[^{89}Zr]Zr-DFO-durvalumab PET/CT to predict responses to neo-adjuvant durvalumab in early-stage non-small cell lung cancer

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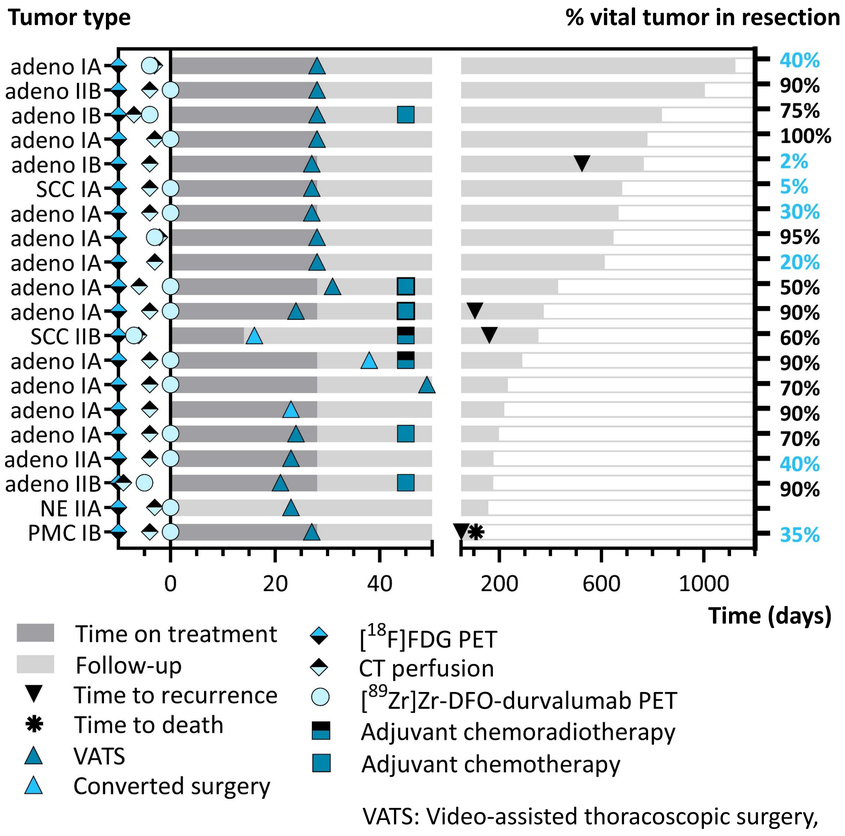
Introduction

Understanding the *in vivo* mechanism-of-action of immune checkpoint inhibitors is critical to guide treatment development in non-small cell lung cancer (NSCLC):

- Complex dose-response relations, involvement of secondary and primary lymphoid organs
- Molecular imaging is a non-invasive biomarker to assess whole body biodistribution of radiolabeled durvalumab
- Imaging-driven translational study on neoadjuvant durvalumab in early-stage NSCLC (NCT03853187)

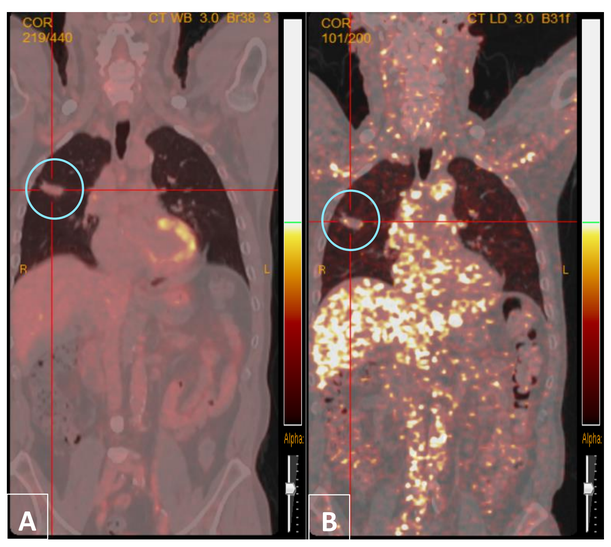
→ *Explore the potential of machine learning algorithms to explore patterns in PET-derived uptake features in tumor and immune-related organs*

