Supplementary material

Definitions of Dose-Limiting Toxicities

A DLT was defined as one of the following toxicities that occurred during a DLT [a] assessment window of 21 days from the first administration of study combination treatment and was considered by the investigator to be related to study treatment.

Any non-hematological toxicity ≥ Grade 3 with the following exceptions:

- Nausea, vomiting, fatigue, diarrhea, oedema, hyperglycemia, and changes in serum electrolytes [b]
- Any Grade 3 immune-related adverse event that resolved to ≤ Grade 1 within 3 weeks of its onset
- Grade 3 skin disorder that resolved to ≤ Grade 1 within 3 weeks of its onset
- Grade 3 arthralgia that could be adequately managed with supportive care or that resolved to Grade ≤ 2 within 7 days
- Grade 3 fever (in the absence of any clinically significant source of fever) that resolved to Grade ≤ 2 within 7 days
- Grade 3 autoimmune thyroiditis or other endocrine abnormality that could be managed by endocrine therapy or hormonal replacement
- Grade 3 tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor

Any laboratory parameters that might have been increased due to decreased clearance in the liver, e.g., (but not limited to) CK, LDH, and transaminases if not associated with clinical signs and symptoms were not considered as DLT.

Hematological toxicities defined as:

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Febrile neutropenia (ANC < 1.0 x 10^9/L and fever ≥ 38.5°C) and/or documented infection with ANC < 1.0 x 10^9/L

Thrombocytopenia Grade 4 or bleeding requiring a platelet transfusion

Any other study drug-related toxicity considered significant enough to be qualified as a DLT in the opinion of the investigators after discussion with the Sponsor.

[a] Hypersensitivity, in particular IRRs, that required removal of patients from the study were considered as treatment-limiting toxicities and not DLTs. Hypersensitivity reactions were idiosyncratic and are not considered as DLTs. For the same reason, hypersensitivity reactions have also been exempt from dose escalation rules.

[b] Nausea, vomiting, diarrhea, hyperglycemia, and changes in serum electrolytes were considered a DLT only in case of non-recovery to Grade ≤ 2 after 3 days (for fatigue and edema ≤ 7 days) of adequate treatment and/or adequate supportive care measures.

Immunohistochemistry method details

All IHC assays were ready-to-use (RTU) as defined by the manufacturer and did not require any dilution steps.

PD-L1 assessments via IHC was performed from archival or screening pre-treatment tumor biopsies. For PD-L1 assay, the U OptiV DAB VENTANA PDL1 (SP142) procedure on the BenchMark ULTRA instrument was used. The tissue sections were treated with Cell Conditioner 1 for 48 min, and then incubated in primary antibody VENTANA PD-L1 (SP142) (Cat. No. 740-4859) for 16 min at 37°C and positive staining was detected with OptiView DAB IHC Detection Kit (Cat. No. 760-700) followed by the OptiView Amplification Kit (Cat. No. 760-099 [50 test] or 860-099

[250 test]). Sections were counterstained with Hematoxylin II (Ventana Medical Systems; Tucson, AZ) for 4 min, bluing solution for 4 min, then dehydrated and cover-slipped. Samples were scored for PD-L1 expression on tumor-infiltrating immune cells (IC), which included macrophages, dendritic cells and lymphocytes. Specimens were scored as immunohistochemistry IC 0, 1, 2, or 3 if <1%, ≥1% but <5%, ≥5% but <10%, or ≥10% of IC were PD-L1 positive, respectively. PD-L1 expression on tumor cells (TC) was scored as immunohistochemistry TC0, 1, 2, or 3 if <1%, ≥1% but <5%, ≥5% but <50%, or ≥50% of TC were PD-L1 positive, respectively.

For Ki67/CD8 assay, the RUO Discovery Universal procedure on Discovery Ultra was used. The tissue sections were treated with Cell Conditioner 1 for 64 min and then incubated in primary antibody CD8 (SP239, 1:12.5, Spring Biosciences) for 32 min at 38°C. Bound CD8 antibody was detected with UltraMap anti-rabbit AP secondary antibody and Discovery Yellow detection kit (Ventana Medical Systems). Subsequently, after heat denaturation, slides were incubated in primary antibody Ki67 (30-9, RTU, Ventana Medical Systems) for 8 min at 38°C. Bound primary antibody was detected with Hapten-linked Multimer anti-rabbit HQ and anti-HQ HRP secondary antibody, followed by Discovery Purple detection kit (Ventana Medical Systems). Sections were counterstained with Hematoxylin II (Ventana Medical Systems) for 8 min, bluing solution for 8 min, then dehydrated and cover-slipped.

