CHMP Oncology Working Party Workshop on: Histology – Independent Indications in Oncology

Non-clinical models: Tumour Models - Proof of Concept

Edward C. Rosfjord – Pfizer Worldwide R. & D.

14 December 2017

Pfizer WORLDWIDE RESEARCH & DEVELOPMENT

SCIENCE FOR LIFE-CHANGING IMPACT

Disclosures

Edward Rosfjord is an employee of Pfizer.

The research described in this presentation was conducted in Pfizer research labs by Pfizer personnel.

All procedures performed on these animals were in accordance with regulations and established guidelines and were reviewed and approved by Pfizer Institutional Animal Care and Use Committee.

Overview of Preclinical Tumour Models

Genetically Engineered Mouse Models (GEM)

Advantages:
– Mice get spontaneous tumours with defined genetics.
– Useful for understanding the biology of an oncogenic driver in an intact animal.
– Intact immune system.

Disadvantages:
– Long latency (>300 days).
– Difficult to evaluate in-life.
– Biology may be limited to the oncogenic driver or be mouse specific.

Human Tumour Cell Line Xenografts (CLX)

Advantages:
– Hundreds of human patient cell line models.
– Permits *in vitro* evaluation and *in vivo* studies.
– Short latency (<30 days).
– Common cell lines.

Disadvantages:
– Immune deficient mice.
– Clonal changes in cell lines adapted to growth *in vitro*.
– Rarely tumour studied in orthotopic space.

Patient-Derived Tumour Xenografts (PDX)

Advantages:
– Complex tumour stroma architecture. May support tissular mechanisms.
– Molecular mechanisms and oncogenic drivers similar to the patient.
– Recapitulates the patient response *in vivo*.

Disadvantages:
– Immune deficient mice.
– Rarely tumour studied in orthotopic space.

Tumour Models For Immuno Oncology

Syngeneic Mouse Models

Mouse tumour cell line models implanted in immunocompetent mice

Advantages:
– Intact mouse immune system.
– Tumours from mouse cell lines or GEM allografts.
– Short latency (<30 days)

Disadvantages:
– Small number of characterized tumour models.
– Small number of molecular subtypes and oncogenic drivers.
– Immune cell biology may be mouse specific or mouse strain specific.

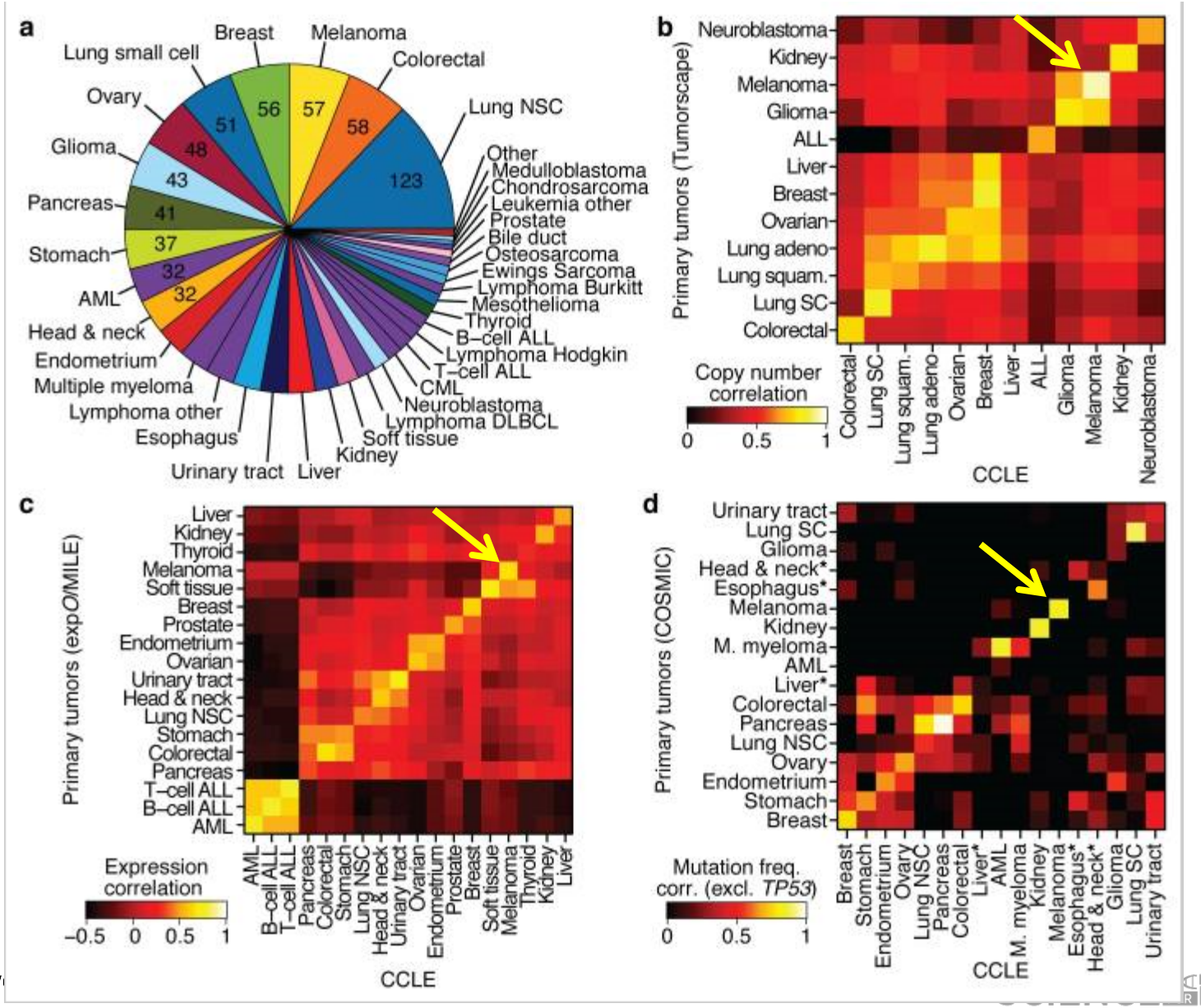
Humanized Mouse Models

Human tumour CLX and PDX implanted in immune deficient mice with a transplanted human immune system

Advantages:
– Utilize the hundreds of human tumour CLX models and PDX models.
– Large number of molecular drivers and tumour subtypes.
– Partial human immune system.

Disadvantages:
– Tumour and immune cells may not be HLA-matched.
– No human spleen or thymus.
– Heterogeneity between different immune transplants – ***reproducibility.***

Analysis of 947 Human Tumour Cell Lines
Cancer Cell Line Encyclopedia - CCLE



Barretina *et al.*, (2012) *Nature* 483:603-607.

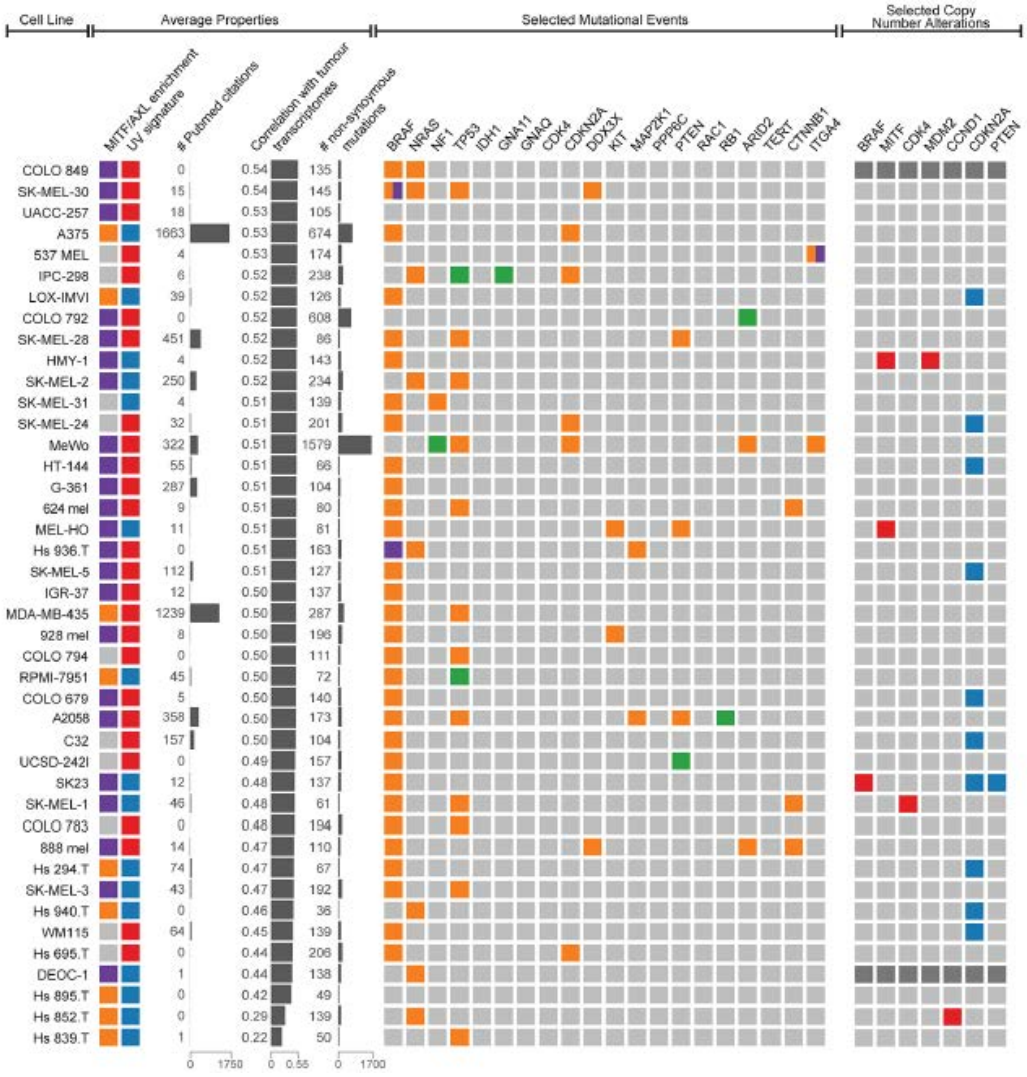
Detailed Analysis of Melanoma Cell Lines Over-Representation of BRAF and TP53 mutations – Decreased Representation of NF1

BRAF mutated in 30/42 (61%) cell lines [1, 2]
NRAS mutated in 8/42 (19%) cell lines [1]
NF1 mutated in 2/42 (5%) cell lines [1]
TP53 mutated in 13/42 (31%) cell lines [1]

BRAF mutated in 52% of patients [3]
NRAS mutated in 28% of patients [3]
NF1 mutated in 14% of patients [3]
TP53 mutated in 15% of patients [3]

– Cell line tumour models do not represent the full diversity of oncogenic drivers inherent in a cancer indication.