Patient characteristics



VATS: Video-assisted thoracoscopic surgery,

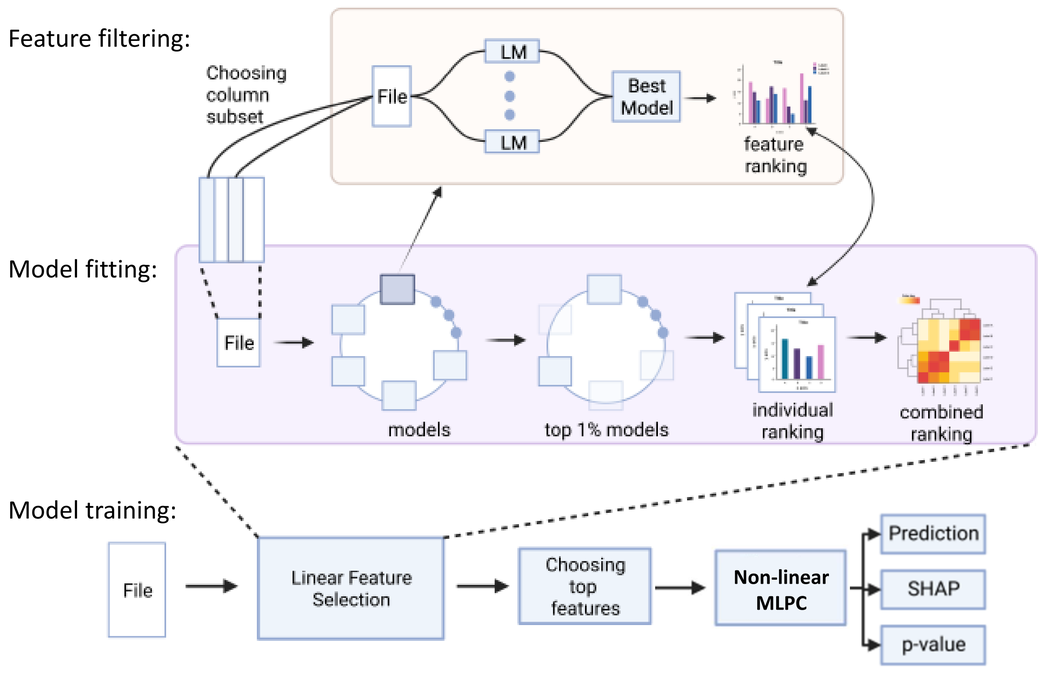
Pathological response: Patients with <40% viable tumor cells after treatment



Imaging example of fused PET/CT coronal view
A: [^{18}F]FDG ***B:*** [^{89}Zr]Zr-DFO-durvalumab

Machine learning model

We compared [^{89}Zr]Zr-DFO-durvalumab PET, [^{18}F]FDG PET and CT perfusion features to pathological response with the help of a machine learning algorithm: Robust feature ranking through an exhaustive exploration strategy, integrated with non-linear model training to capture complex dependencies within the most important feature.