For CD163/CD68 assay, the XT IHC DS oDAB-uRed v4 procedure on Benchmark XT was used. The tissue sections were treated with Cell Conditioner 1 for 32 min, and then incubated in primary antibody, CD163 (MRQ-26, RTU, Ventana) for 16 min at 37°C. Bound primary antibody was detected by the OptiView DAB IHC detection kit (Ventana Medical Systems). Subsequently, slides were incubated in primary

antibody CD68 (KP-1, RTU, Ventana) for 16 min at 37°C. Bound primary antibody was detected by the UltraView Universal AP Red detection kit (Ventana Medical Systems; Tucson, AZ). Sections were counterstained with Hematoxylin II (Ventana Medical Systems; Tucson, AZ) for 8 min, bluing solution for 8 min, then dehydrated and cover-slipped.

For CSF-1R assay, the XT Optiview DAB IHC v4 procedure on Benchmark XT was used. The tissue sections were treated with Cell Conditioner 1 for 32 min, and then incubated in primary antibody CSF-1R (clone 1A10, RTU, Roche) for 32 min at 37°C. Positive staining was detected with OptiView DAB detection kit (Ventana Medical Systems). Sections were counterstained with Hematoxylin II (Ventana Medical Systems) for 4 min, bluing solution for 8 min, then dehydrated and cover-slipped.

For FoxP3 assay, the XT Optiview DAB IHC v4 procedure on Benchmark XT was used. The tissue sections were treated with Cell Conditioner 1 for 32 min, and then incubated in primary antibody FoxP3 (236A-E7, 1:100, Abcam) for 60 min at 37°C and positive staining was detected with OptiView DAB detection kit (Ventana Medical Systems). Sections were counterstained with Hematoxylin II (Ventana Medical Systems; Tucson, AZ) for 8 min, bluing solution for 8 min, then dehydrated and cover-slipped.

For all assays, appropriate negative and positive controls were performed. Algorithms for the detection and classification of IHC stained objects on a whole-slide basis were written in Matlab. Following brightfield stain unmixing, IHC-stained objects were detected as cell candidates. For all cell candidates, quantitative features were extracted. Then, candidates were being classified into the various cell classes (e.g. CD8+/Ki67- cells) using supervised machine learning. The classification

method was trained using a ground truth gallery of true and false stained objects (provided by a pathologist). Finally, classified cells and tumor areas (provided by a pathologist trough digital slide annotation) were being reported and QC images being generated for pathology review. The results of automated digital slide analysis were reported for tumor areas as follows: Ki67-/CD8+, Ki67+/CD8+, total CD8+ and FOXP3 cell densities (number of cell counts per mm^2), CD68+/CD163+, CD68+/CD163-, total CD163+ and CSF1R percent of area coverage (area coverage in relation to the whole tumor area).

For non-PD-L1 IHC scoring, an automated counting using an in-house developed algorithm was used. The algorithm was trained by two pathologists who provided annotations for cell objects after previous alignment on the IHC positivity criteria. In the validation phase of the algorithm, the concordance of the algorithm with the mean of two pathologists using at least 100 fields of view (FOVs) was measured. The acceptance criterion for the algorithm's validation was a concordance above 85%.

Additional safety information

Infusion-Related Reactions (IRRs)

There were 16 AEs of IRR reported in 12 of 221 patients (5%; 5 patients with Grade 1, 4 patients with Grade 2, and 3 patients with Grade 3). IRRs experienced by 4 patients (1.8%) were considered related to emactuzumab and 5 patients (2.3%) were considered related to atezolizumab and for 3 patients (1.4%) related to both study drugs. One patient (0.5%) was withdrawn from treatment because of a Grade 3 IRR.

Skin and Subcutaneous Tissue Disorders

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Overall, 281 AEs belonging to the skin and subcutaneous tissue disorders SOC were reported in 121 of 221 patients (55%). Of these, 113 patients (51%) reported AEs that were related to emactuzumab and/or atezolizumab. Overall, 84 patients (38%) reported Grade 1 AEs, 42 patients (19%) reported Grade 2 AEs, and 28 patients (13%) reported Grade 3 AEs. Most common AEs (≥10%) were rash (59 patients [27%]), pruritis (56 patients [25%]) and dry skin (23 patients [10%]). Four patients (2%) were withdrawn from treatment due to rash and one patient (0.5%) each were withdrawn due to eczema, pruritus and psoriasis.

Elevation of Serum Enzymes

A number of patients experienced shifts from NCI-CTC Grade 0 to 2 at baseline to Grade 3 or 4 during treatment for liver-related serum enzymes, including AST (51 patients [23%]) , ALT (8 patients [4%]), GGT (80 patients [36%]), and ALK (28 patients [13%]). There was no apparent trend related to emactuzumab dose.

The abnormal liver enzyme parameters reported as AEs included the following: AST increased occurred in 39 patients (18%), ALT increased occurred in 17 patients (8%), ALP increased occurred in 14 patients (6%), and GGT increased occurred in 13 patients (6%).

