DUKE UNIVERSITY MEDICAL CENTER

An Autologous Humanized Patient-Derived Xenograft (PDX) model for evaluation of Immunotherapy in Renal Cell Cancer

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A National Cancer Institute-designated Comprehensive Cancer Center

KidneyCancerAssociation® IN PARTNERSHIP WITH UTSouthwestern Medical Center Kidney Cancer Program

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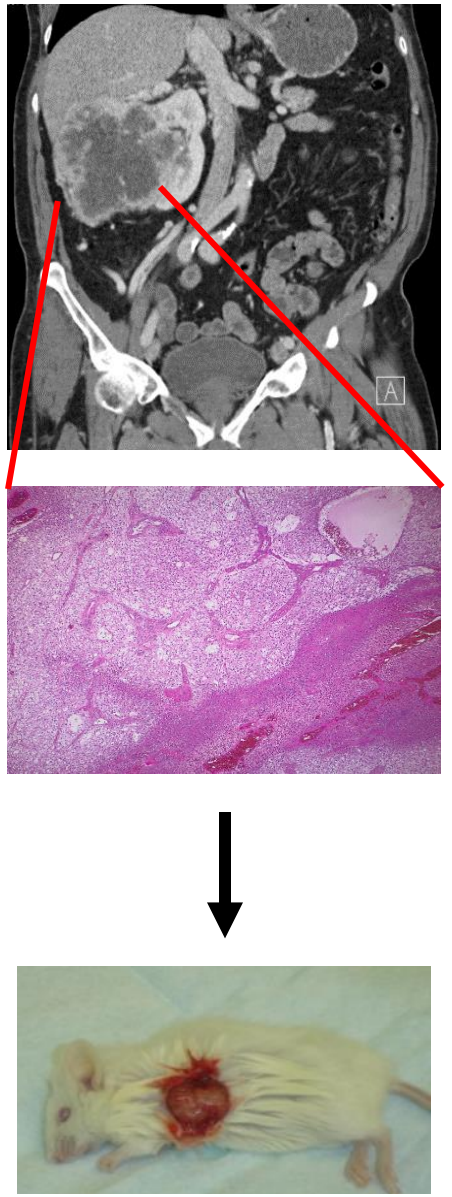
Disclosures

- Co-Founder Xilis

Case Study

- 68 year old Caucasian man initially presented to the Duke Cancer Center in Jan 2014 with persistent gross hematuria in and was found to have a 13 cm right renal solid, enhancing mass with invasion into the liver and left hepatic lobe metastatic lesions
- Initially enrolled on the Argos ADAPT clinical trial of cytoreductive nephrectomy followed by randomization to sunitinib +/- AGS-003 (a personalized tumor derived RNA vaccine)
- He underwent a cytoreductive right nephrectomy and left adrenalectomy, vena caval reconstruction and caval thrombectomy with partial liver resection. Pathology from this surgery was diagnostic of clear cell renal cell carcinoma
- Sample obtained from resected specimen, injected into a NOD.SCID mice and PDX was made



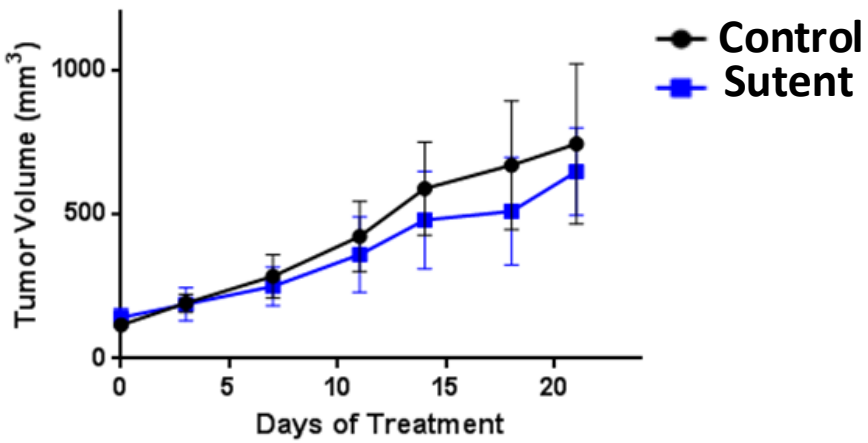
Kang, Armstrong and Hsu, Stem cell Investigation (2022)

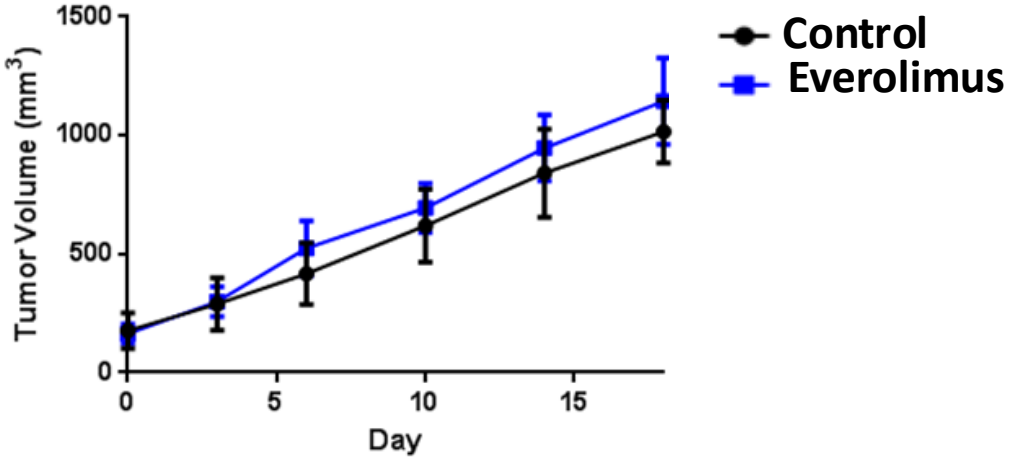
Case (continued)

- Post surgery, started on sunitinib plus AGS-003. However this was stopped after 6 months due to disease progression with increase in size and number of bilateral pulmonary nodules, and a new 1.4 cm right adrenal nodule.
- 2nd line therapy - initiated on axitinib, but within three months had disease progression again. He developed pleural effusions causing hypoxia.
- 3rd line therapy - initiated on third line bevacizumab with disease progression following a few months later.
- 4th line therapy – initiated on everolimus with disease progression five months later
- 5th line therapy – initiated on cabozantinib for only a few weeks while awaiting approval for nivolumab, which had just become USFDA approved for metastatic renal cell carcinoma.

Kang, Armstrong and Hsu, Stem cell Investigation (2022)

Meanwhile in the lab…..





- Treatment of PDX with sutent and everolimus showed no response
- As next line of therapy is nivolumab, can we develop a correlative model?