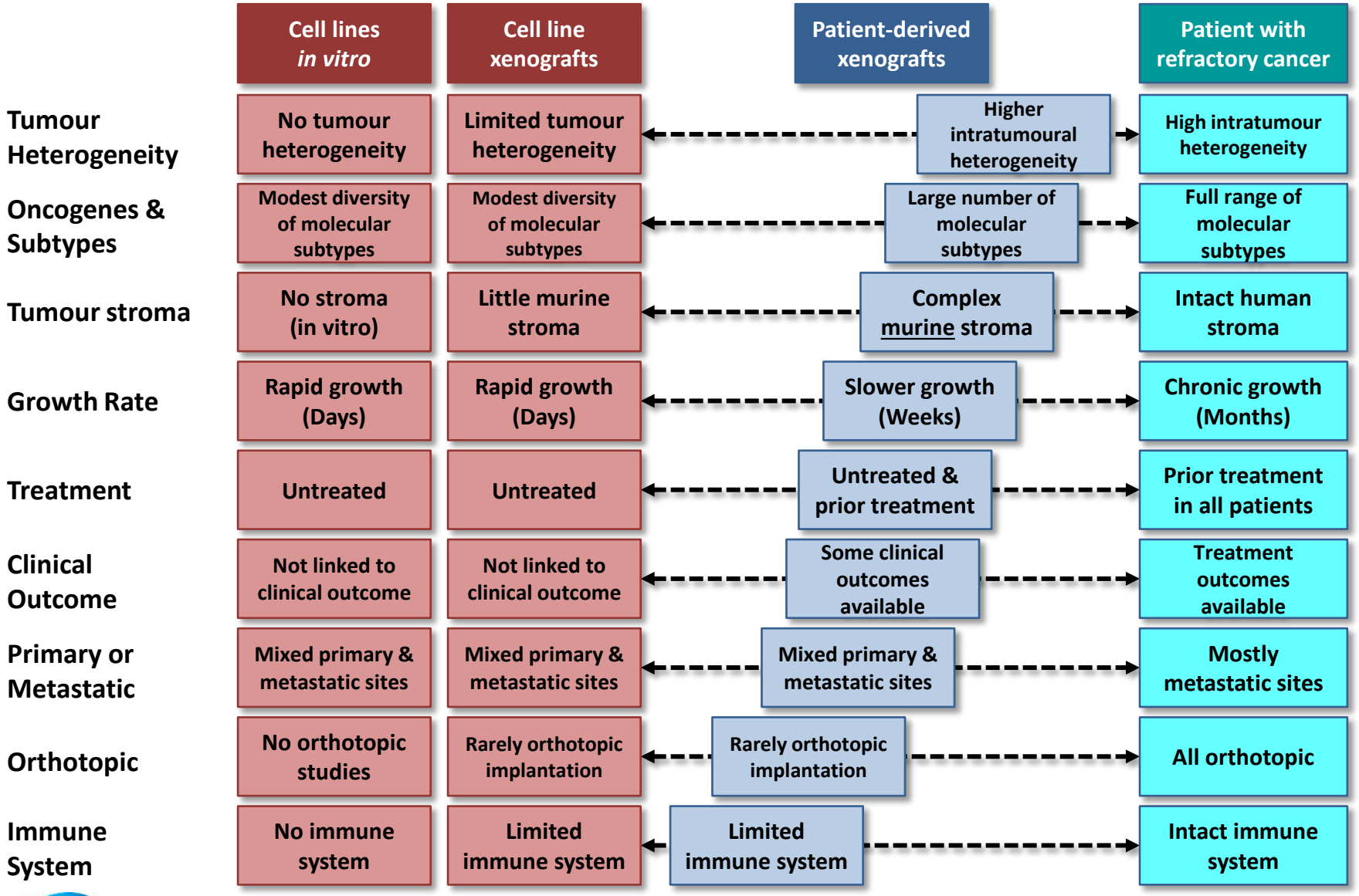
– Some oncogenic drivers may be over represented as a consequence of in vitro growth and selection.



[1] Vincent and Postovit, (2017) *Oncotarget* 8: 10498-10509
[2] Davies et al., (2002) *Nature* 417: 949-951.
[3] Cancer Genome Atlas Network. (2015) Cell 161: 1681-96