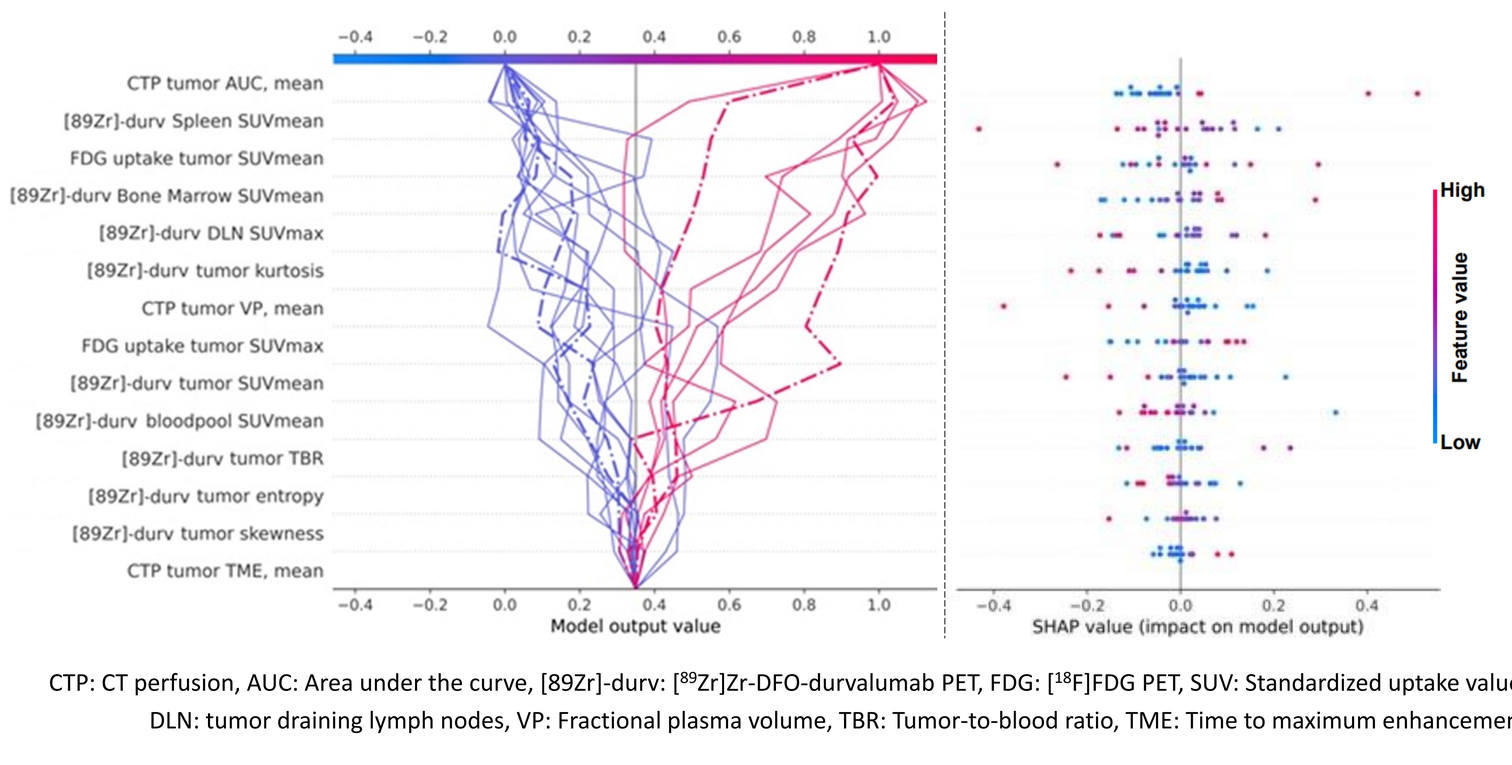
LM: Linear Model, SHAP: Shapley Additive explanation, MLPC: Multilayer Perceptron classifier

*Adjusted from: Agrawal et al.(2022)Nuklearmedizin-NuclearMedicine DOI 10.1055/s-0042-1746015

Data-subsets were evaluated to provide performance metrics & variable ranking using LM. The model's whole dataset AUC is used to filter our the top 1% performing models, and their variable rankings are aggregated to estimate the most informative features. These features are used to train a non-linear MLP classifier model with hyperparameter tuning done using Weights & Biases platform.

Results

- Most relevant features for response prediction relate to total perfusion in the tumor and [^{89}Zr]Zr-DFO-durvalumab distribution in lymphoid organs
- The whole dataset accuracy is 80% with permutation test *p=0.069*, suggesting non-random relationships between the features and the target label.
- The False Negative rate is 10% (2/20), due to missing values (16/18) of 1 sample and 1 outlier showing very high [^{89}Zr]Zr-DFO-durvalumab tumor SUVmax, in a rare histological subtype.
- False Positives (rate 10%) could be attributed to abnormal CTP features. One of the samples had missing CTP features the other had abnormally high mean total perfusion (which is a characteristic of pathological response), in comparison to CTP VP mean.



CTP: CT perfusion, AUC: Area under the curve, [89Zr]-durv: [^{89}Zr]Zr-DFO-durvalumab PET, FDG: [^{18}F]FDG PET, SUV: Standardized uptake value, DLN: tumor draining lymph nodes, VP: Fractional plasma volume, TBR: Tumor-to-blood ratio, TME: Time to maximum enhancement

Conclusion

We present an **innovative approach** to integrate the contribution of multimodal imaging features in predictive modelling.

Our data suggests that **total contrast enhancement and durvalumab distribution in lymphoid organs** outweigh conventional tumor-uptake parameters to predict pathological response upon neoadjuvant durvalumab in early-stage NSCLC

Concerning [^{89}Zr]Zr-DFO-Durvalumab distribution **in the tumor; a high kurtosis is linked to lower response rates**, suggesting the importance of a more homogenous distribution of durvalumab

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