Two patients (1%) were withdrawn due to an elevated AST and one patient (0.5%) was withdrawn from treatment because of elevated ALT levels, respectively. Additionally, one patient (0.5%) was withdrawn due to elevation in transaminase levels.

Within the SOC of hepatobiliary disorders, 12 of 221 patients (5%) reported 13 AEs. Five patients (2%) experienced AEs of hepatocellular injury (Grade 3: 2 patients; Grade 2: 1 patient: Grade 1: 2 patients), experienced an AE of jaundice or hepatic

hematoma (Grade 3: 1 patient: Grade 1: 1 patient) and all other events were in one patient each.

Supplementary Table 1 Listing of adverse events leading to withdrawal from emactuzumab and/or atezolizumab

Patient number	Adverse event	Related to emactuzumab	Action taken with emactuzumab	Related to atezolizumab	Action taken with atezolizumab
1022	Left ventricular dysfunction	Yes	Withdrawn	Yes	Withdrawn
1222	Alanine aminotransferase increased	Yes	Withdrawn	No	Withdrawn
	Aspartate aminotransferase increased	Yes	Withdrawn	No	Withdrawn
1121	Osteonecrosis	No	Withdrawn	No	Withdrawn
1232	Aspiration	No	Withdrawn	No	Withdrawn
1132	Leukemia	No	Withdrawn	No	Withdrawn
2017	Subdural hemorrhage	Yes	Withdrawn	No	Interrupted
	Sepsis	Yes	Withdrawn	Yes	Interrupted
2103	Tumor pain	Yes	Withdrawn	No	Dose not changed
2107	Respiratory failure	Yes	Withdrawn	Yes	Withdrawn
2112	Rash	Yes	Withdrawn	No	Withdrawn
2002	Pneumonia aspiration	No	Withdrawn	No	Withdrawn
2127	Respiratory distress	No	Withdrawn	No	Withdrawn
2602	Periorbital edema	Yes	Withdrawn	Yes	Dose not changed
2603	Transaminases increased	Yes	Withdrawn	Yes	Withdrawn
2604	Pneumonitis	Yes	Withdrawn	Yes	Withdrawn
2607	Rash	No	Withdrawn	No	Withdrawn
2016	Fatigue	Yes	Withdrawn	Yes	Dose not changed
2114	Porphyria	No	Withdrawn	No	Withdrawn
2123	Sepsis	No	Withdrawn	No	Withdrawn
2023	Immune-mediated pneumonitis	Yes	Withdrawn	Yes	Withdrawn
2227	Xerosis	No	Dose not changed	No	Withdrawn
2230	General physical health deterioration	Yes	Withdrawn	No	Interrupted

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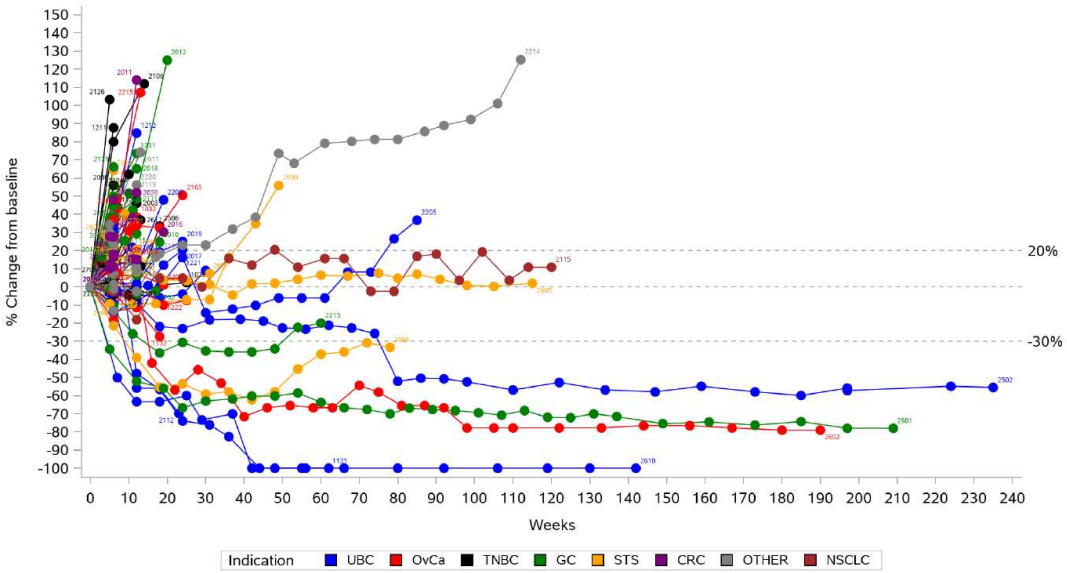
2128	Eczema	Yes	Withdrawn	Yes	Interrupted
	Pruritus	Yes	Withdrawn	Yes	Interrupted
	Psoriasis	Yes	Withdrawn	Yes	Interrupted
2134	Cytokine release syndrome	Yes	Withdrawn	No	Dose not changed
2142	Rash	No	Withdrawn	No	Interrupted
	Rash	No	Withdrawn	No	Dose not changed
2144	Thrombosis	No	Withdrawn	No	Dose not changed
2146	Hepatocellular injury	Yes	Withdrawn	Yes	Withdrawn
2802	Confusional state	Yes	Withdrawn	Yes	Withdrawn
2903	Rash	Yes	Withdrawn	Yes	Withdrawn
2507	Dyspnea	Yes	Withdrawn	Yes	Withdrawn
2301	Infusion-related reaction	Yes	Withdrawn	No	Withdrawn
3001	Pneumonitis	No	Withdrawn	Yes	Interrupted
	Myocarditis	No	Not applicable	Yes	Withdrawn
2147	Interstitial lung disease	No	Withdrawn	Yes	Withdrawn
2706	Aspartate aminotransferase increased	Yes	Withdrawn	Yes	Withdrawn
2614	Agitation	Yes	Withdrawn	Yes	Withdrawn

