

# Combinatorial CD8(+) and PD-L1(+) Cell Densities Correlate with Response and Improved Survival in NSCLC Patients Treated with Durvalumab

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1. Definiens  
2. MedImmune/AstraZeneca

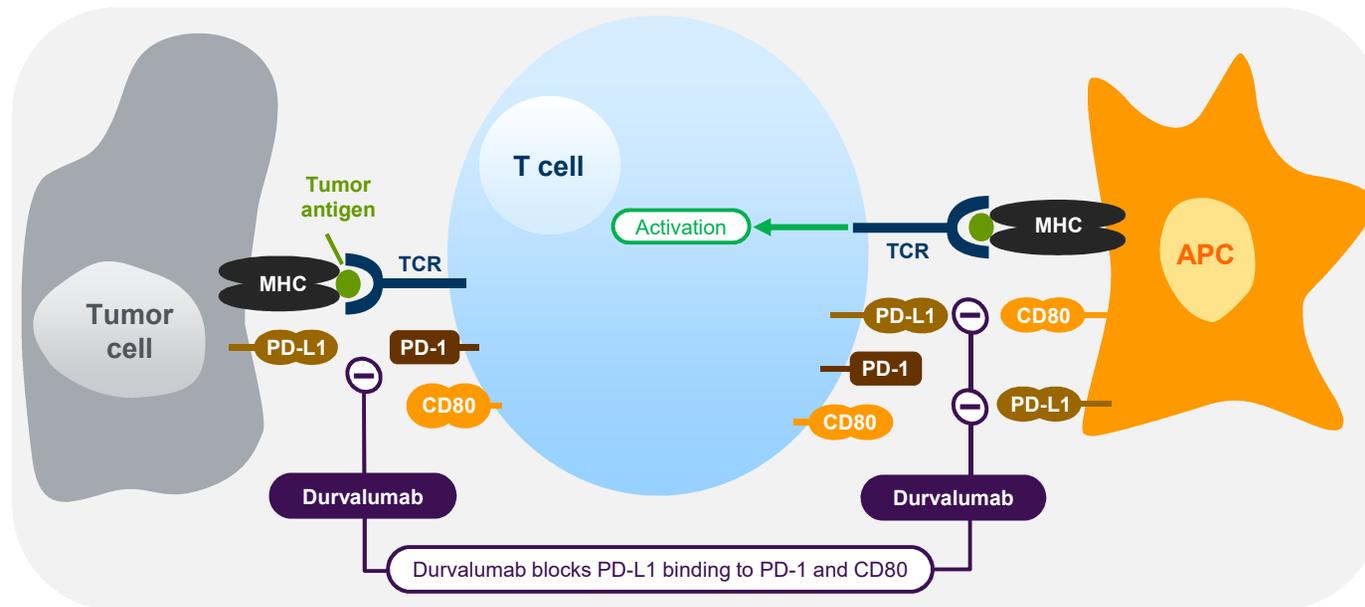
## Disclosures

MedImmune/AstraZeneca is developing durvalumab (MEDI4736), an  $\alpha$ -PD-L1 monoclonal antibody therapy in NSCLC and other indications

All authors of this presentation are full-time employees of MedImmune or Definiens (owned by MedImmune/AstraZeneca).

# Background and Motivation

- PD-L1 may act as molecular “shield” to protect tumor cells from the attack of CD8(+) T cells<sup>1</sup>
- Can we improve the predictive utility of PD-L1 IHC to identify responders to durvalumab ( $\alpha$ -PD-L1) treated NSCLC patients?
- Hypothesis: Interaction of PD-L1(+) and CD8(+) cells is associated with enhanced response to durvalumab



Mechanism of action of durvalumab ( $\alpha$ -PD-L1)

# Methods

## **A Phase 1/2 Study to Evaluate Durvalumab (NCT01693562)**

- Non-randomized trial
- Objective response was evaluated w.r.t. RECIST v1.1
- Efficacy data presented at ASCO 2016 with cut-off date of 04-29-2016

## **Description of Analysed Data**

- 163 NSCLC patients were analysed (77% were previously treated)
- Matched CD8 (SP239) and PD-L1 (SP263) IHC stained sections from baseline tumor tissue blocks
- PD-L1 high:  $\geq 25\%$  PD-L1+ tumor cells with membrane staining at any intensity