Attempt 1 – Allogenic Transplant

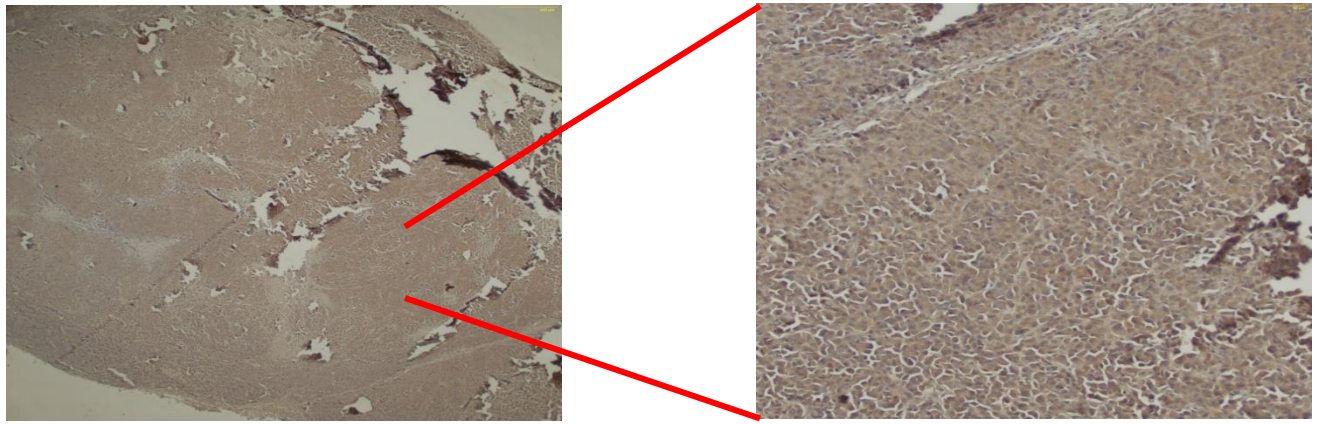
- Cord blood samples were obtained from Carolinas Cord Blood Bank
- Human CD34 cells were isolated from cord blood samples using CD34 MicroBead kit (Miltenyi Biotec Inc).
- ~0.5 x 10^6 CD34 cells was isolated from one unit of cord blood (35ml) with 97% purity
- 8-12 weeks old NSG (NOD/SCID IL-2γ Null) mice were radiated with 150 rad using cesium irradiator (total of 10 mice).
- Within 2 hours after the irradiation, the NSG mice were injected intravenously with the isolated human CD34 cells (150,000 cells/mouse).

	CD45+%	CD45+CD4+%	CD4+%	CD45+CD8+%	CD8%	CD45+CD19%	CD19%	CD45+CD16+%	CD16+%
NSG-1	12.9	8.6	1.11	6.33	0.82	71.9	9.27	8.6	1.109
NSG-2	16.2	1.18	0.19	2.35	0.38	80	12.96	1	0.162
NSG-3	2.59	9.09	0.24	7.44	0.19	60.3	1.567	1.65	0.043
NSG-4	26.2	7.72	2.02	4.36	1.14	80.9	21.19	0.5	0.131
NSG-5	30.8	7.16	2.21	6.87	2.12	82.5	25.41	0.5	0.154
NSG-6	32.2	1.12	0.36	4.49	1.45	72.5	23.34	1.12	0.361
NSG-7	12.7	5.91	0.75	5.71	0.73	70.3	8.93	0.59	0.075
NSG-8	24.7	5.74	1.42	6.4	1.58	73.6	18.18	0.99	0.245
NSG-9	32.4	2.22	0.72	8.77	2.84	80	25.92	1.35	0.437

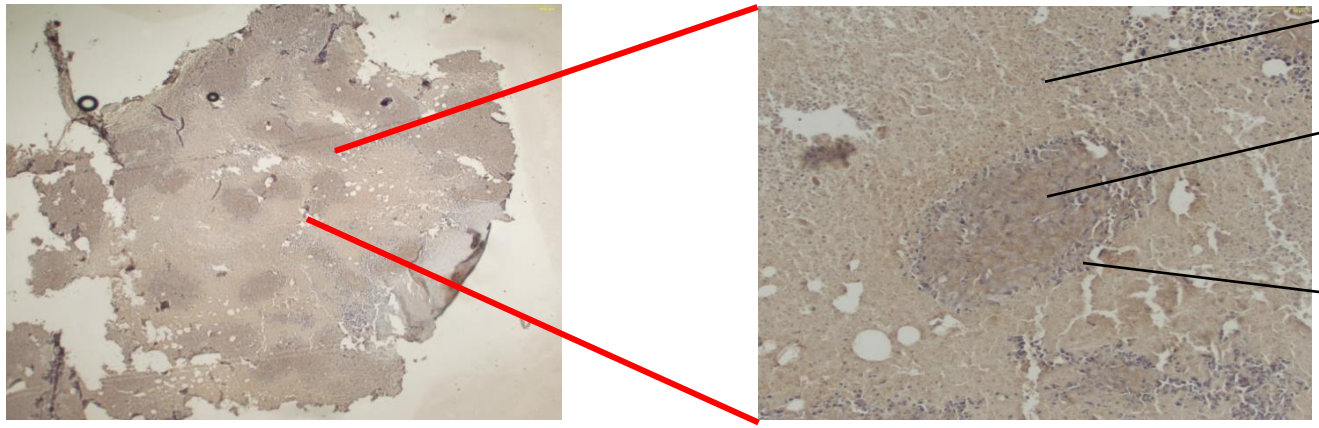
Attempt 1 – Allogenic Transplant

- After reconstitution of a human immune system in NSG, each mice was injected with PDX tumor
- Growth of tumor monitored and growth to 1 X 1 cm was achieved after 4 weeks