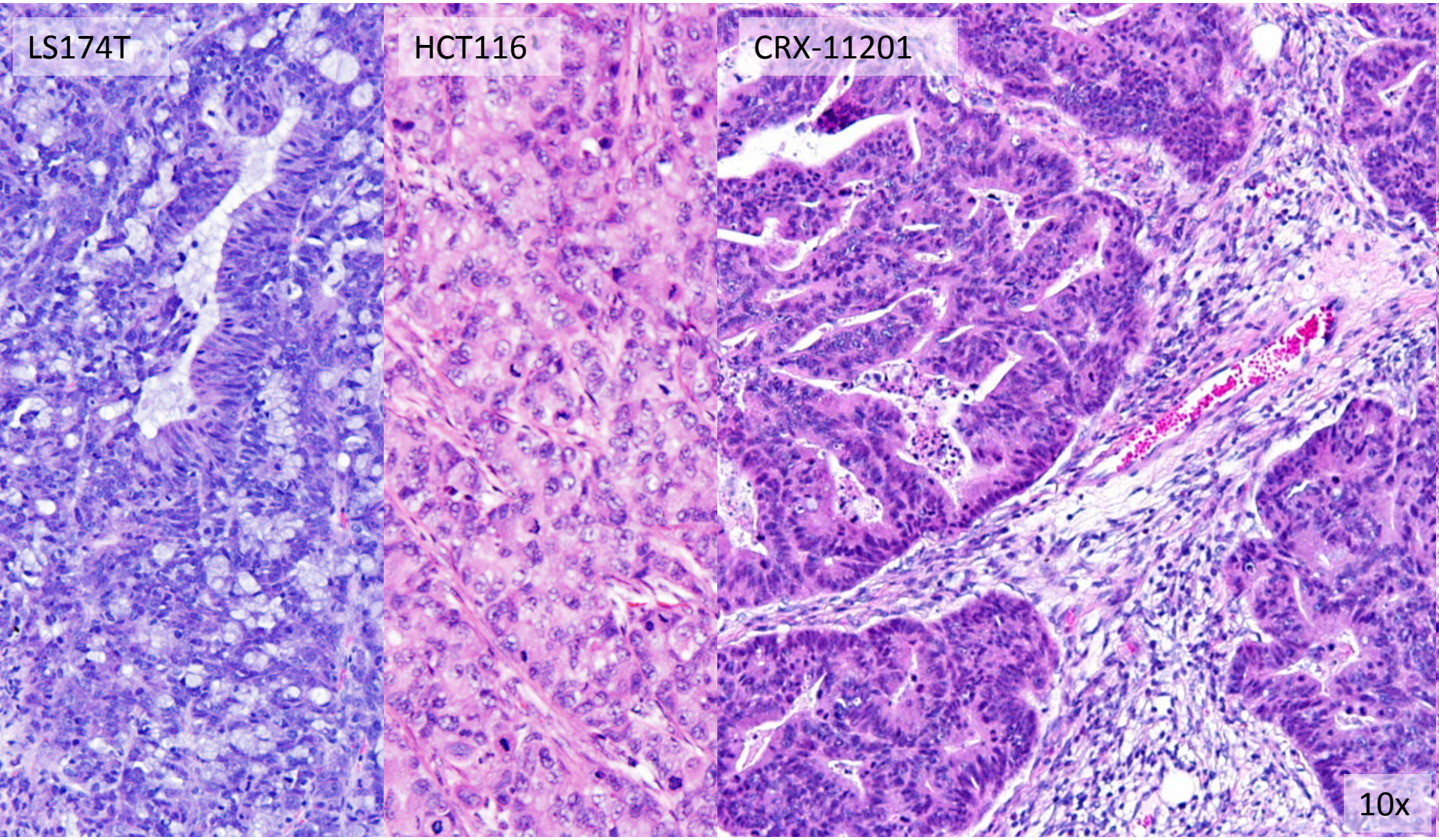
SCIENCE FOR LIFE-CHANGING IMPACT

Detailed comparison of CLX and PDX preclinical models

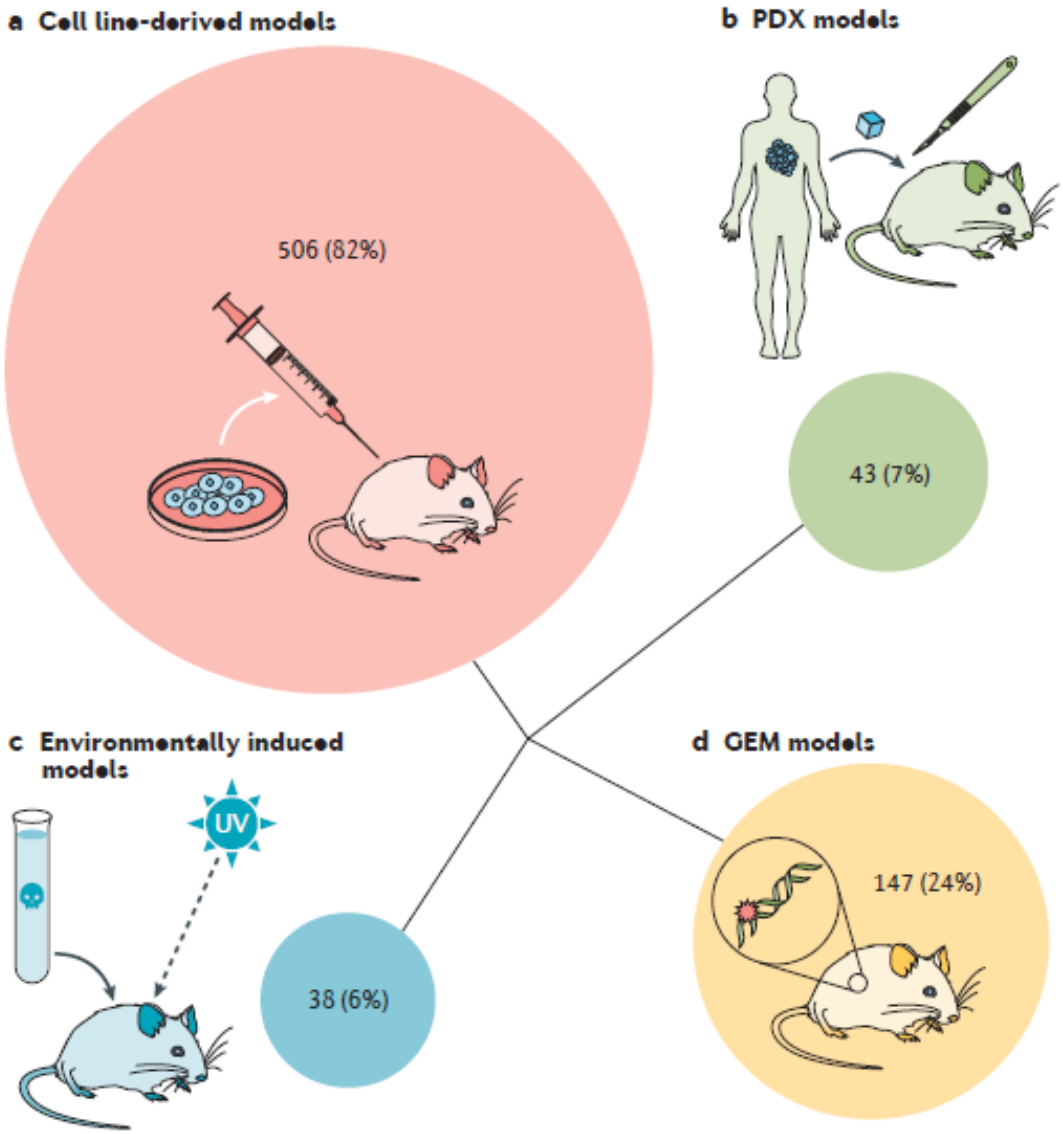


Adapted from Kopetz et al., (2012) *Clin. Cancer Res.* 18(19) 5160-62.

Primary Colon Xenografts Histology
Distinct From Cell Line Derived Tumours

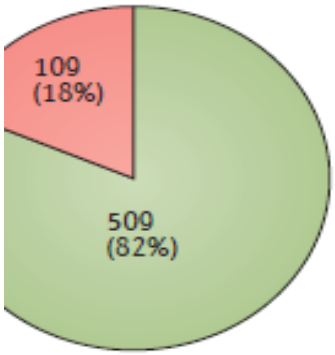


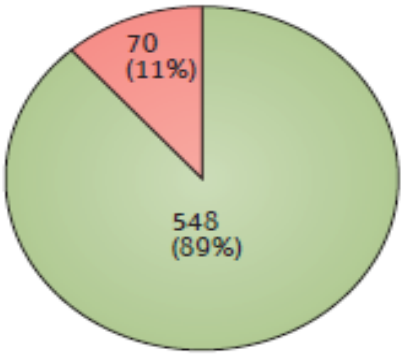
Frequency of the Use of Different Preclinical Models

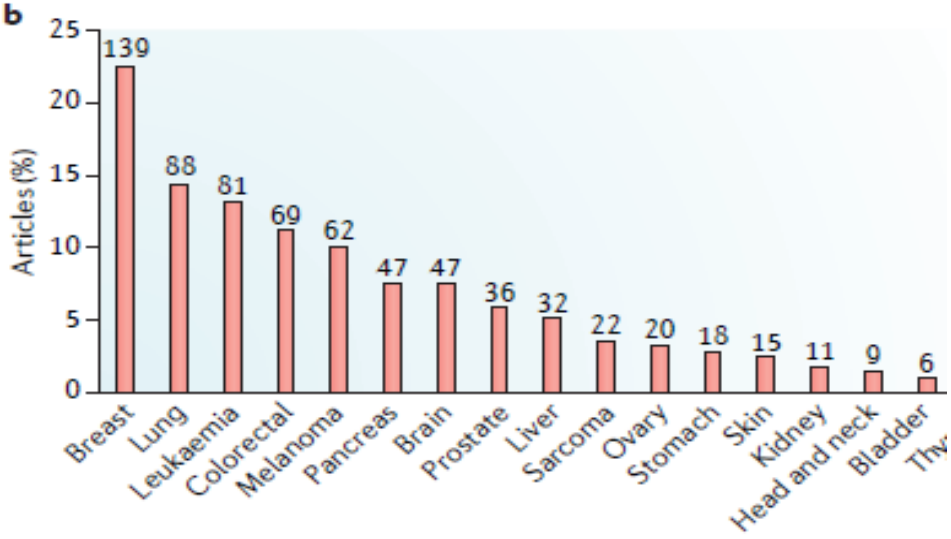


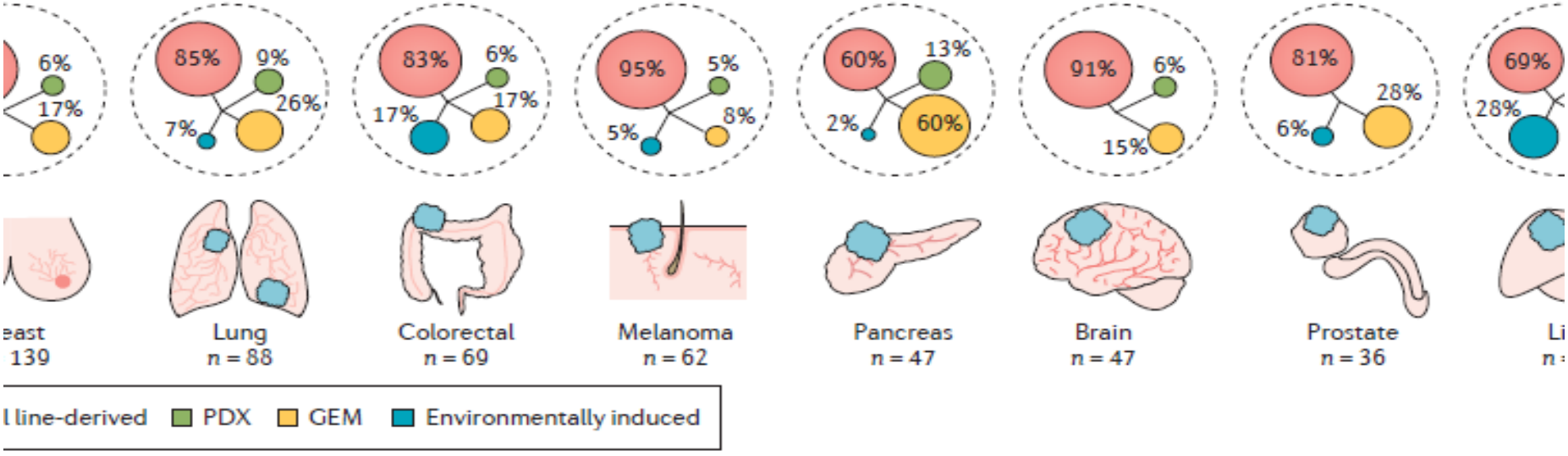
Gengenbacher N., Singhal M., and Augustin H.G. (2017) Nature Reviews Cancer 17:751-765

Types of Models Used For Eight Cancer Indications



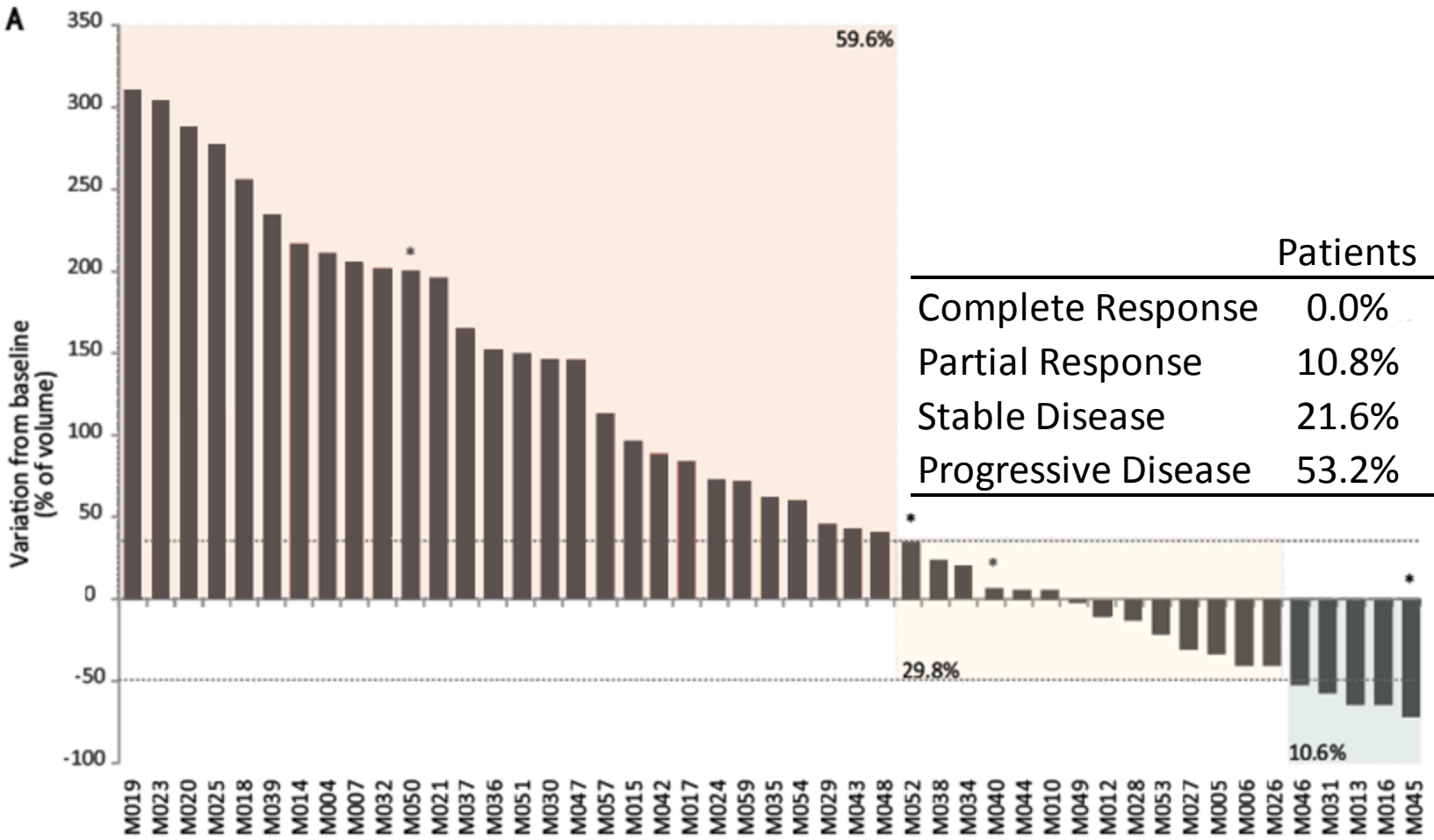






Gengenbacher N., Singhal M., and Augustin H.G. (2017) Nature Reviews Cancer 17:751-765