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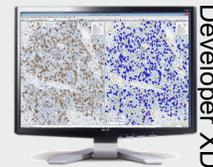
## Tissue Phenomics Workflow

Expert knowledge from Pathologists

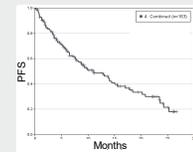
- Contextual concepts
- Annotations
- Hypotheses



Image analysis



Outcome data



Signature Discovery



Definiens®

# Hypothesis-driven Signature Discovery

## 1) Discovery Phase

Combination of CD8(+) and PD-L1(+) cells show predictive character for the response to durvalumab

## 2) Hypothesis Refinement Phase

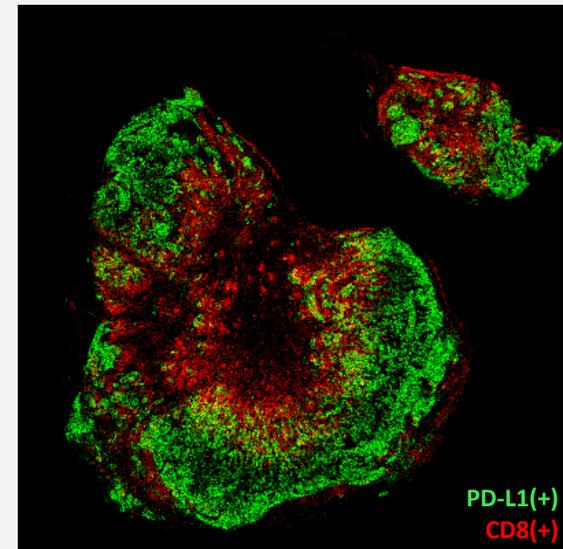
Selected top 5 from 12 similar hypotheses for the interplay of CD8(+) and PD-L1(+) cells

## 3) Confirmation Phase

Analysing accuracy and robustness on training & test set with balanced objective response rates, prevalence of PD-L1 status, line of therapy, etc.

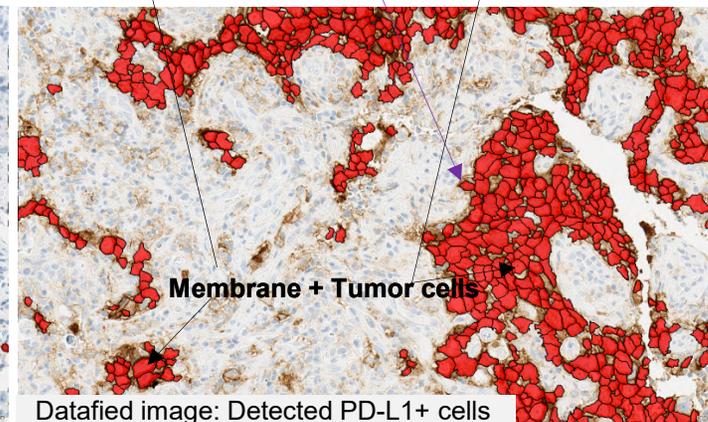
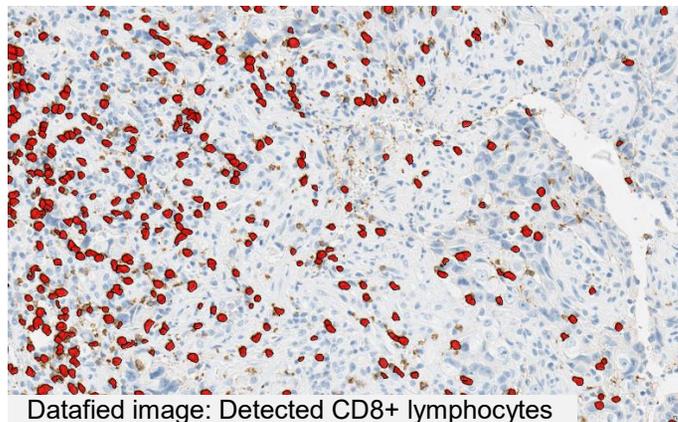
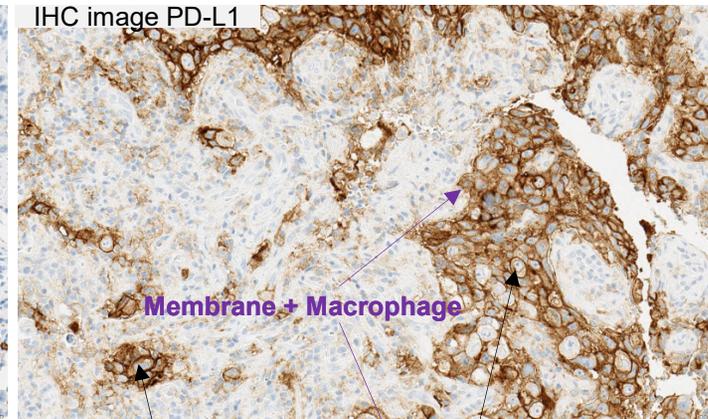
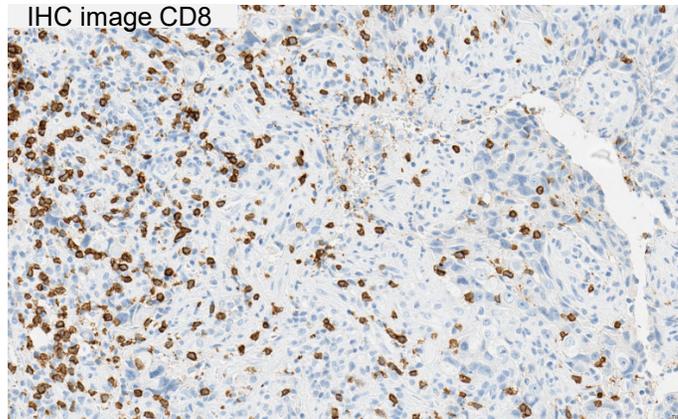
## 4) Evaluation Phase