WT NSG

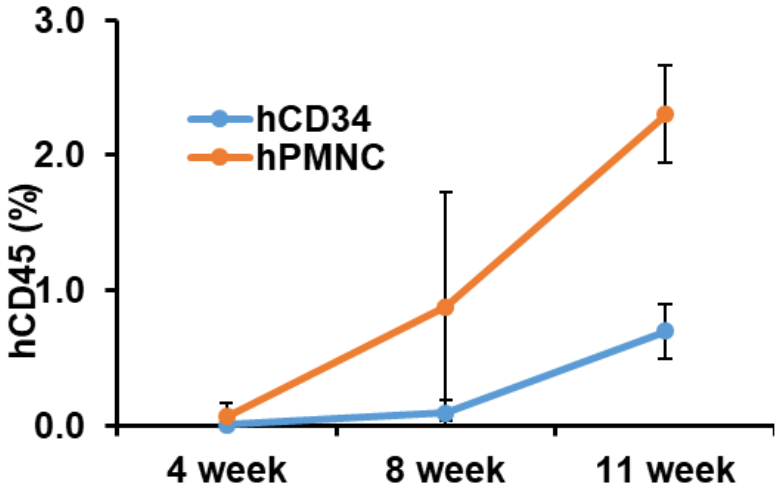


CD34 Reconstituted NSG

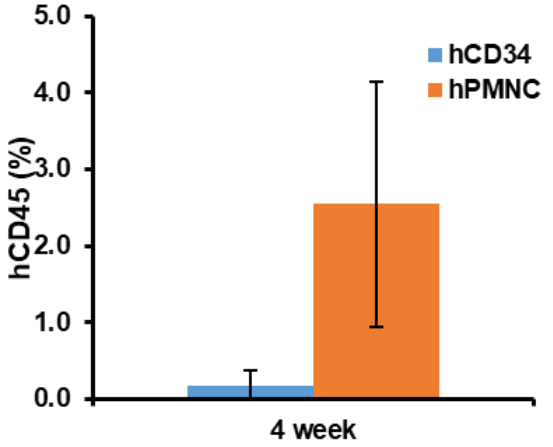


Attempt 2 – Autologous Transplant

- Bone marrow aspirate obtained from patient
- Human CD34 cells were isolated from cord blood samples using CD34 MicroBead kit (Miltenyi Biotec Inc).
- 8-12 weeks old NSG (NOD/SCID IL-2γ Null) mice were radiated with 150 rad using cesium irradiator (total of 10 mice).
- Within 2 hours after the irradiation, the NSG mice were injected intravenously with the isolated human CD34 cells (150,000 cells/mouse).
- 12 week later, engrafted mice injected with PDX



Peripheral blood analysis

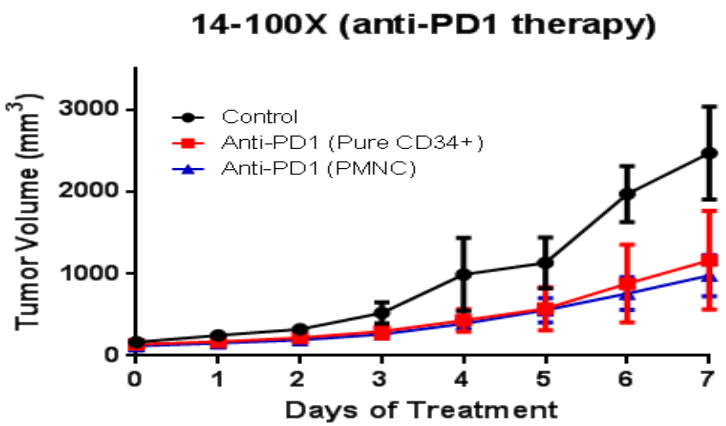


Bone marrow analysis after 13 week (at the end of PDX experiment)

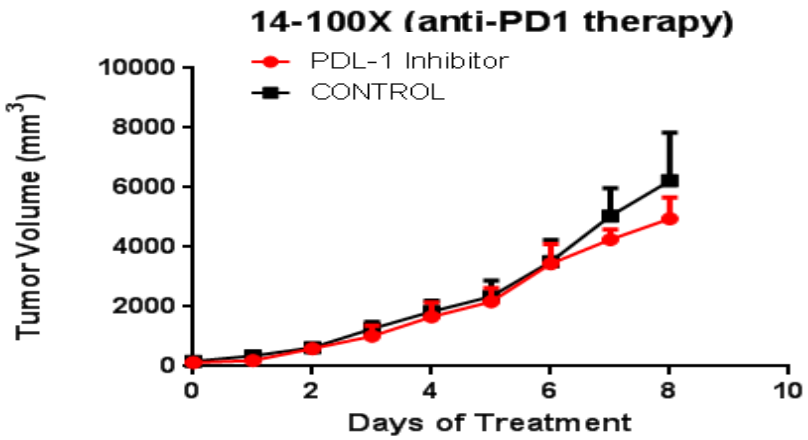
Kang, Armstrong and Hsu, Stem cell Investigation (2022)

Treatment with Checkpoint Inhibitors

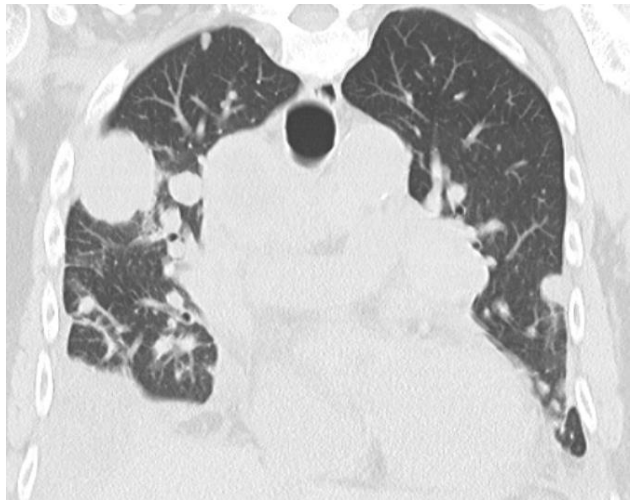
Reconstituted NSG mice



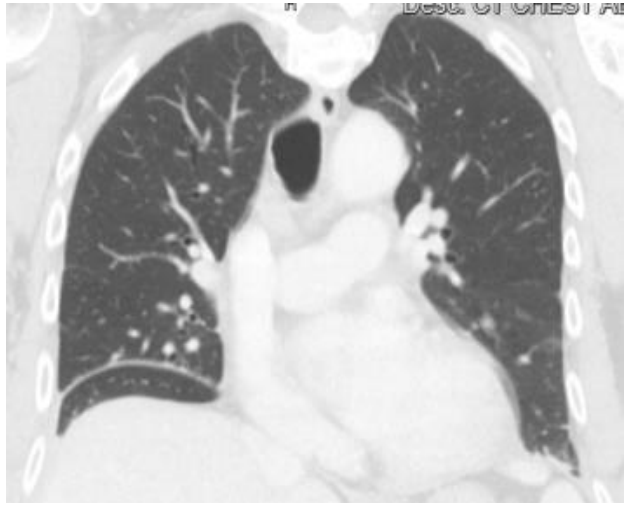
Non-Reconstituted NSG mice



Patient



Nivolumab



Kang, Armstrong and Hsu, Stem cell Investigation (2022)

Case (continued)

- 6th line therapy – initiated on nivolumab
- He received 60 cycles total of nivolumab and achieved complete remission.
- Today, five years after initiation, he is still on no therapy and continues to be in complete remission and enjoying a prolonged treatment free interval free of disease or symptoms from his cancer. While dealing with Parkinson's disease, he no longer requires home oxygen, pleural effusions resolved, and is doing well.