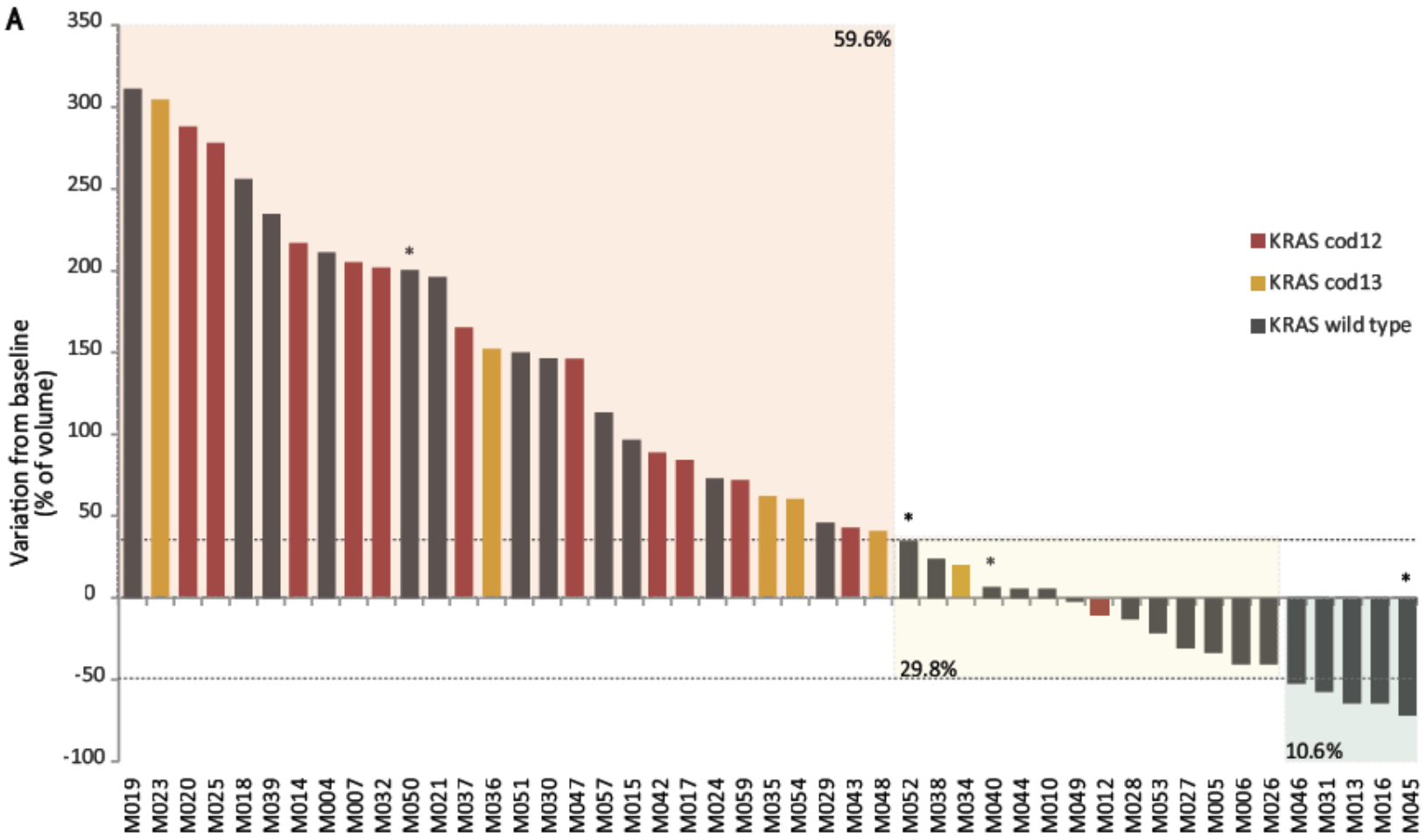
PDX Recapitulate Results Seen In Clinical Trials



	Patients	PDX
Complete Response	0.0%	0.0%
Partial Response	10.8%	10.6%
Stable Disease	21.6%	29.8%
Progressive Disease	53.2%	59.6%

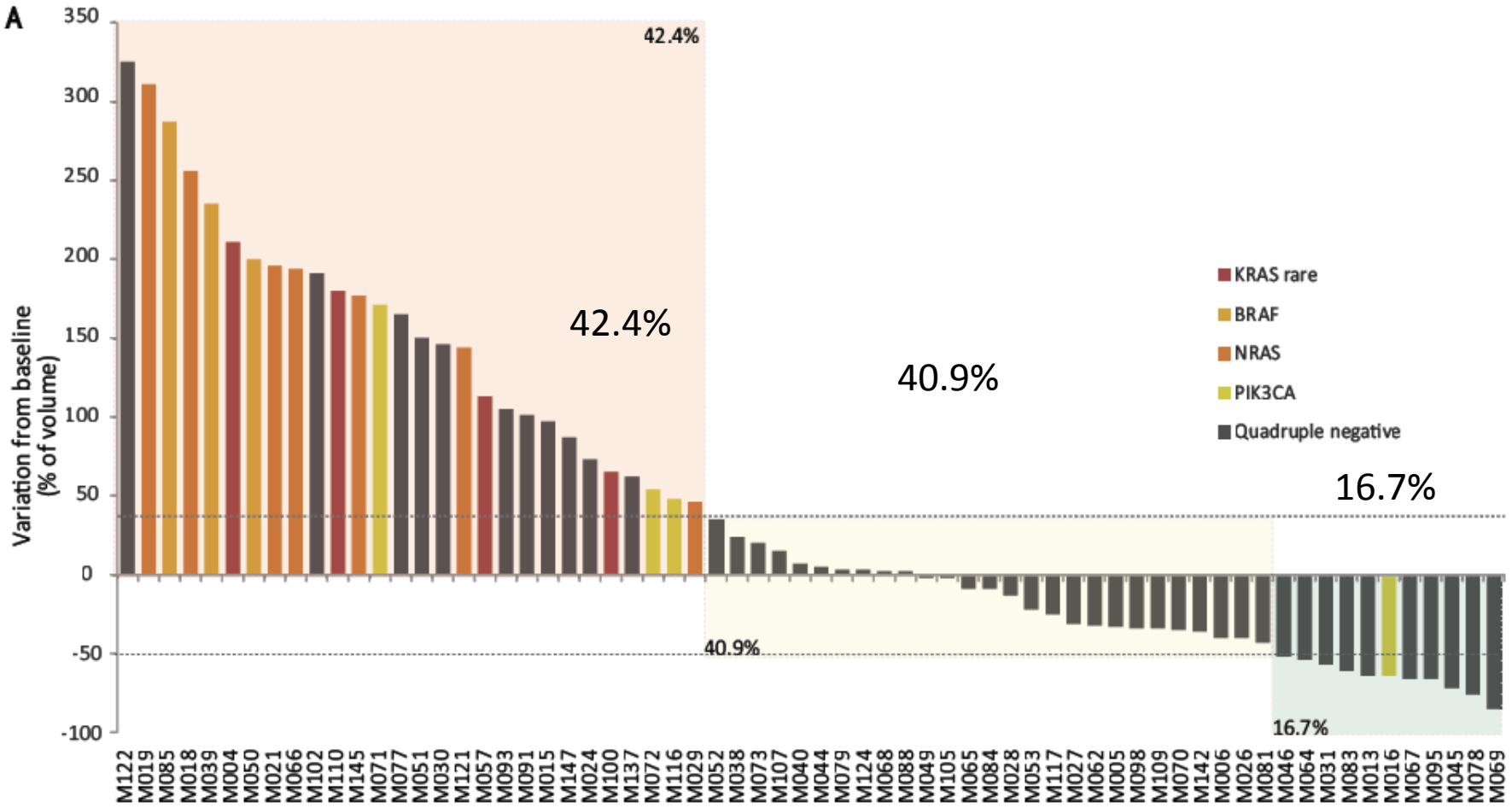
Modified from Bertotti et al., (2011) *Cancer Discovery 508-523.*

PDX Facilitate Biomarker Development – K-Ras



Modified from Bertotti et al., (2011) *Cancer Discovery 508-523.*

PDX Facilitate Biomarker Development – K-Ras



Modified from Bertotti et al., (2011) *Cancer Discovery 508-523.*

Results in PDX Similar to Clinical Trial Results

	n	Progressive Disease	Stable Disease	Partial Response	Complete Response	
PDX	**47**	**59.6%**	**29.8%**	**10.6%**	**0.0%**	**Bertotti et al., 2011**
Patients	**111**	**53.2%**	**21.6%**	**10.8%**	**0.0%**	**Cunningham et al., 2004**
K-Ras WT						
PDX	**66**	**42.4%**	**40.9%**	**16.7%**	**0.0%**	**Bertotti et al., 2011**
Patients	**119**	**36.0%**	**34.0%**	**17.0%**	**0.0%**	**Amado et al., 2008**