Most accurate & robust predictive signature:  
**CD8\*PD-L1 cell densities**



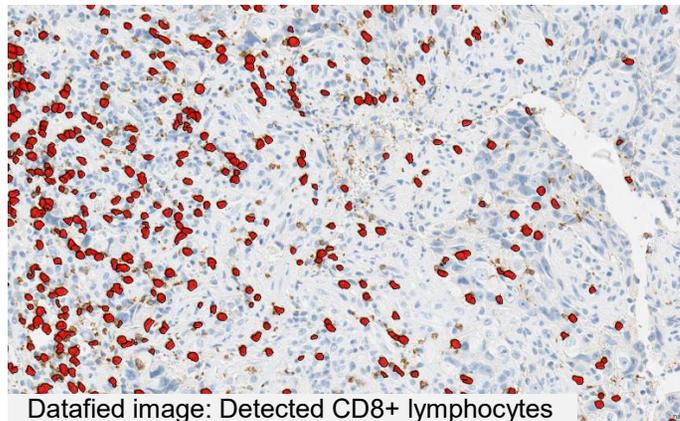
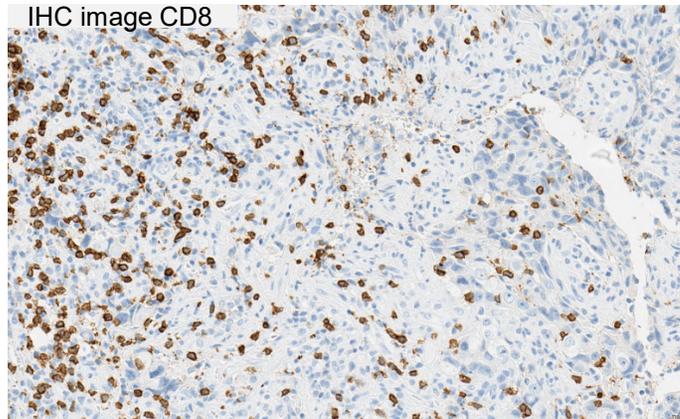
Cell density heatmap