Kang, Armstrong and Hsu, Stem cell Investigation (2022)

Conclusions

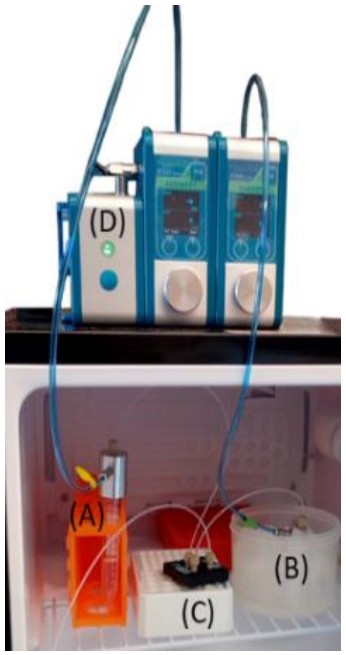
- Autologous transplant (bone marrow biopsy) is a way of studying immune-oncology in the lab
- Unfortunately, extremely time consuming and expensive
- Allogenic transplant (cord blood) is improving with decreased rejection by using matched cord blood
- Are there other patient derived models of cancer that can be used to study immune-oncology?

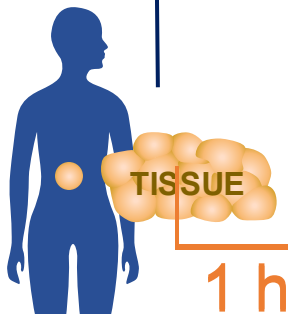
MicroFluidics to Develop MicroOrganoSpheres