Similar clinical benefit for K-Ras WT observed in Karapetis et al., 2008

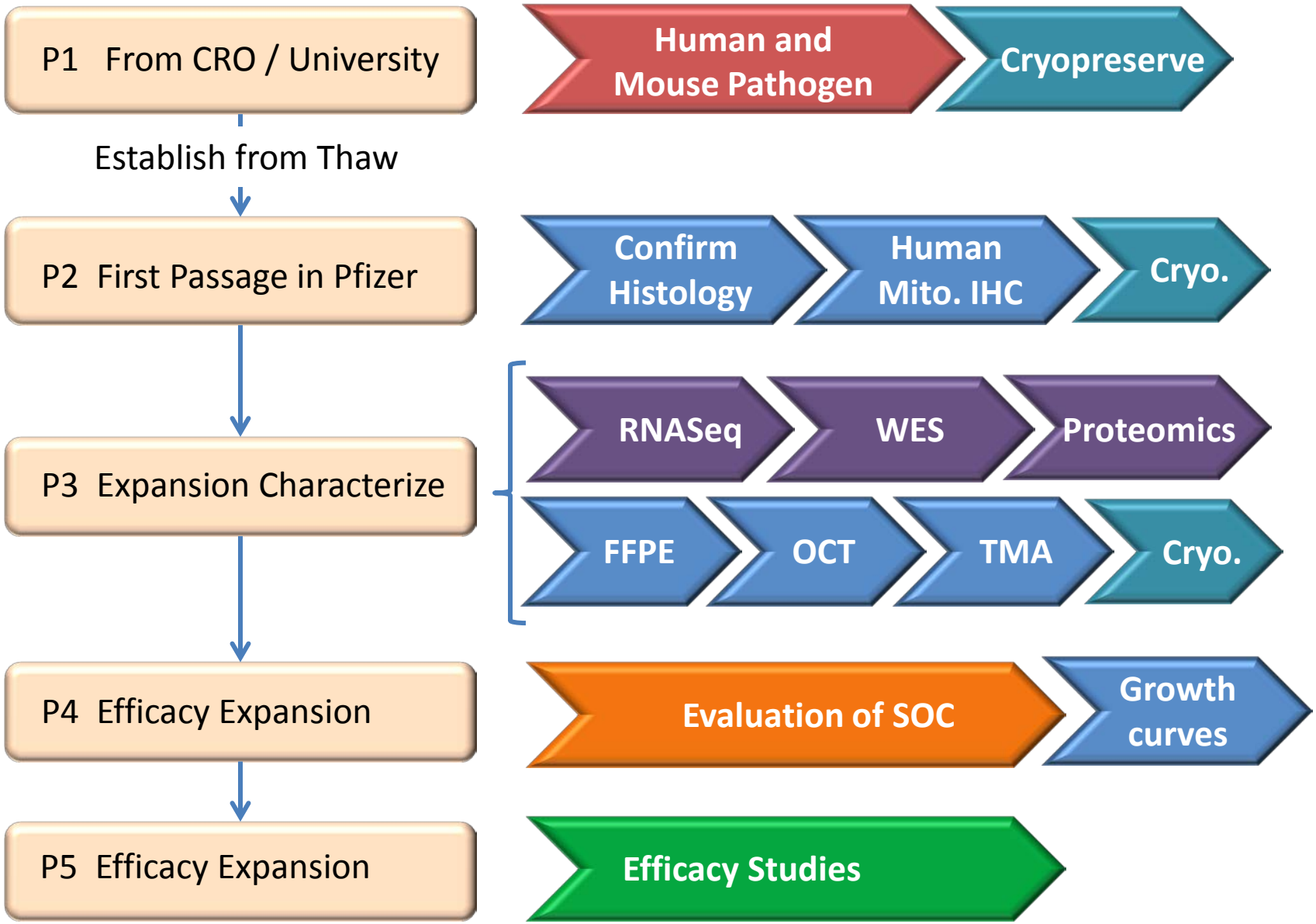
The response rate observed in Bertotti and the role of WT K-Ras was also observed in
R. Krumbach et al., 2011 Eur J. Cancer (30 mg/kg q7d x3)
S. Julien et al., 2012 Clin Cancer Res (40 mg/kg q4d x4)

Pfizer PDX Collection

Cancer Indication	U.S. Incidence	Not Treated	Pretreated / Refractory
Lung Cancer - NSCLC	194,190	60	51
Colorectal Cancer	134,490	50	52
Breast Cancer - TNBC	40,000	33	23
Pancreas	53,070	27	24
Ovarian	22,280	27	21
Lung Cancer - SCLC	34,000	31	25
Head & Neck	41,380	14	20
		242	216

- **Nearly all pretreated PDX received combination therapies or multiple single-agent therapies.**
- **A panel of treated PDX aids oncology target discovery in a treated patient population. Useful for developing combination therapies or second-line therapies.**