# Digital Detection & Quantification: CD8(+) and PD-L1(+) Cells

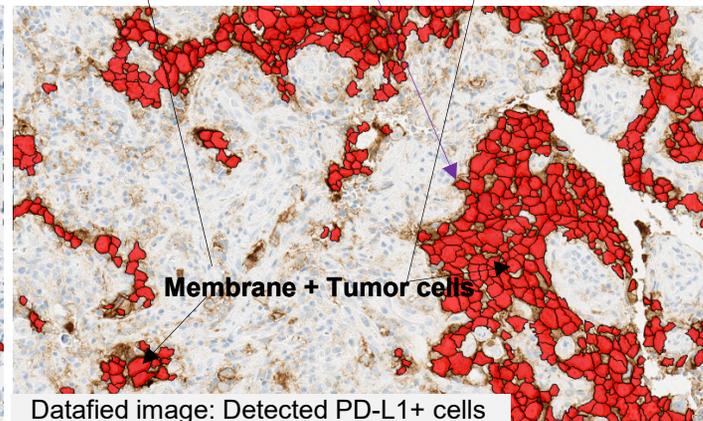
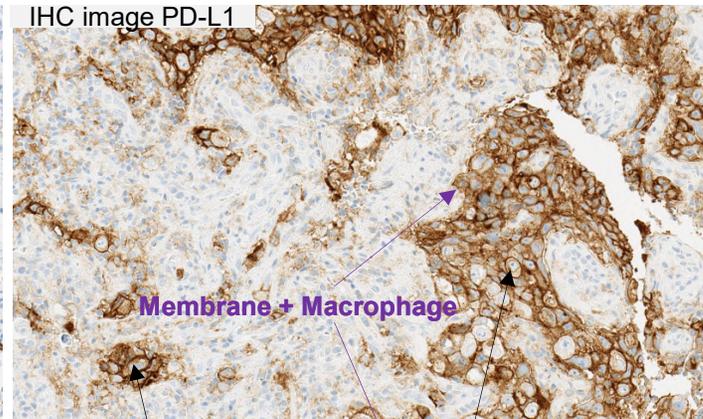


# Digital Detection & Quantification: CD8(+) and PD-L1(+) Cells

Signature based on positive cell densities\* in the annotated tumor area



Datafied image: Detected CD8+ lymphocytes

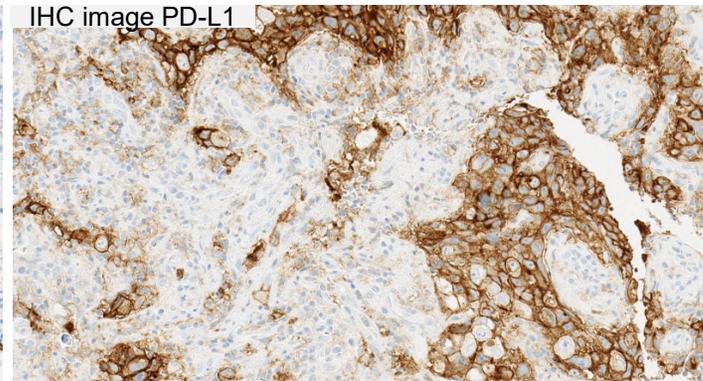
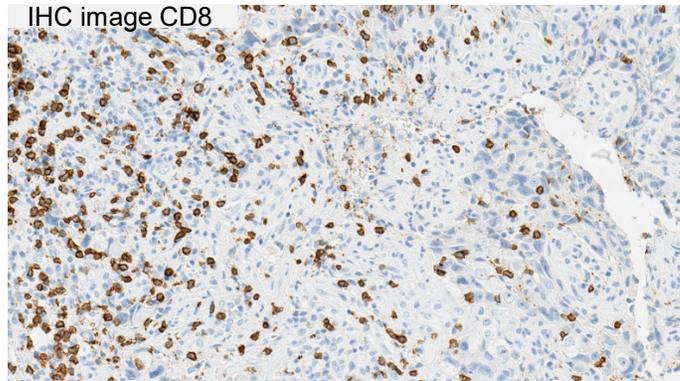