Dissociated Cells

Oil

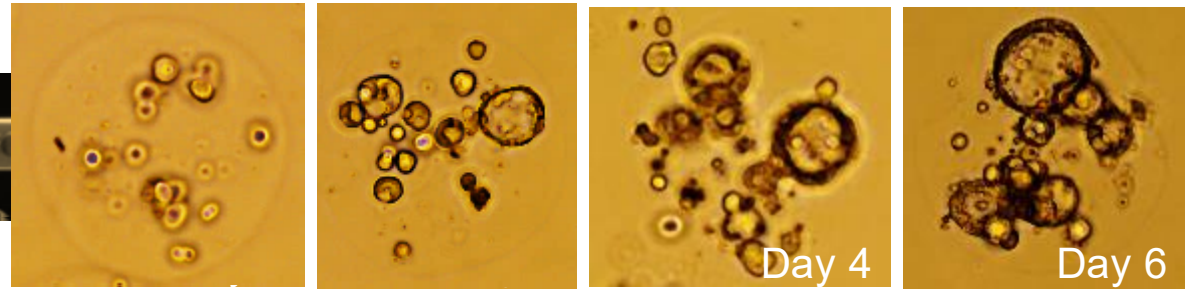
Micro Fluidic Based Technology





1 hr

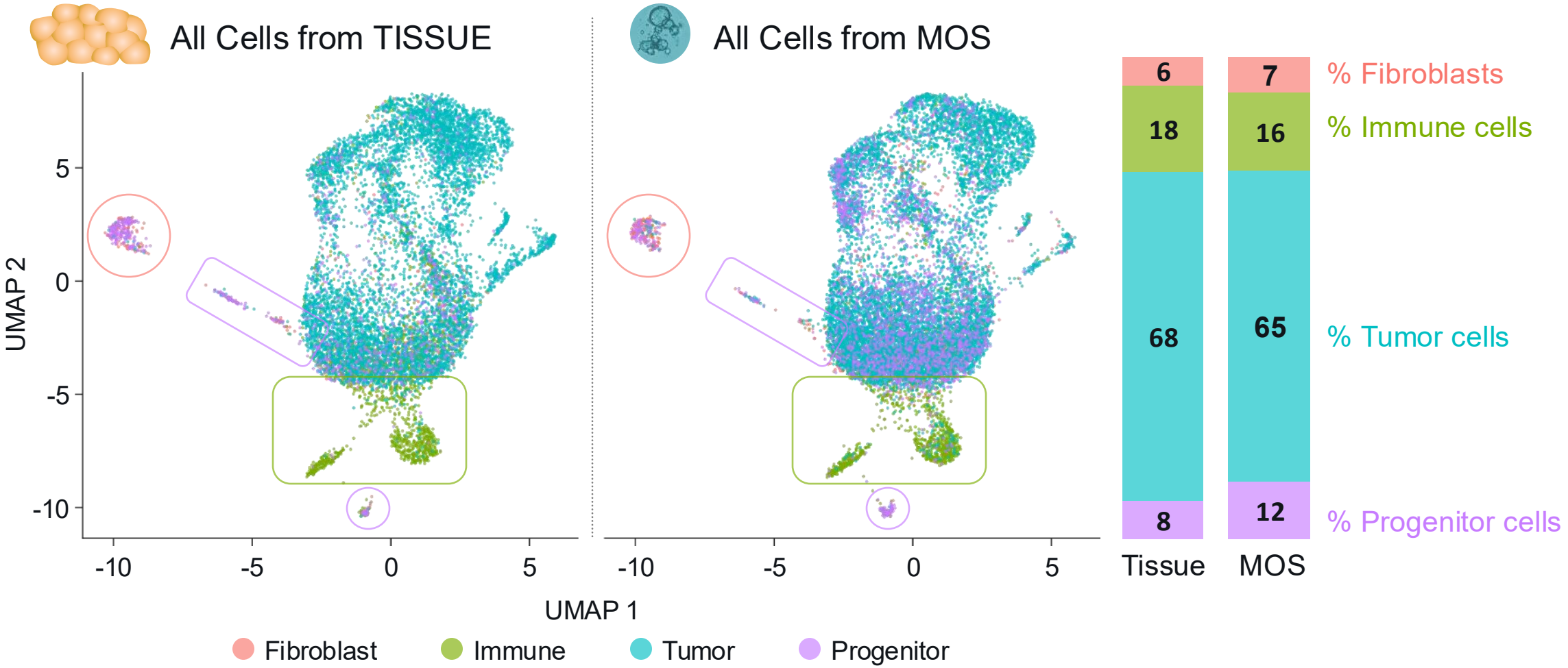
MOS



Rapid growth

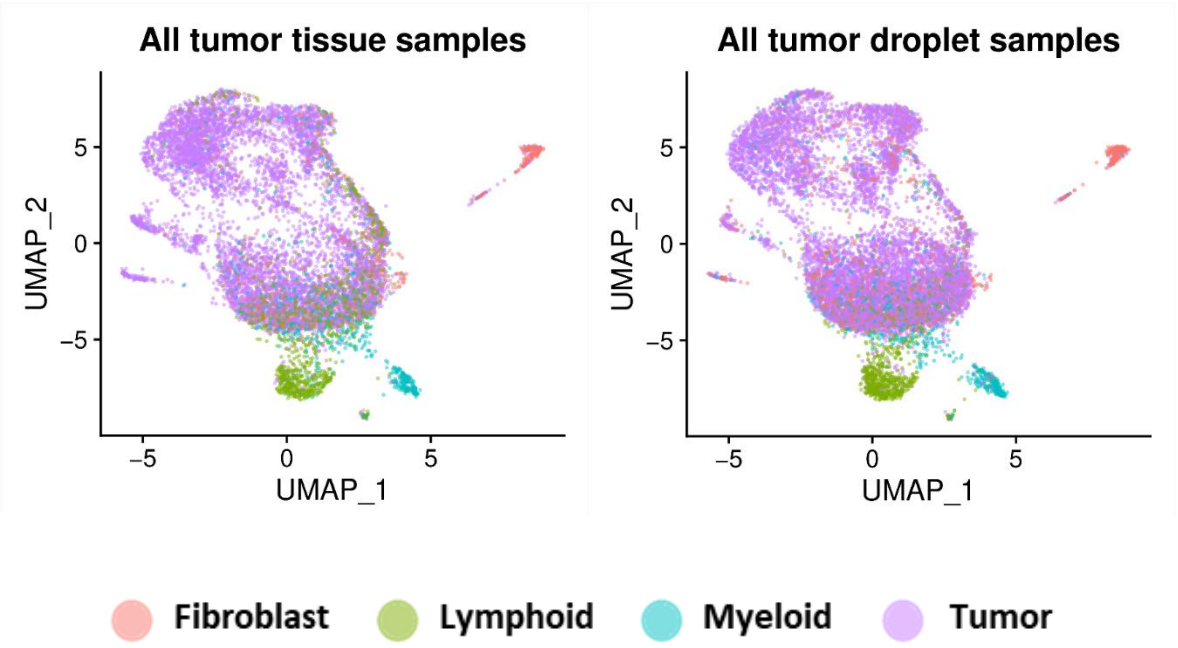
Functional Assays

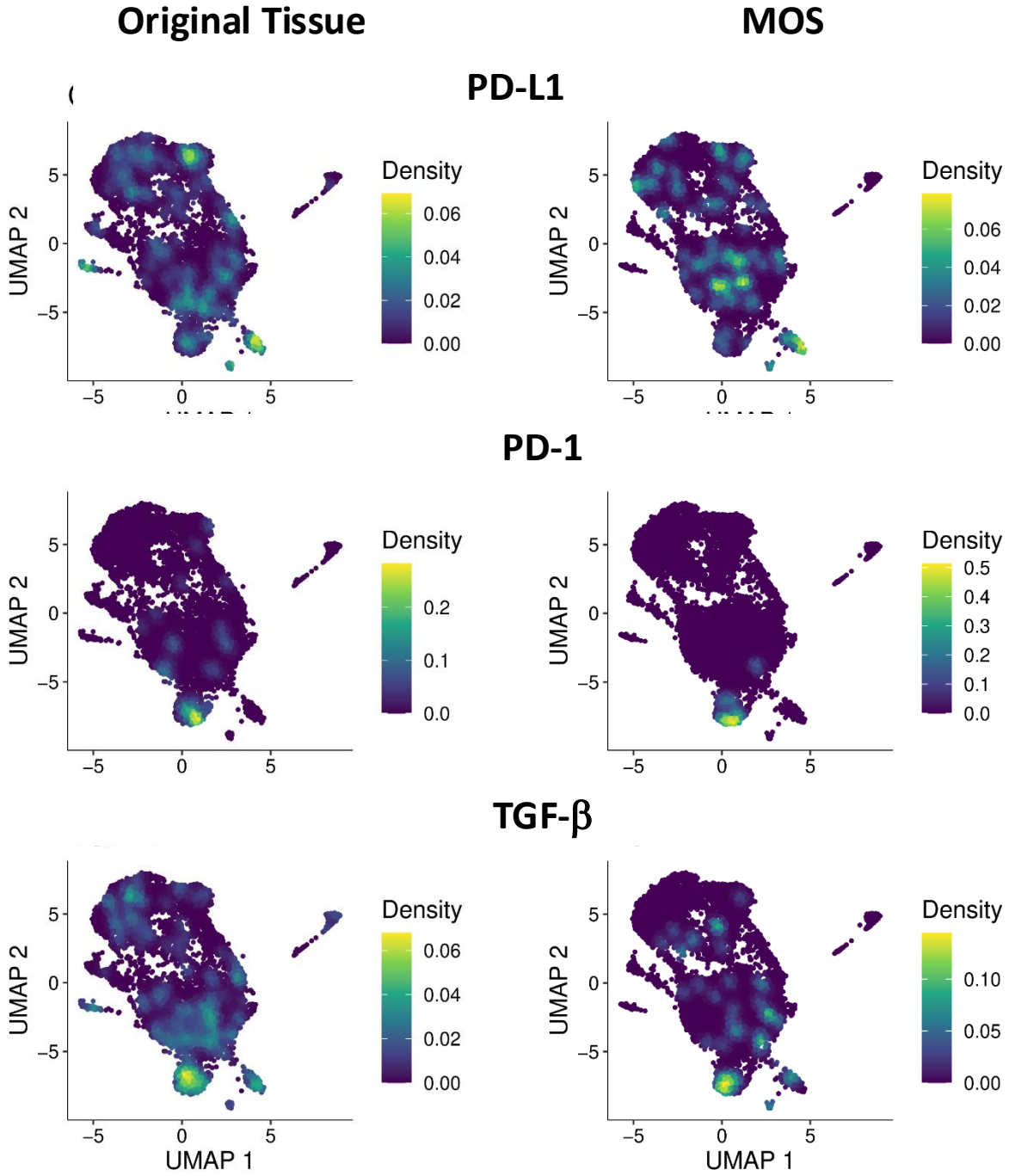
MOS captures entire patient tumor including TME