Pfizer PDX Workflow

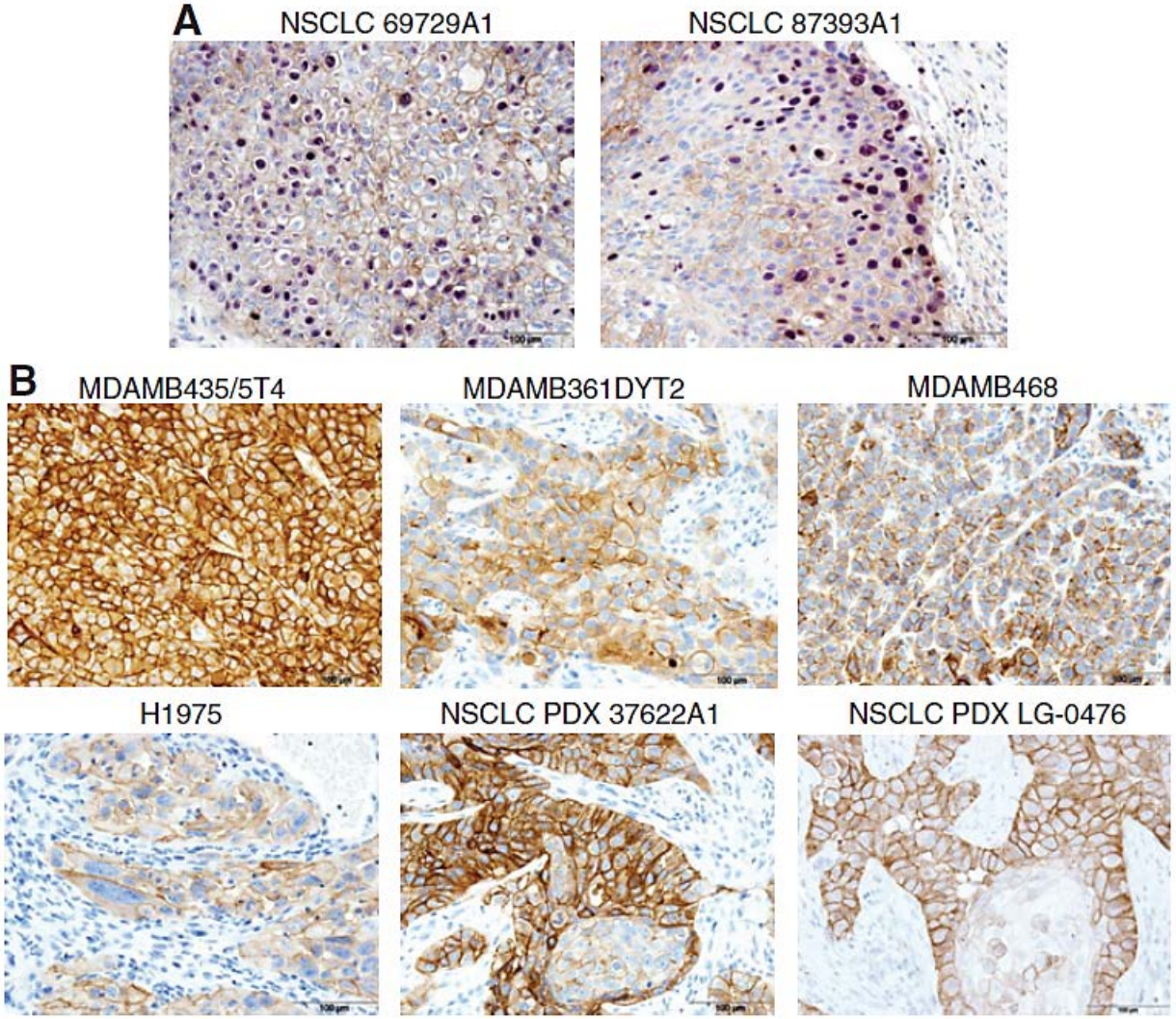


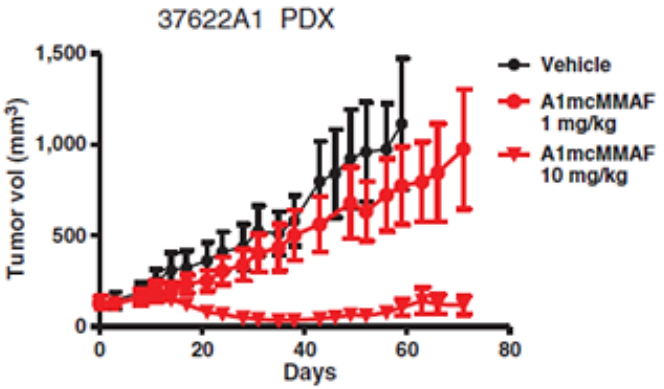
Case Study

5T4 ADC – PDX “All Comers” Trial

Histology agnostic omics to identify cancer indications

5T4 (TPBG) Expressed in Squamous NSCLC PDX

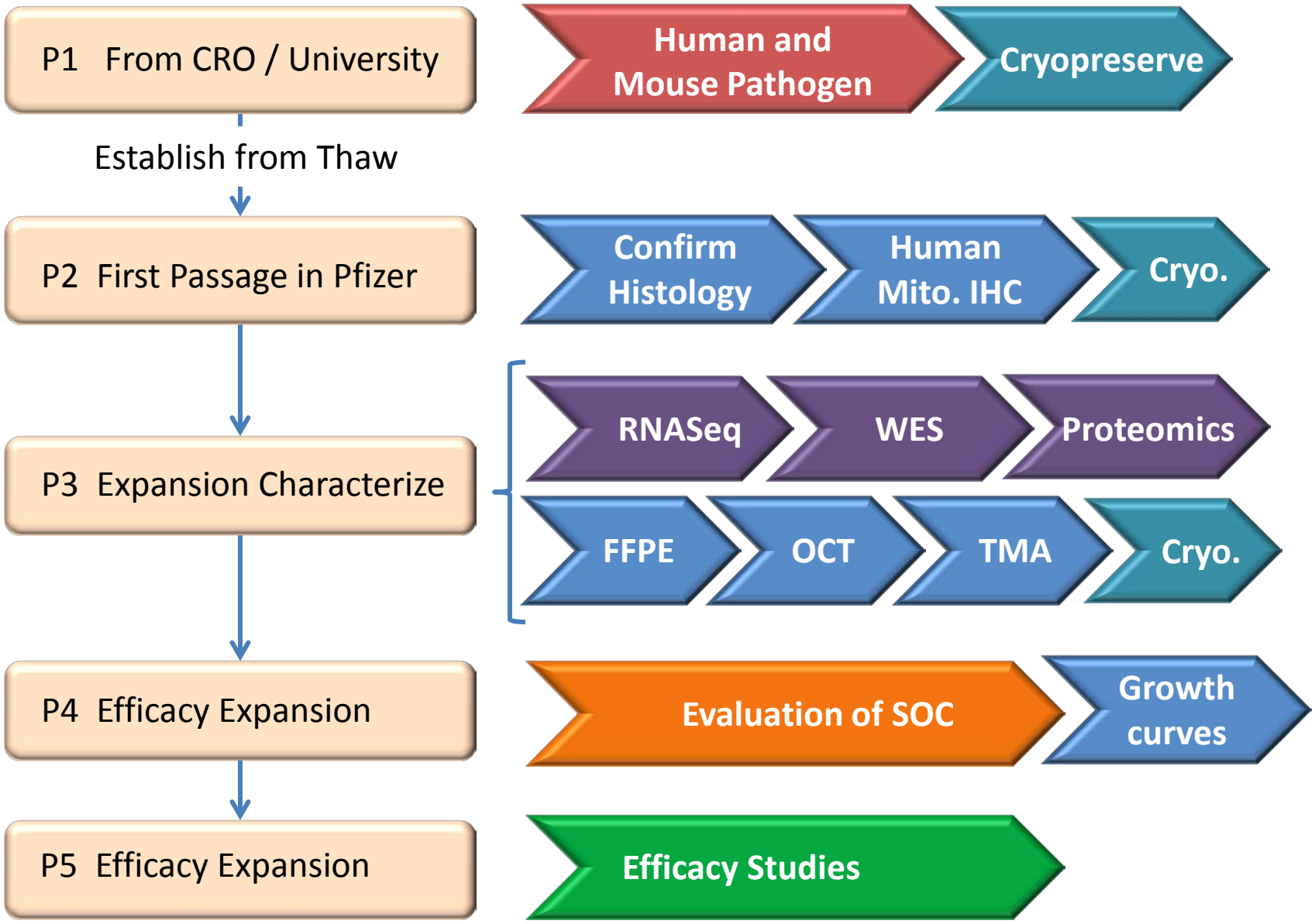




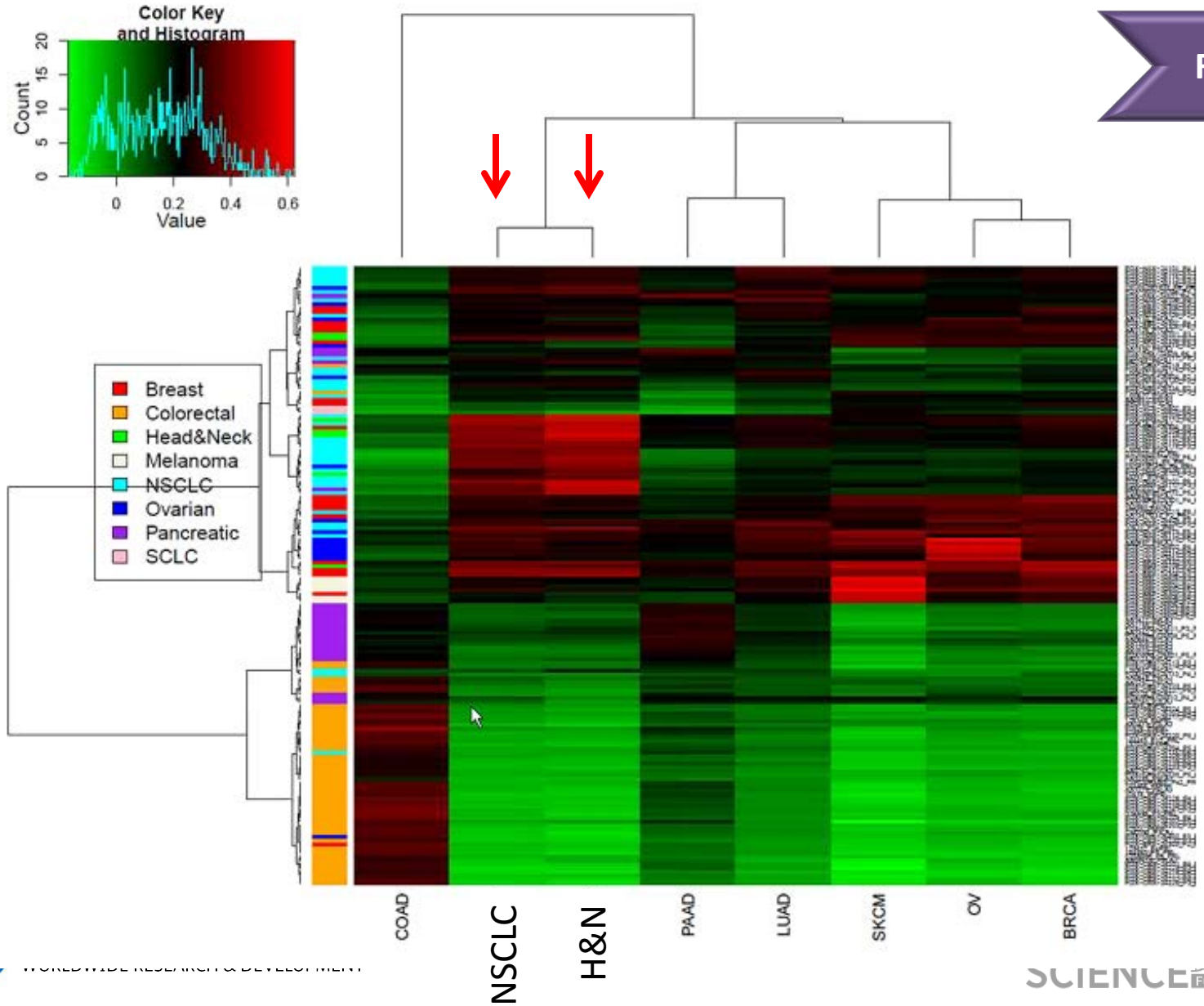
NSCLC PDX 37622
Responds to 5T4 ADC

Sapra *et al.*, (2013) *Mol. Cancer Ther.* 12: 38-47

Pfizer PDX Workflow

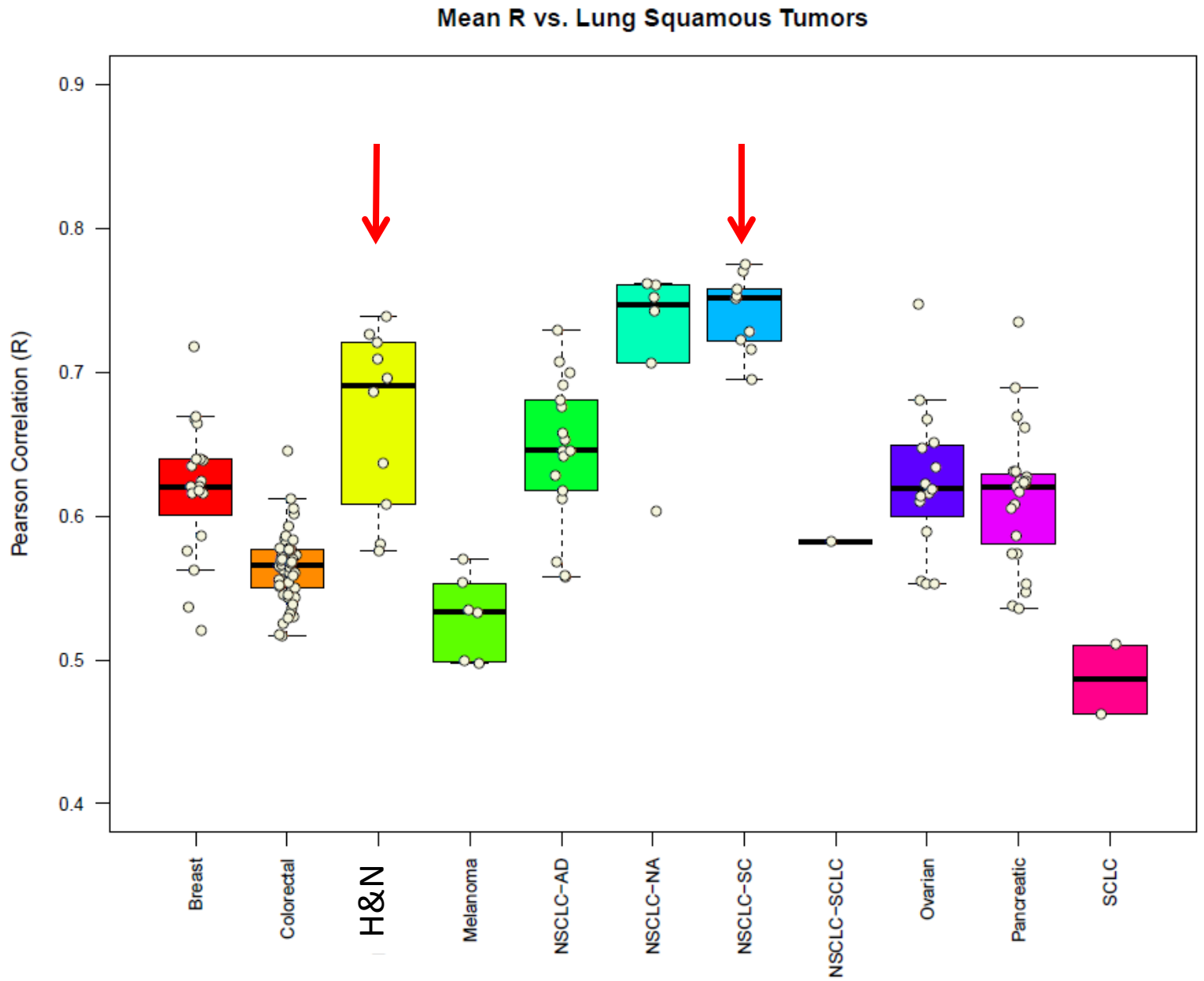


Molecular Profile of Squamous NSCLC Similar to Head & Neck

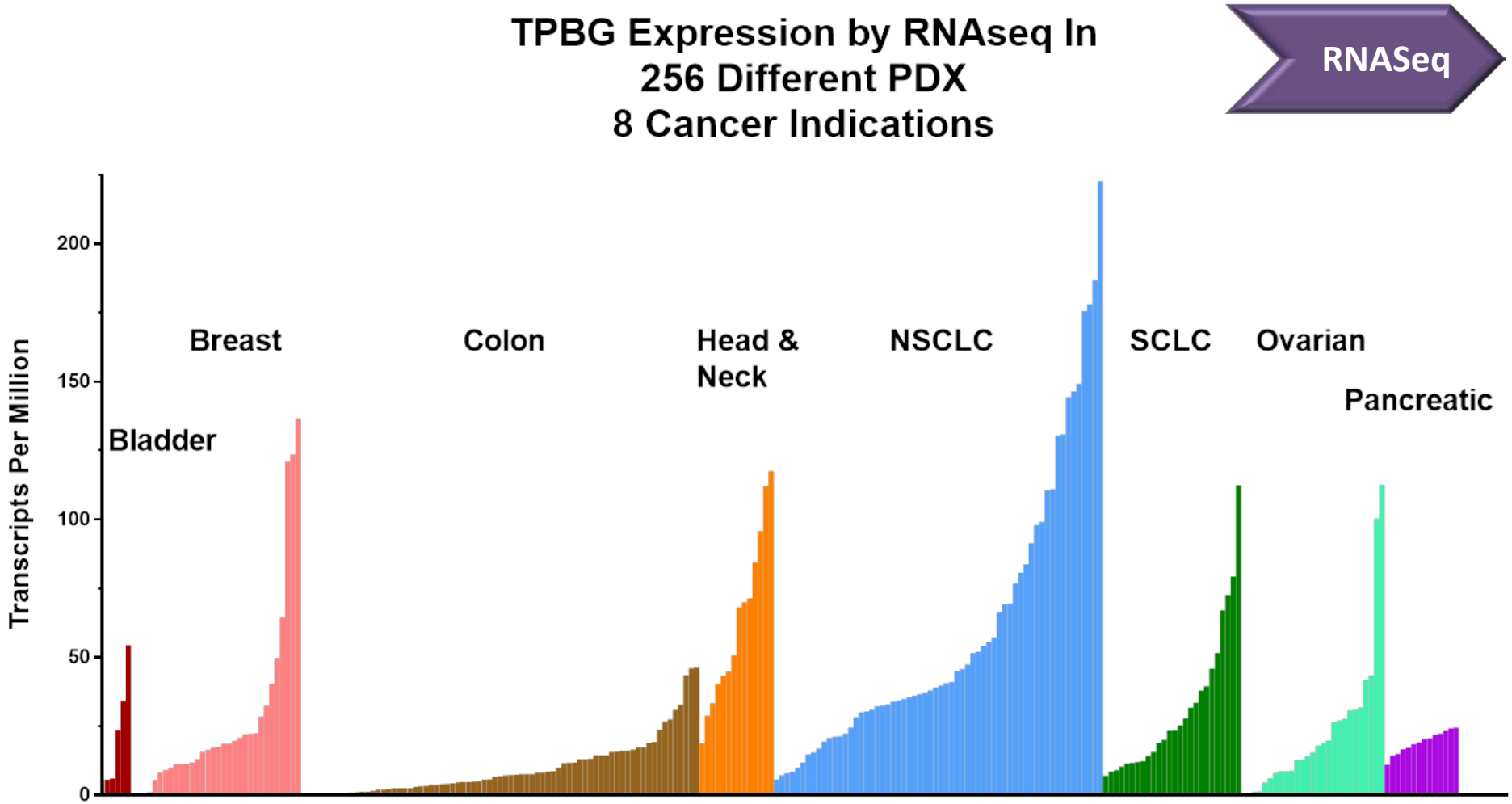