Datafied image: Detected PD-L1+ cells

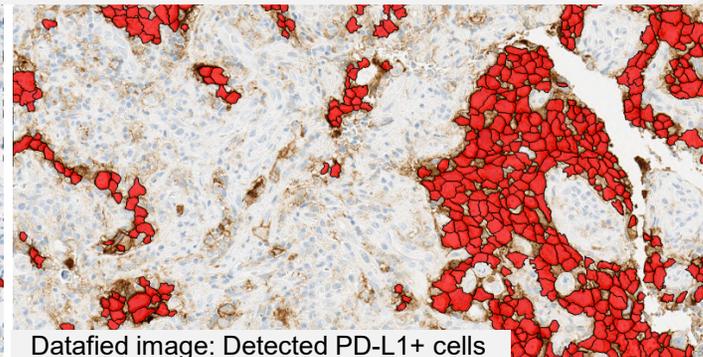
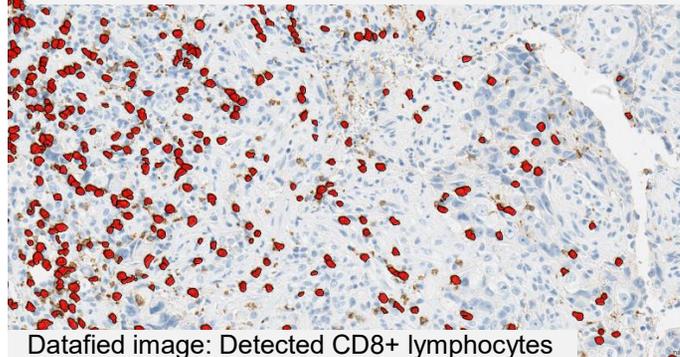
$$*density = \frac{\text{cell count}}{\text{area (mm}^2\text{)}}$$

# Digital Detection & Quantification: CD8(+) and PD-L1(+) Cells

Signature based on positive cell densities\* in the annotated tumor area

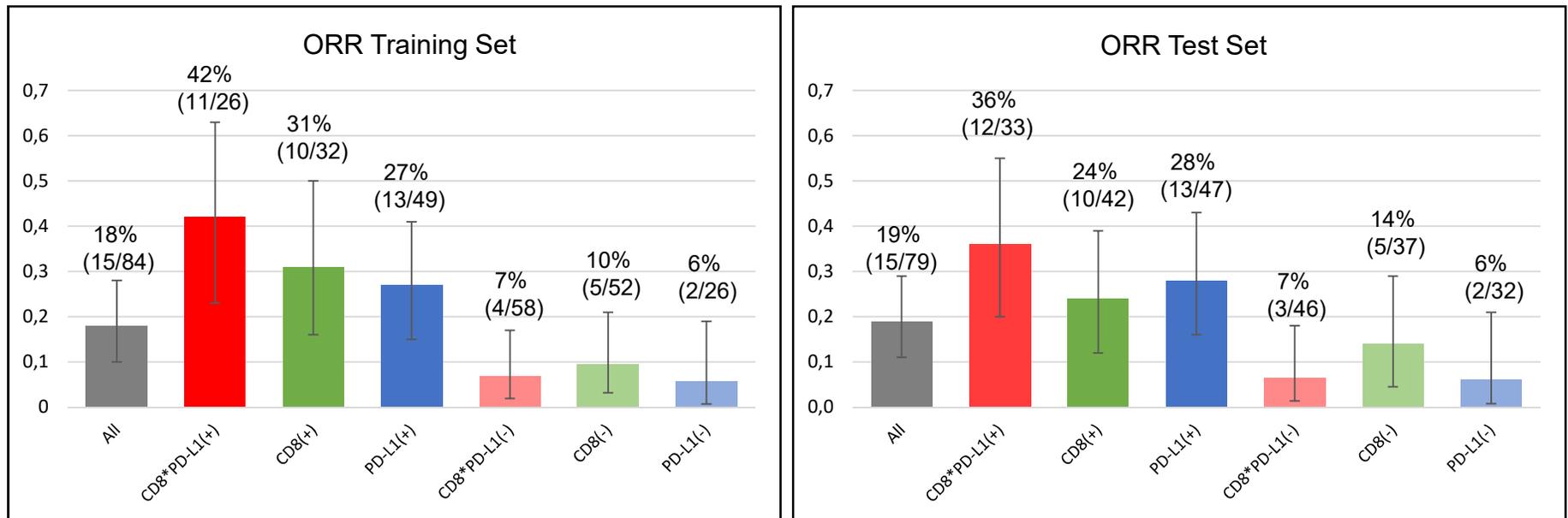


**Hypothesis:** For enhanced clinical benefit from durvalumab treatment both cell populations need to be present in the tumor tissue to at least a moderate degree