Supplementary Figure 1 Spider plot based on RECIST criteria per investigator assessment, sum of lesion diameters depicted as percentage change from baseline

a.) Patients of Part 1 (dose escalation) and Group 1 to 3 of Part 2 (extension)



b.) ICB-naïve UBC patients

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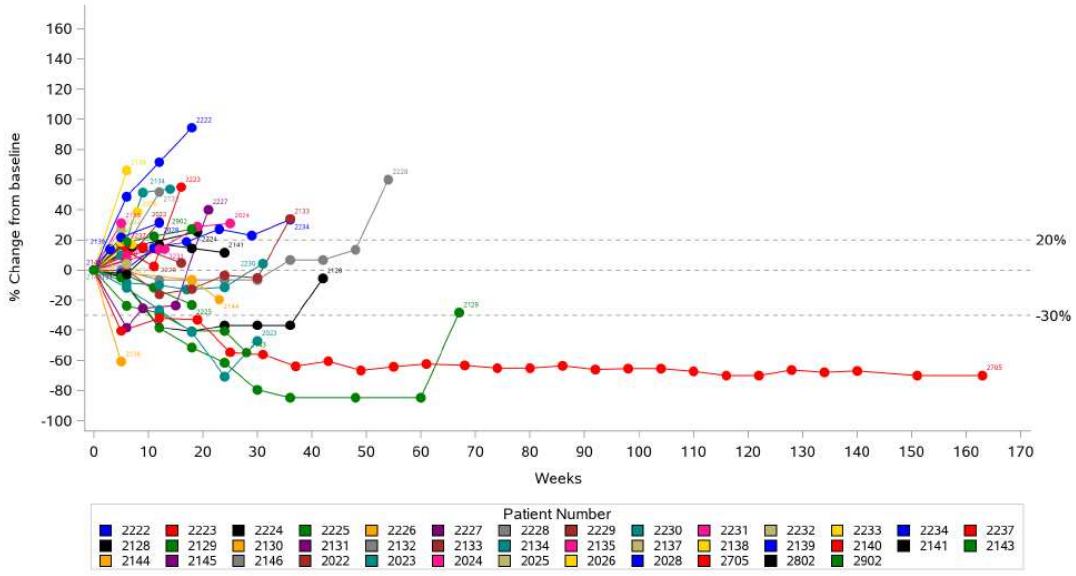
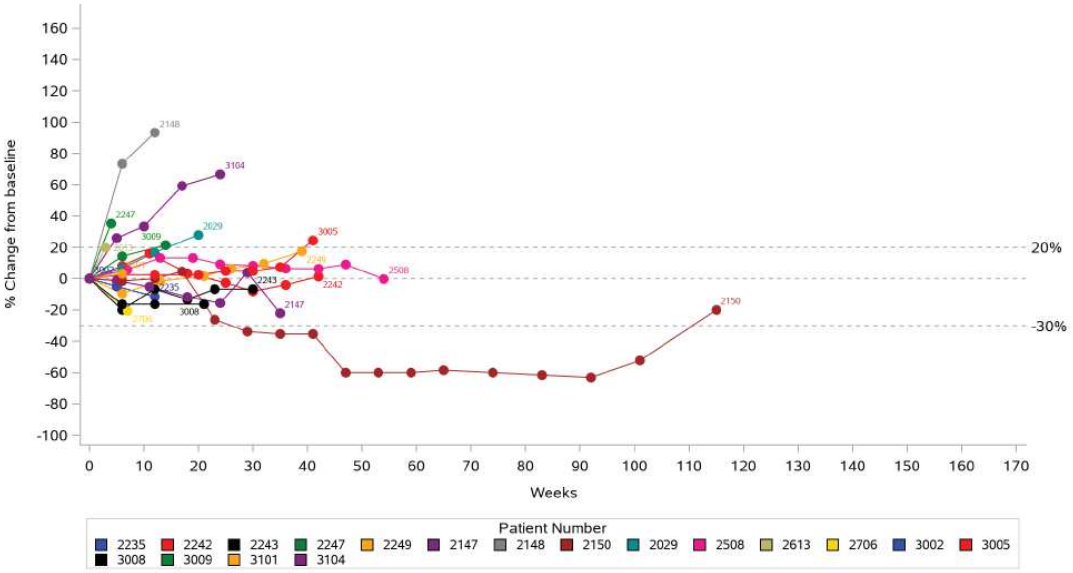