Genetic Correlation between squamous NSCLC and Head & Neck

Expression profile of 10,000 genes per PDX sample



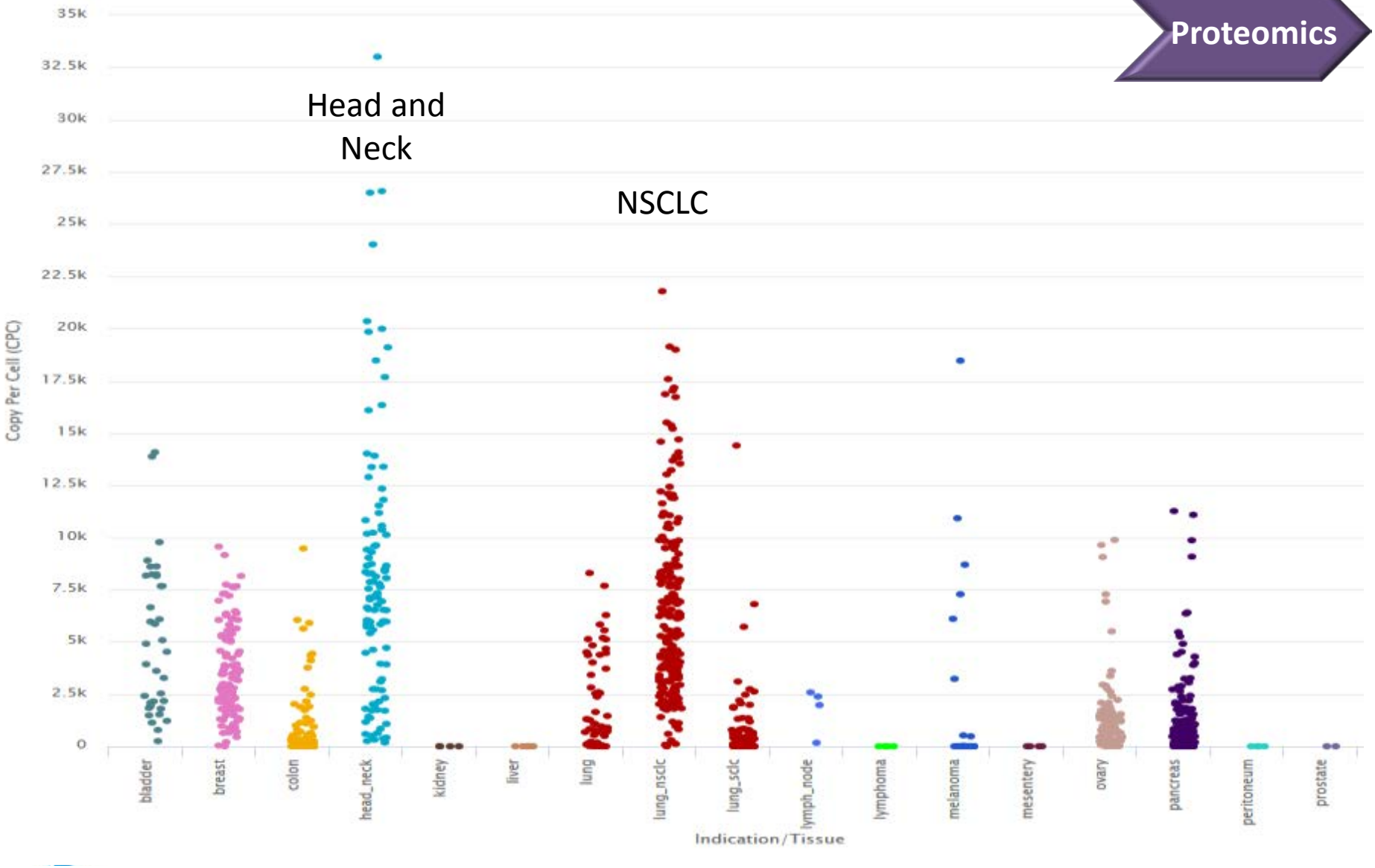
5T4 (TPBG) Expression by RNASeq in 256 Different PDX In Eight Cancer Indications



Modified from Rosfjord et al., (2015) AACR Annual Meeting. Abstract 1469

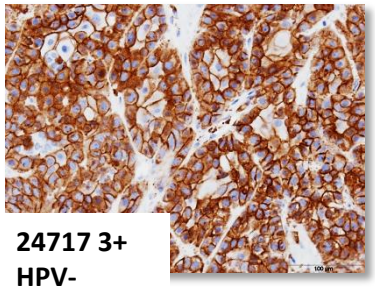
5T4 Expression Proteomics Evaluation In PDX
284 NSCLC samples and 102 H&N samples

Proteomics

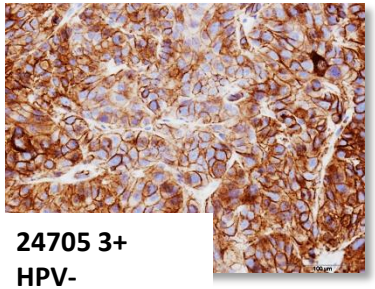


Modified from Rosfjord et al., (2015) AACR Annual Meeting. Abstract 1469

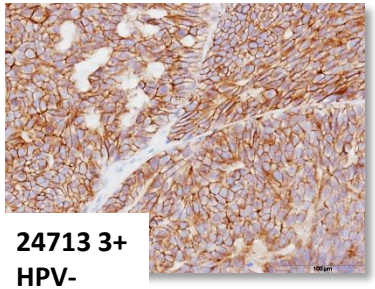
5T4 Protein IHC in Head & Neck PDX Models



