treatment and in combination or not with chemotherapy. Some patients also underwent corticosteroid treatments.

Indication	N
NSCLC	9
RCC	15
Melanoma	11
Bladder, Gastric, Esophageal, Head & neck	1

Setting:
- Advanced or Metastatic Solid Malignancies
- Multi-site
- Pre treatment and On treatment imaging.

Treatments:
- Pembrolizumab / Nivolumab
- Atezolizumab
- Ipilimumab
- Bevacizumab
- Chemotherapy

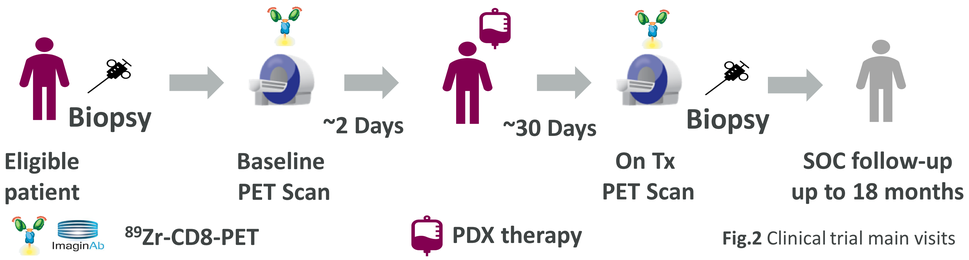

Fig.2 Clinical trial main visits

- A certified radiologist performed detailed 3D annotation of all lesions.
- Standard Uptake Values (SUV) in each lesion and several "healthy" tissue were measured for all patients (aorta, liver, spleen, muscle, bone marrow).
- For a patient subset, SUV were measured in organs with tabulated mRNA expression profiles.
- In all available follow-up "RECIST" scans, each lesion size was evaluated.

Results

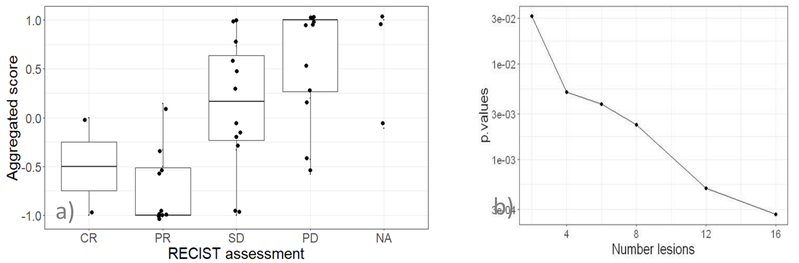

Fig.3 Patient score using AZ (CPM) developed algorithm against best RECIST evaluation.
a)The score is computed using early infiltration and volume changes. Time to assessment using CD8-PET (~35D) is much shorter than time to best RECIST score (~100D). All annotated lesions included.
b) **t-test** *responders* (CR+PR) vs. *non responders* (SD+PD) p-value as function of number of lesions included in patient score calculation.

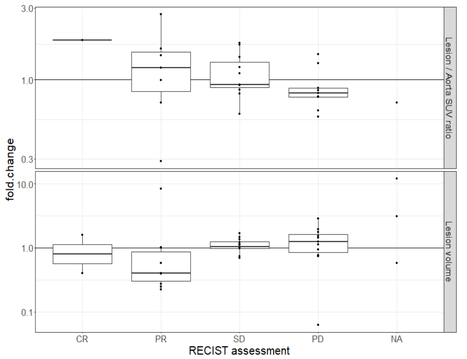

Fig.4 Normalised lesion uptake & volume fold changes against best RECIST evaluation.
While CD8+ infiltration change is the best predictor to response to IOT, volume change does provide complementary information.

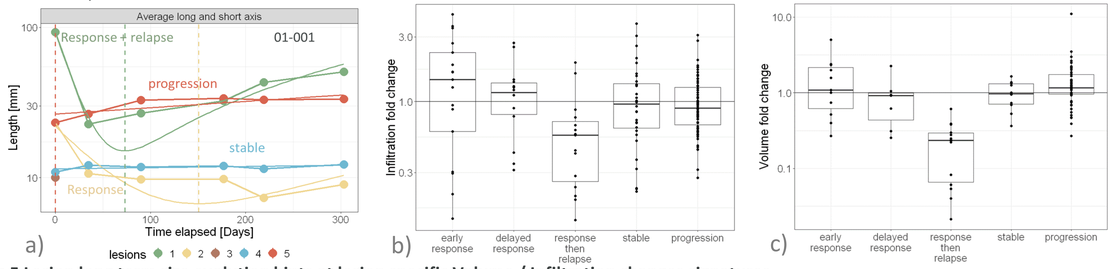

Fig.5 Lesion long term size evolution hints at lesion specific Volume / Infiltration changes signatures.
a) Within one patient (here 01-001) lesions can exhibit very different size evolution patterns following IOT. Each lesion is automatically classified according to 5 possible classes *(early response, late response, response then relapse, stable, progression).*
b) & **c)** Intra lesion CD8+ cells infiltration and volume changes according to lesion classes.
Note: large lesion volume changes lead to a lack of precision of the CD8 infiltration measurement for technical reasons (partial volume effect).

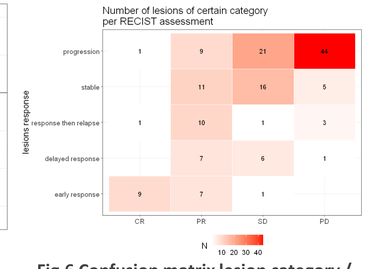

Fig.6 Confusion matrix lesion category / best of RECIST assessment.
CR and PD patients' lesions have largely homogenous phenotypes while PR and SD patients' lesions are more heterogeneous.

Discussion

By utilizing both volume and CD8 infiltration changes measured from pre-and early on-treatment CD8-PET data, the developed algorithm can accurately predict a patient's response to IOT (as depicted in Figure 3a). However, Figure 3b highlights that the predictive power of the algorithm is greatly dependent on the number of lesions analyzed, indicating that intra-patient heterogeneity plays a critical role in assessing an individual's response to IOT. Figure 4 shows that both CD8 infiltration and volume changes are only indicative of long-term patient response (stratification is statistically not significant) but convey complementary information. In addition, the lesion-wise analysis presented in Figure 6 enables the discrimination between several phenotypes of lesion response to IOT. For instance, early responding lesions exhibit a volume increase, which is consistent with a significant increase in CD8+ cells in the tumor volume. One hypothesis is that lesions with delayed response would only differ in the speed of the influx of immune cells in the lesion. On the other hand, stable and progressive lesions exhibit both a decrease in CD8 infiltration even early in the treatment. Lesions with a response then relapse phenotype single out by their strong volume decrease, which makes the CD8 infiltration unreliable. But as highlighted by figure 6 (and consistently with RECIST PR assessment) they are also typically present in patients with a high level of heterogeneity at the patient level, enabling an accurate prediction of the overall patient response.

Conclusion

This study CD8-PET can be used as an early biomarker of response to IOT. It also offers great promises as a tool to investigate the mechanism of action of IO treatment. These results, if confirmed by a larger cohort of patients data, could be the basis for future personalised patient treatment strategies.