c.) ICB-experienced MEL patients



d.) ICB-experienced NSCLC patients

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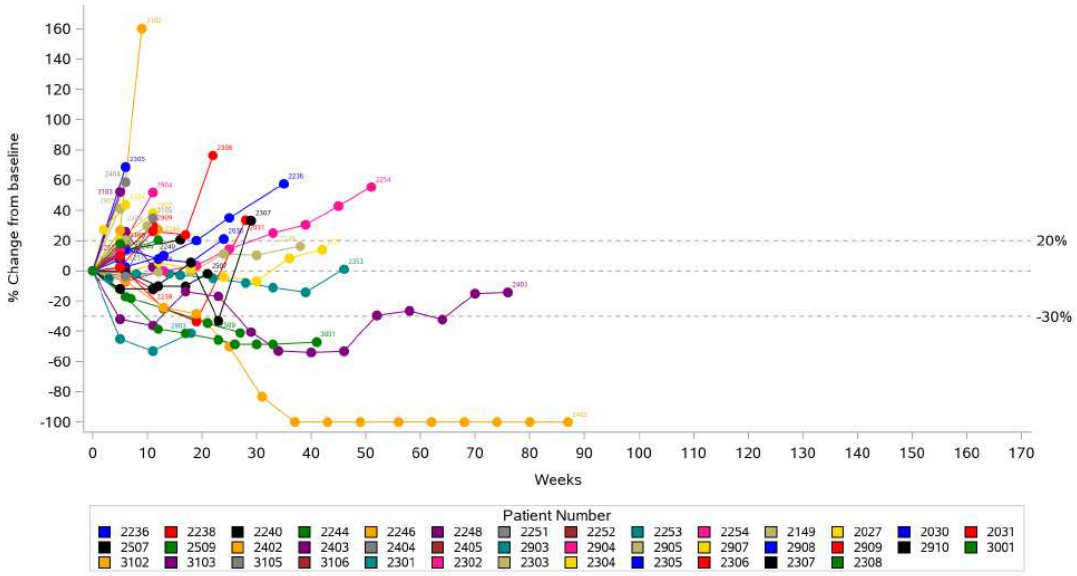
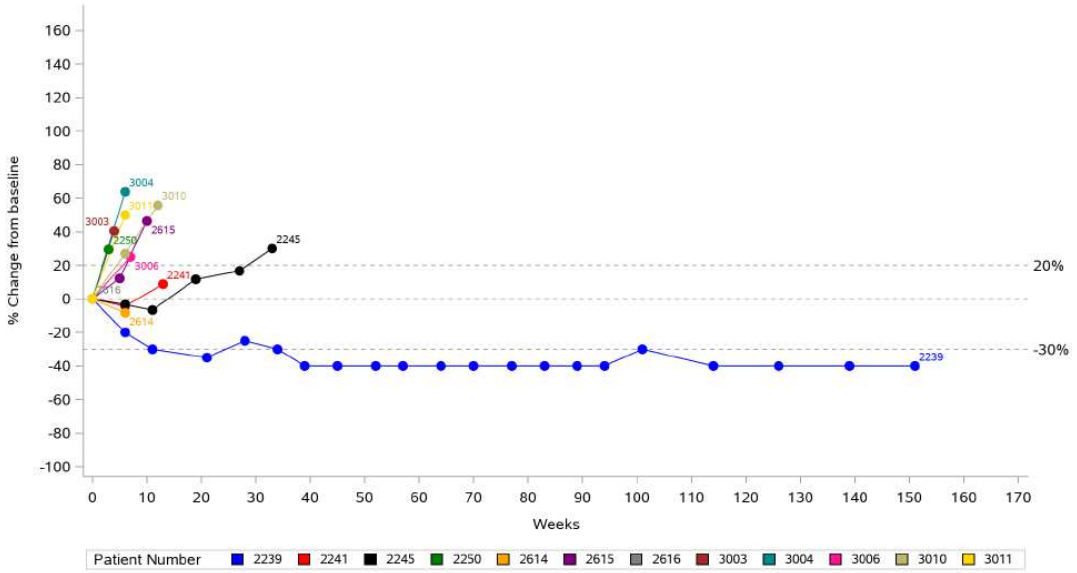


e.) ICB-experienced UBC patients



Supplementary Figure 2 Baseline comparison of TAMs and tumor-infiltrating T cells and comparison of progressive disease patients versus non-progressive disease patients in the UBC ICB-naïve cohort. Clinical responses are indicated. % Area Coverage indicates the percentage of the respective tissue area in a given section that is populated by TAMs.