Ding et al., Cell Stem Cell, 2022

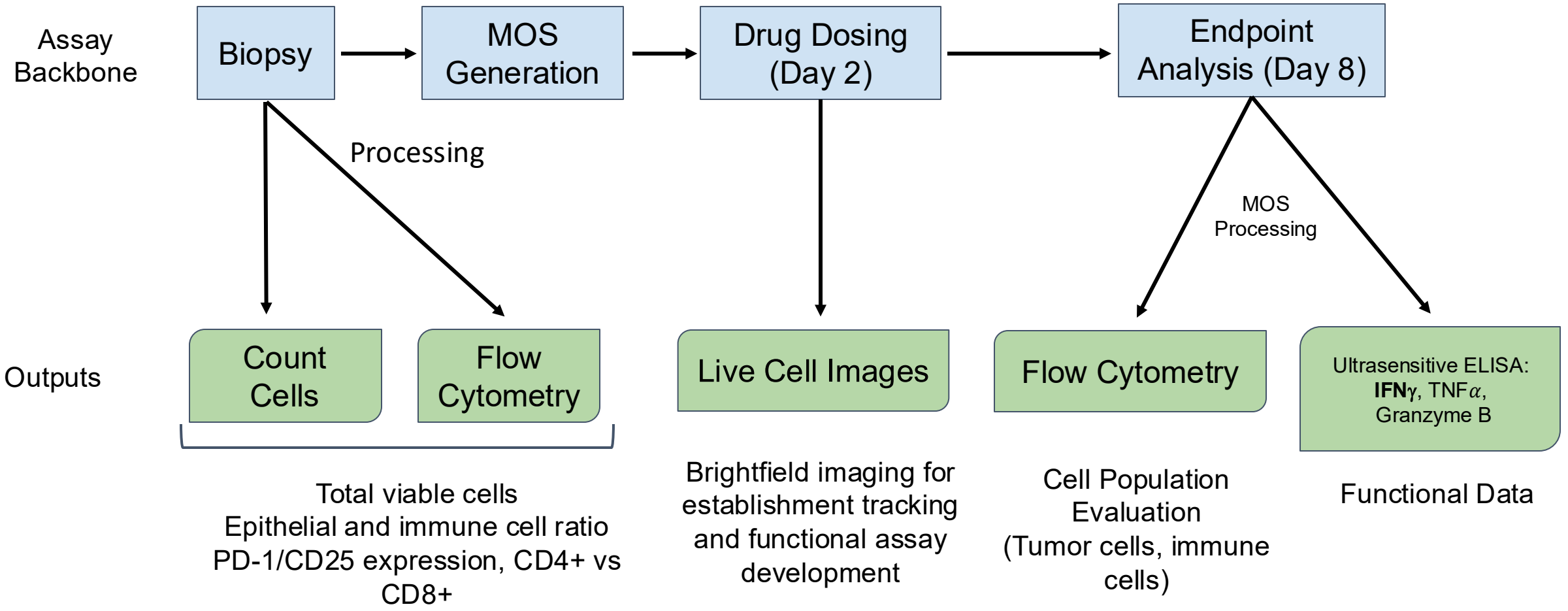
Protein marker concordance between tissue and organoids



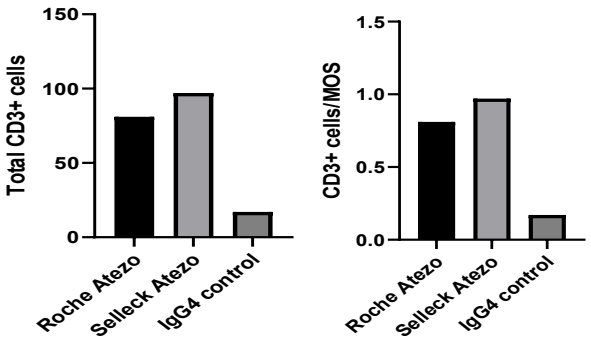


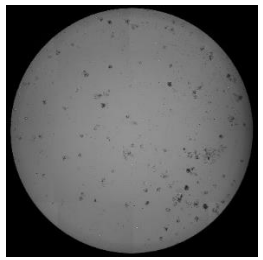
Ding et al., Cell Stem Cell, 2022

Duke ImmunoOncology (IO) Diagnostic Assay



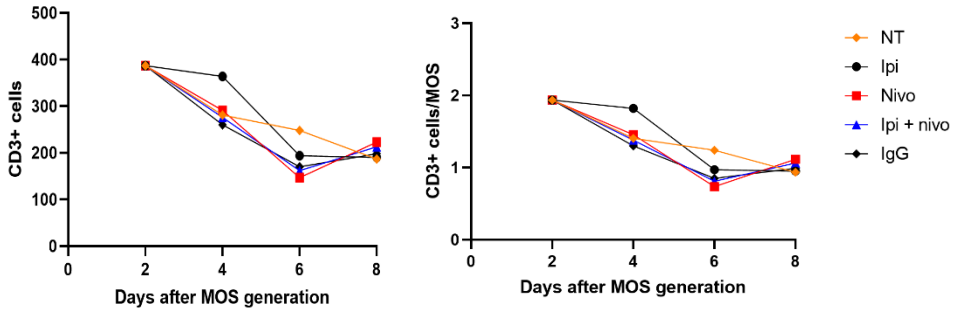
Patient 1 (HCC)

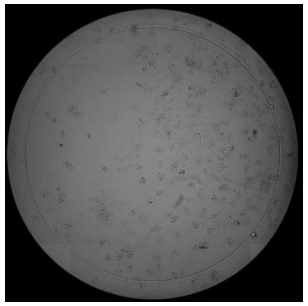


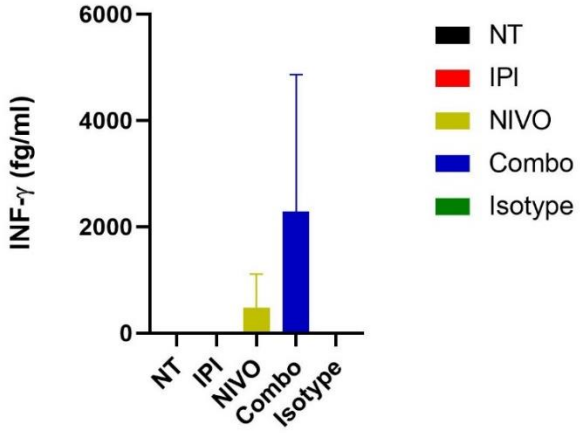


Sample	Assay	Detection Range	Signal
HCC-D8-R-Atezo1	IFN-γ	Below Fit Curve Range	182
HCC-D8-R-Atezo	IFN-γ	Below Fit Curve Range	126
HCC-D8-SC-Atezo1	IFN-γ	Below Fit Curve Range	105
HCC-D8-SC-Atezo2	IFN-γ	Below Fit Curve Range	246
HCC-D8-IgG1	IFN-γ	Below Fit Curve Range	124
HCC-D8-IgG2	IFN-γ	Below Fit Curve Range	123
HCC-D8-IgG3	IFN-γ	Below Fit Curve Range	116

Patient 2 (Melanoma)