$$*density = \frac{\text{cell count}}{\text{area (mm}^2\text{)}}$$

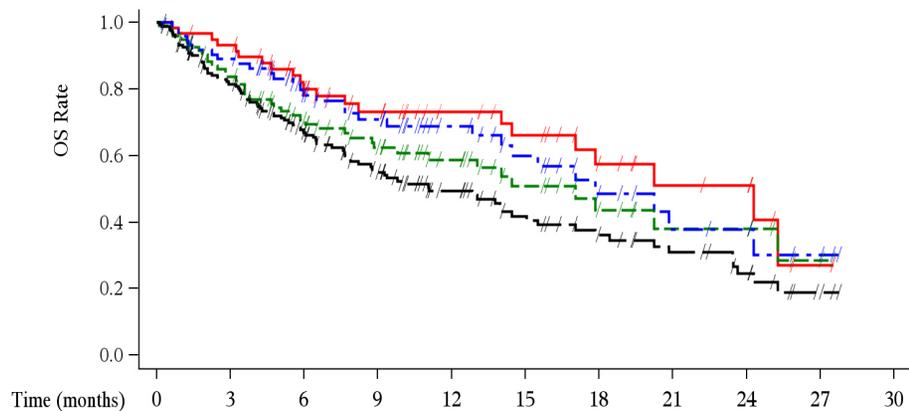
# CD8\*PD-L1 Appears to be a Better Predictor Compared to CD8 or PD-L1 in Terms of Objective Response Rate (ORR)



PD-L1(+) = PD-L1 status determined manually ( $\geq 25\%$  PD-L1+ tumor cells)

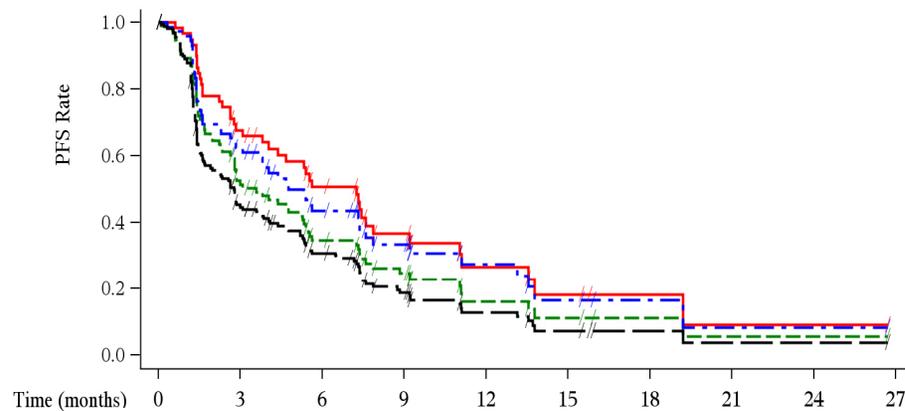
# CD8\*PD-L1 Appears to be a Better Predictor Compared to CD8 or PD-L1 in Terms of Survival

Overall Survival - Combined Set



	CD8*PD-L1(+)	PD-L1(+)	CD8(+)	All
#Subjects (#Events)	59 (21)	96 (41)	74 (29)	163 (89)
Median (95% CI)	24.3 (14.5, NE)	17.1 (9.8, 25.3)	17.8 (14.0, NE)	11.1 (7.9, 15.0)

Progression Free Survival – Combined Set



	CD8*PD-L1(+)	PD-L1(+)	CD8(+)	All
#Subjects (#Events)	59 (40)	96 (73)	74 (50)	163 (129)
Median (95% CI)	7.3 (4.0, 7.9)	3.6 (2.6, 5.3)	5.3 (3.1, 7.4)	2.8 (1.7, 3.8)

# Summary and Conclusion

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1. Our findings should be confirmed by an independent study
2. The quantification of CD8(+) and PD-L1(+) cell densities was made possible by automated image analysis
3. Patients with high pre-treatment CD8(+) and PD-L1(+) cell densities (prevalence=36%) show improved ORR, OS, and PFS compared to those with high CD8(+) or high PD-L1(+) cell densities alone

# Acknowledgements

We sincerely thank the patients and their families, the investigators, coordinators and research staff who have participated in study NCT01693562.

More Tissue Phenomics Studies:  
Poster #109 (melanoma) and #110 (prostate cancer)