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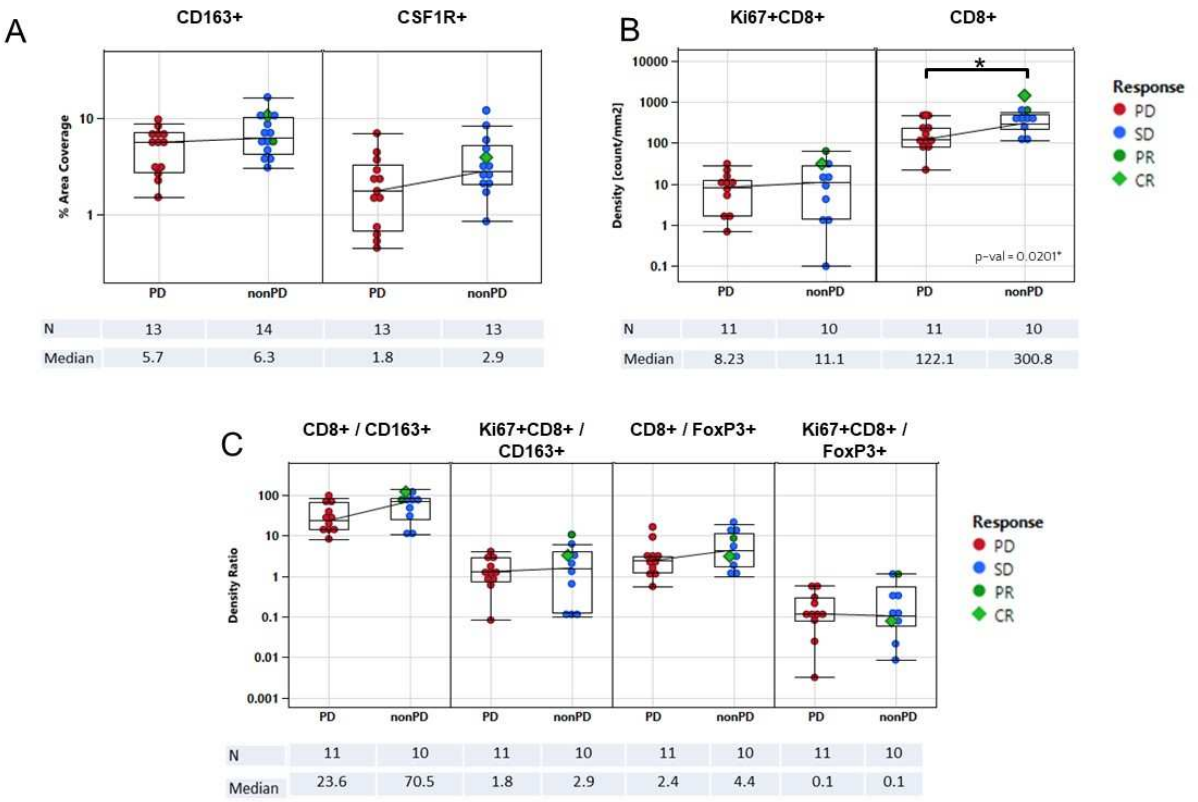

Supplementary Figure 3 Change from baseline of TAMs, tumor-infiltrating T cells and respective ratios in paired biopsies and comparison of progressive disease group versus non-progressive disease group in the ICB-naïve UBC patients