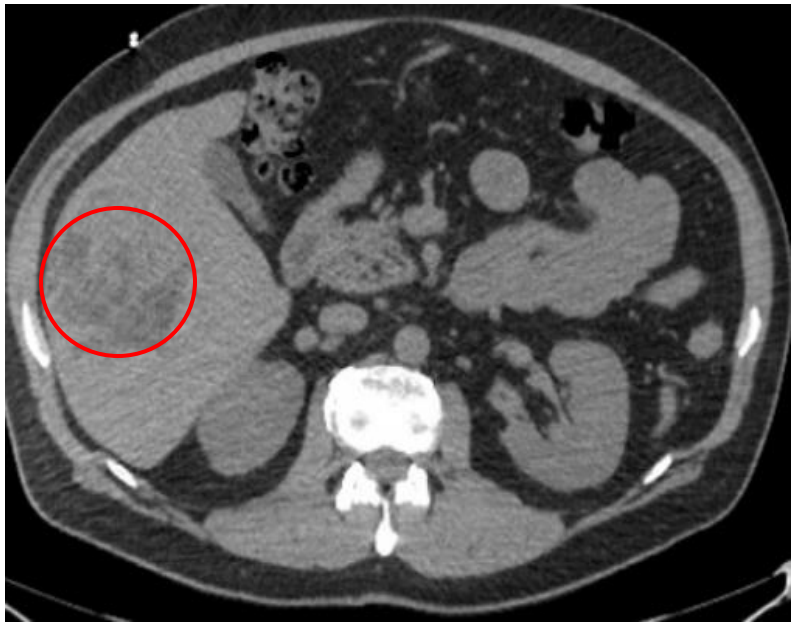
Duke IO Assay – 1) Patient 1 would not respond to IO therapy

2) Patient 2 would respond to combination therapy only

Clinical Applicability (Case 1)

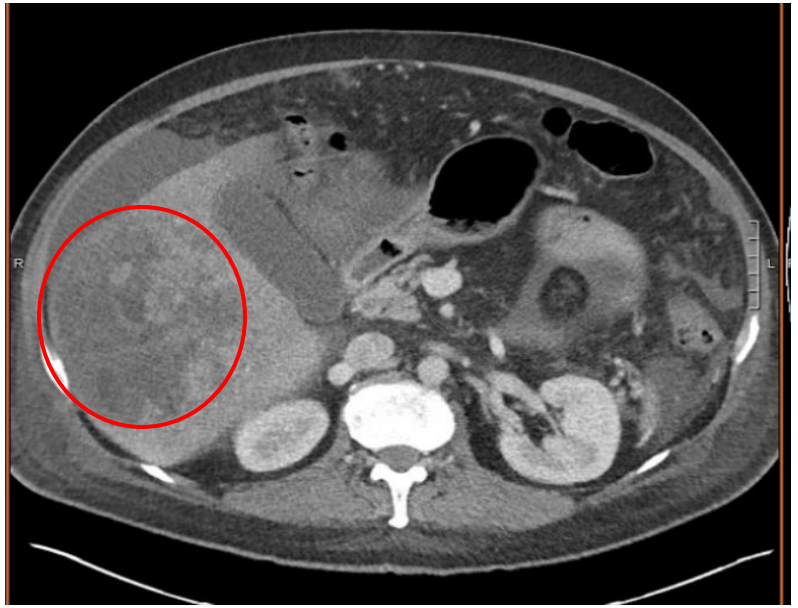
Patient 1

- Presented with metastatic Hepatocelluar Carcinoma (HCC)
- **AFP = 184,567** (normal <5)



Atezolizumab
+
Bevacizumab

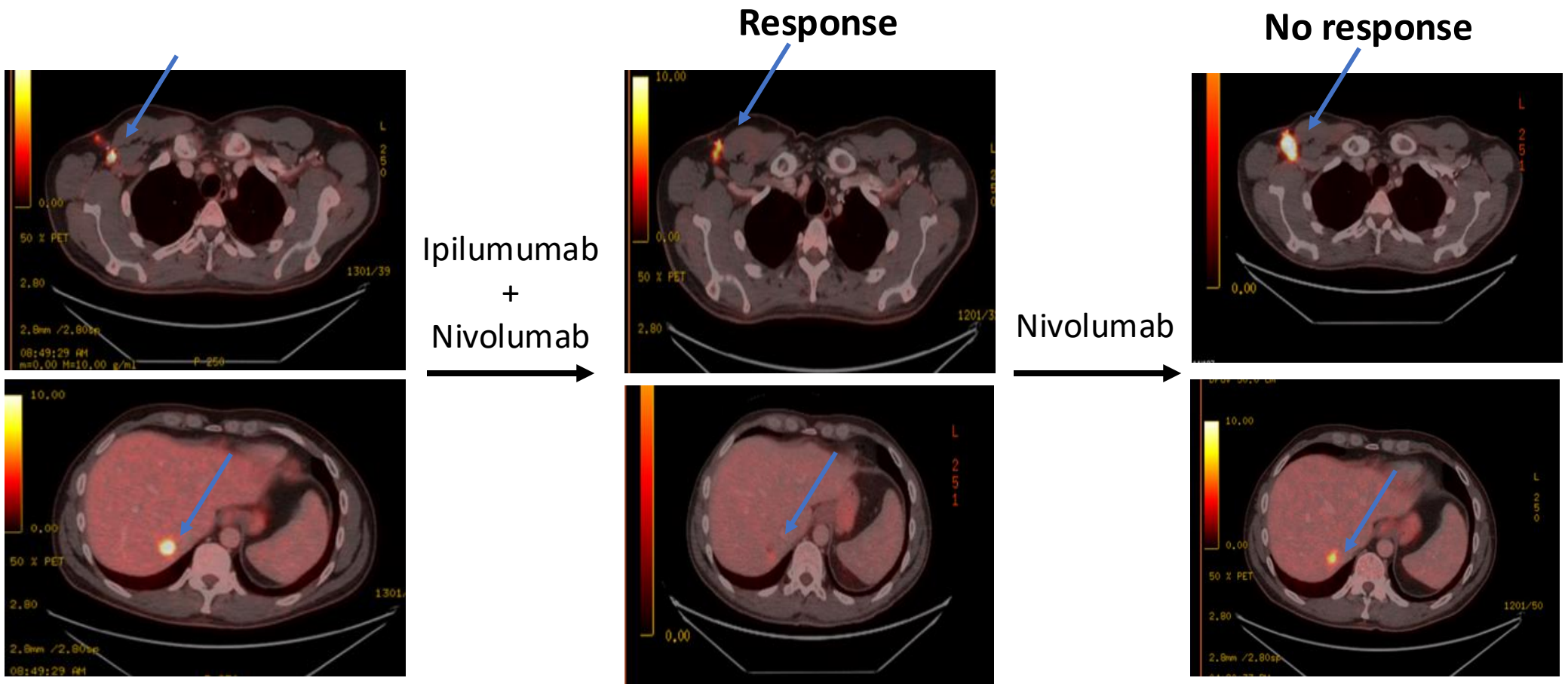
AFP = 470,950



Clinical Applicability (Case 2)