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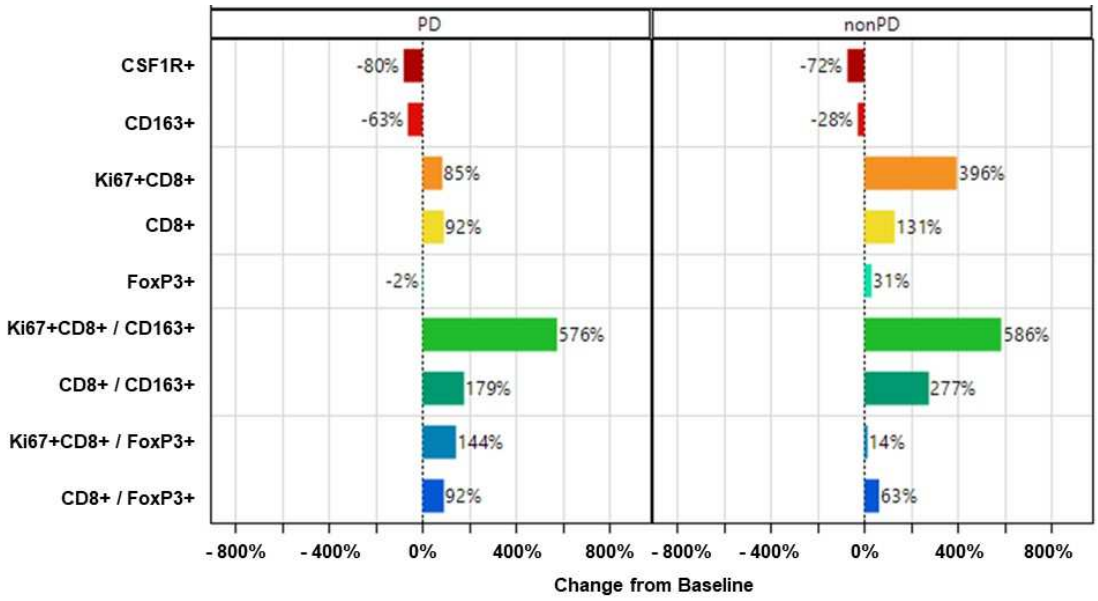
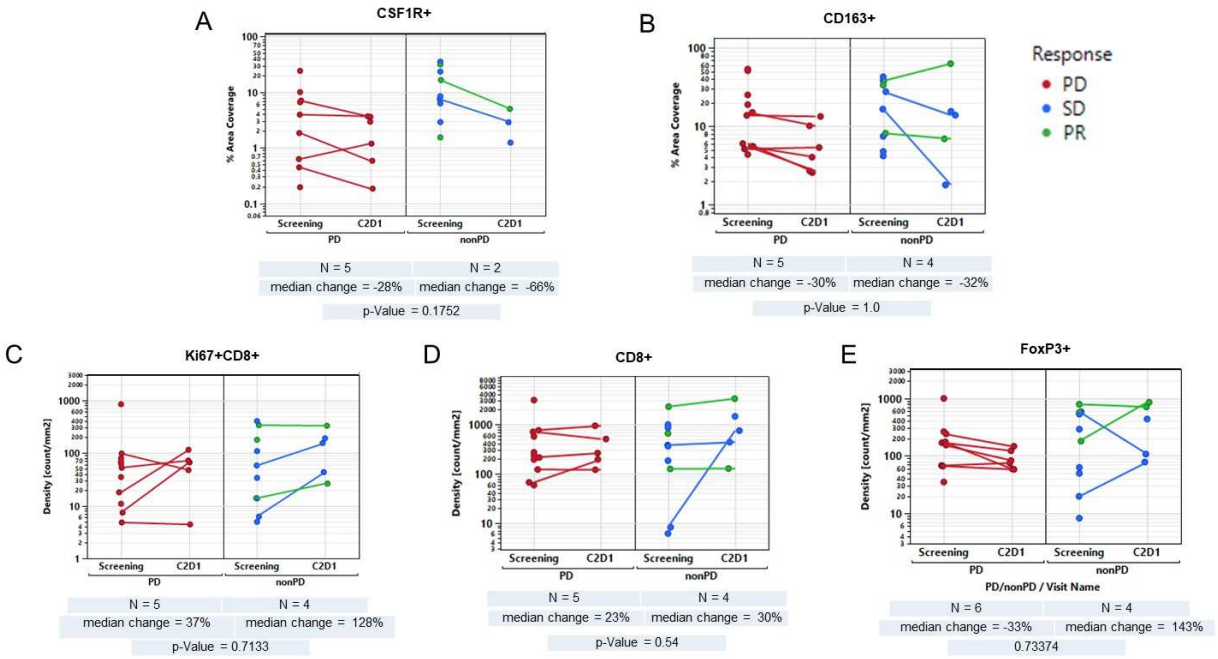


Supplementary Figure 4 Change from baseline of TAMs and tumor-infiltrating T cells in paired biopsies and comparison of progressive disease group versus non-progressive disease group in the ICB-experienced NSCLC cohort. Clinical responses are indicated.