Patient 2

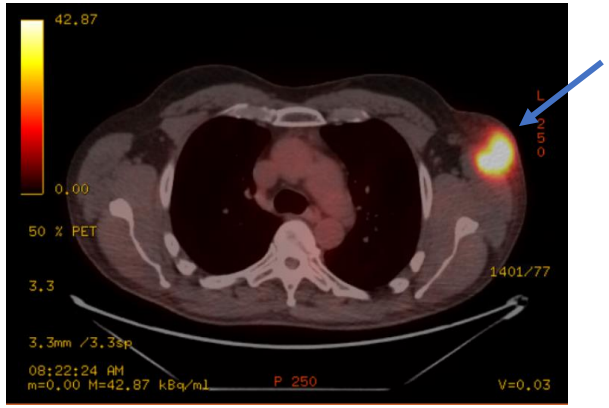
- Presented with metastatic melanoma



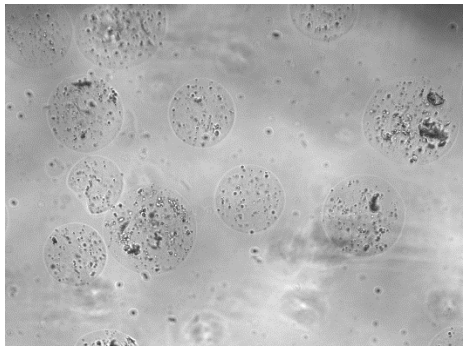
Clinical Applicability (Case 3)

Patient 3

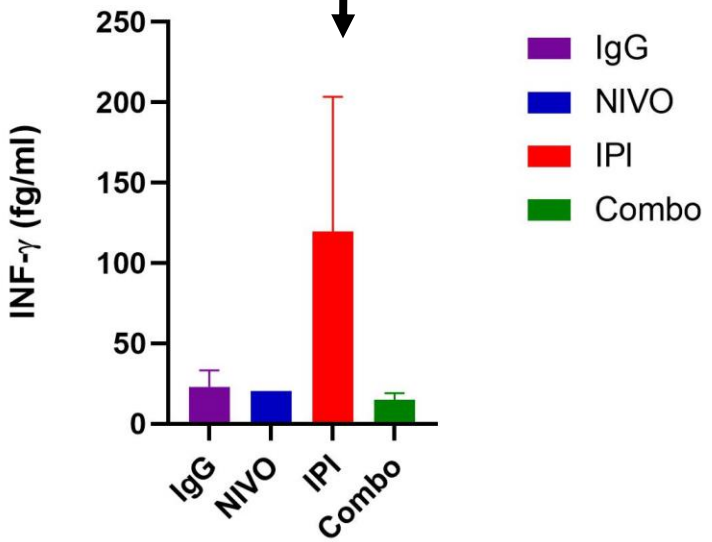
- Presented with melanoma to left chest wall



MOS



Duke IO Diagnostic Assay



Enrolled in Neoadjuvant Melanoma Study

Received Nivolumab (Expected Response Rate = 30-35%)

Resection

DIAGNOSIS

A. Left chest wall mass, excision:

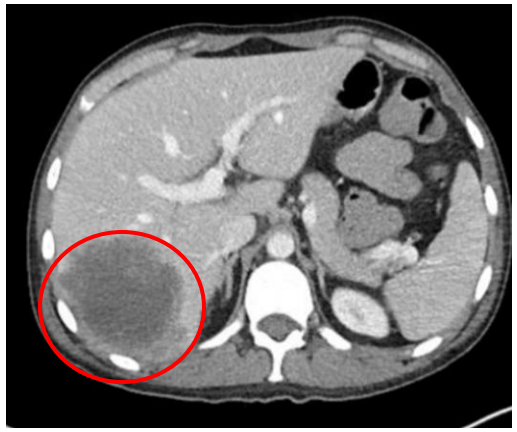
VIABLE INVASIVE MELANOMA (90% viable) WITH OVERLYING HEALED SURGICAL WOUND, MARGINS ARE FREE.

Prediction – no response to nivolumab

Clinical Applicability (Case 4)

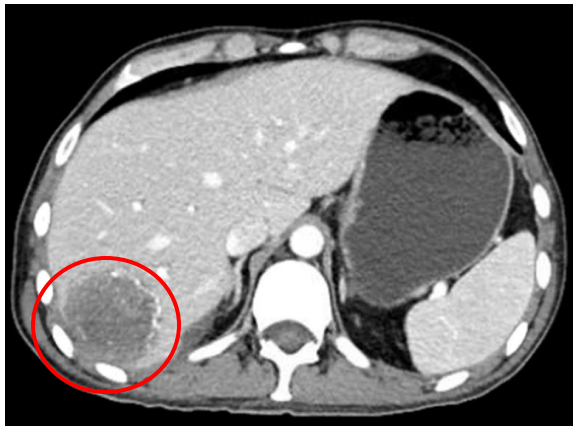
Patient 4

- Presented with metastatic CRC to liver
- Tumor found to be Microsatellite Instable (MSI)
- Initiated on combination of ipilumumab + nivolumab
- CEA 52

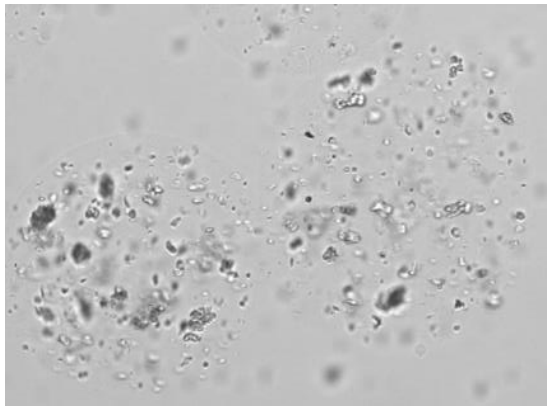


Size : 7.3 X 5.8 cm

Ipilumumab
+
Nivolumab

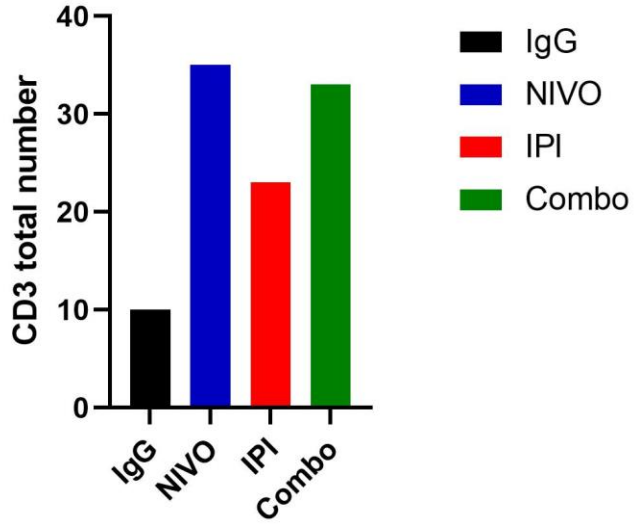


Size : 5.9 X 4.9 cm
CEA 2



MOS Generated from Primary Site

Duke IO Diagnostic Assay



Thank you for your time