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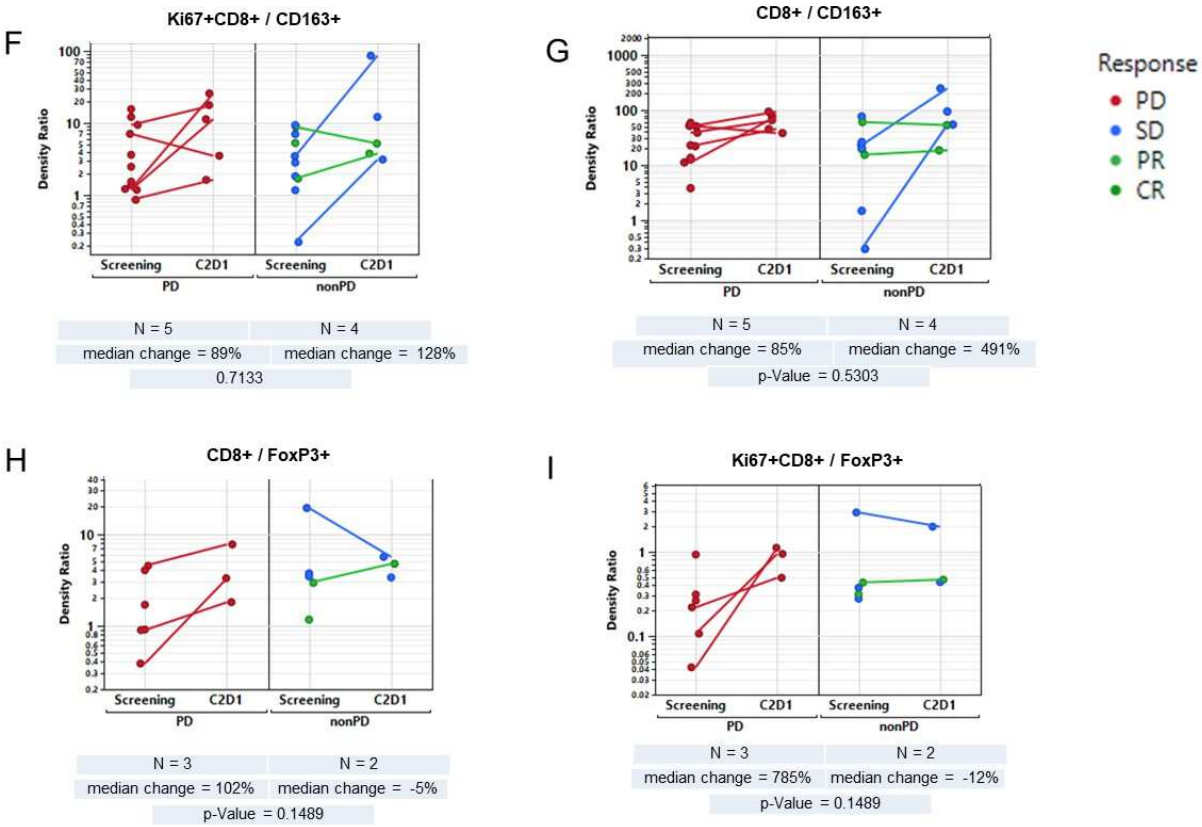

Supplementary Figure 5 Change from baseline of tumor-infiltrating T cells, TAMs and respective ratios in paired biopsies and comparison of progressive disease group versus non-progressive disease group in the ICB-experienced NSCLC cohort

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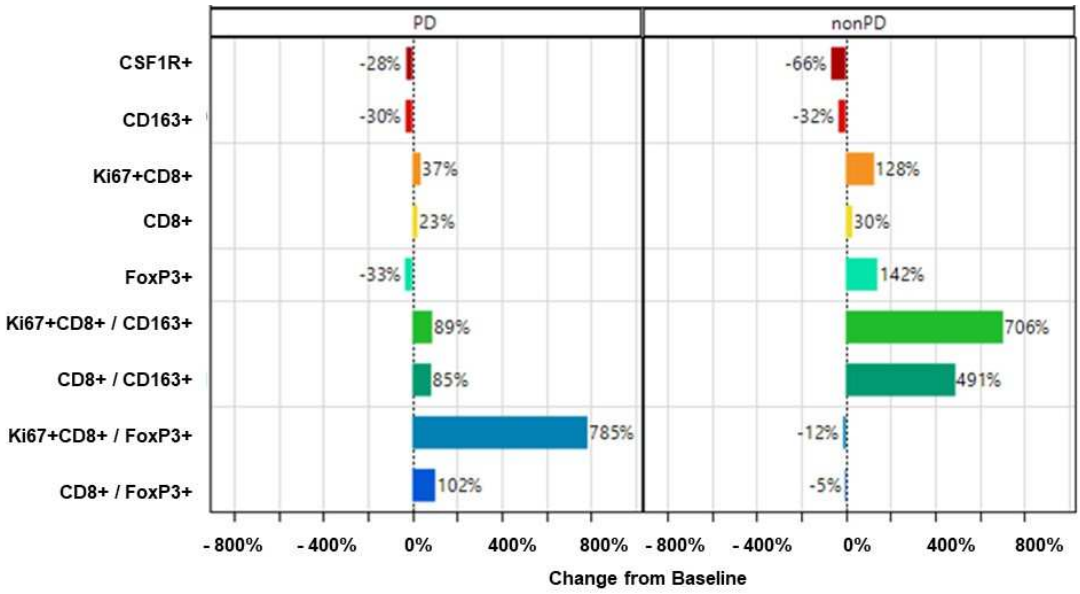

Supplementary Figure 6 Correlations of CD163+ or CSF-1R+ TAMs vs. CD8+ T cells or Ki67+CD8+ T cells in ICB-naïve UBC patients

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