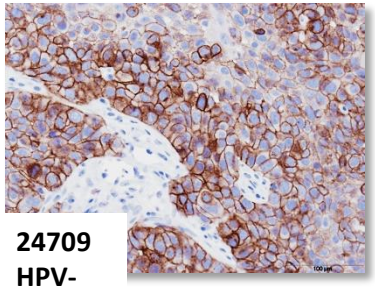
24717 3+
HPV-
Metastasis



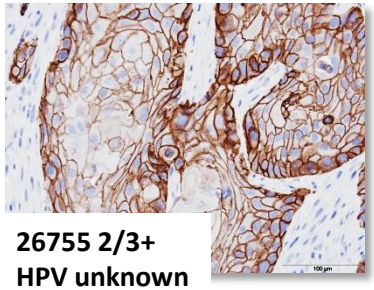
24705 3+
HPV-
Pyriform sinus



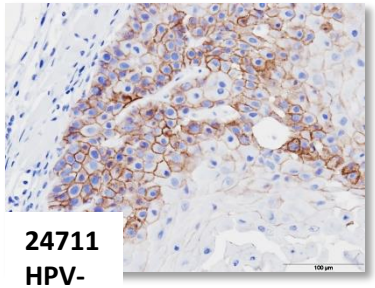
24713 3+
HPV-
Salivary



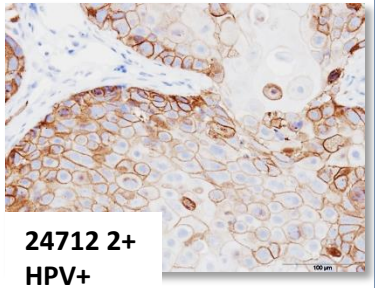
24709
HPV-
Tongue



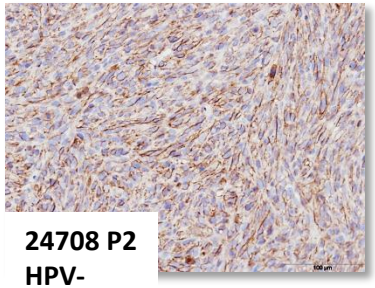
26755 2/3+
HPV unknown
Hard palate



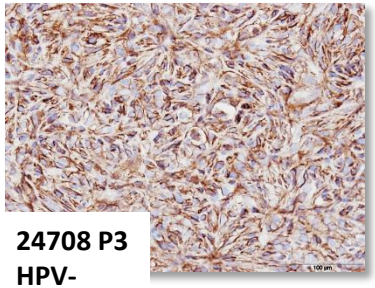
24711
HPV-
Buccal



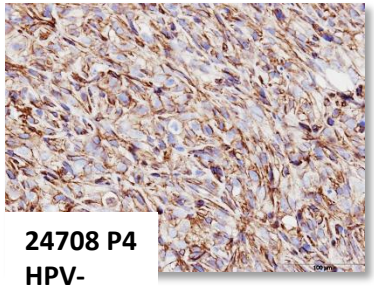
24712 2+
HPV+
Mandible



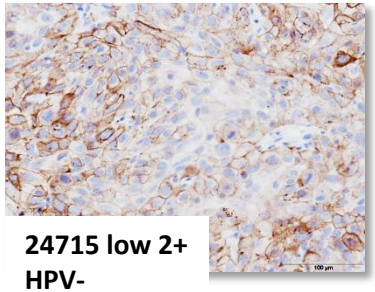
24708 P2
HPV-
Tonsil



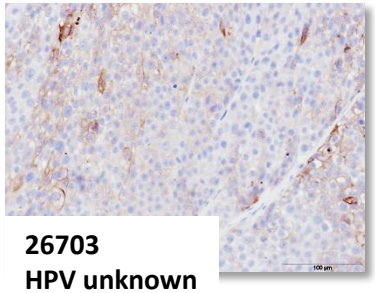
24708 P3
HPV-
Tonsil



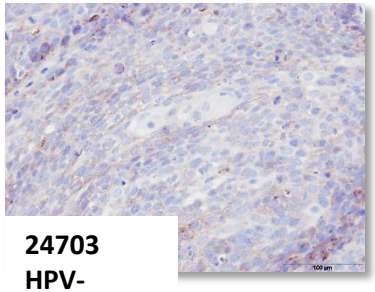
24708 P4
HPV-
Tonsil



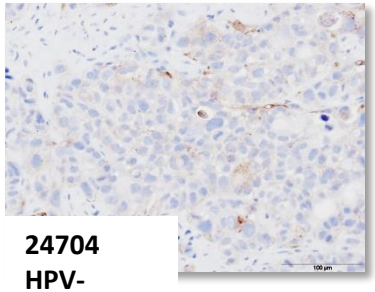
24715 low 2+
HPV-
Metastasis



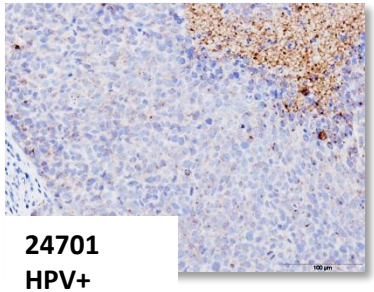
26703
HPV unknown
Metastasis



24703
HPV-
Metastasis

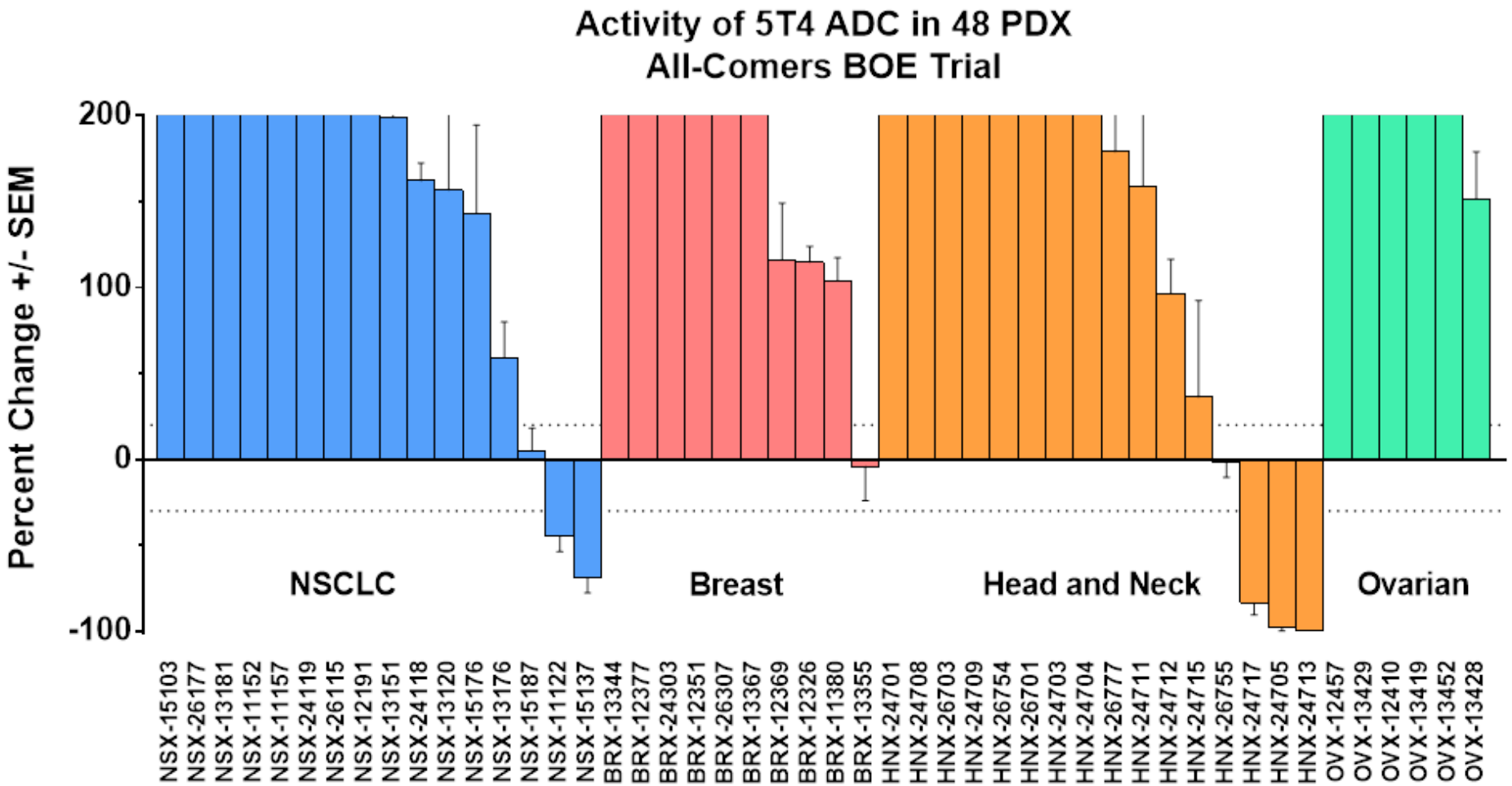


24704
HPV-
Metastasis



24701
HPV+
Metastasis

5T4-ADC Indication-agnostic Breadth of Activity Trial

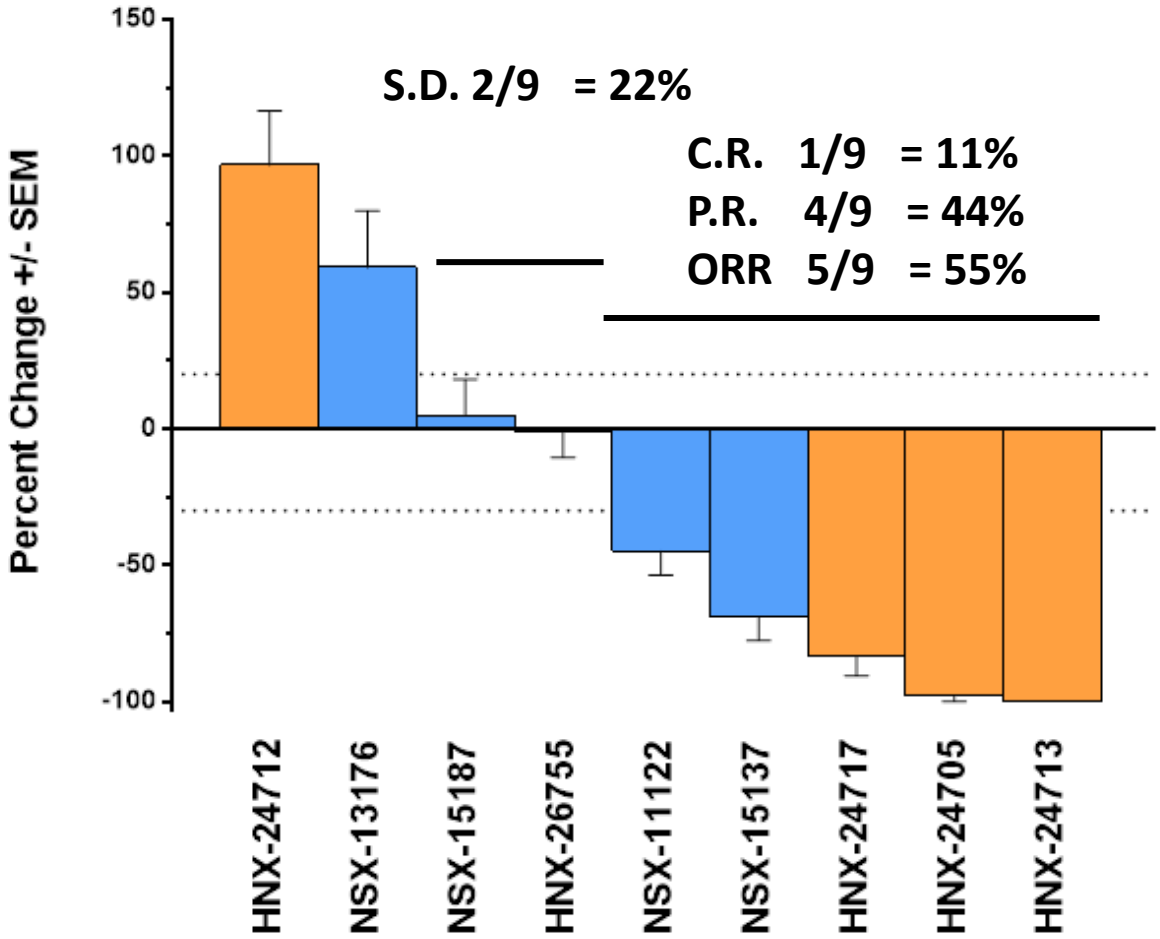


ORR 5 / 48 = 10%

Modified from Rosfjord et al., (2015) AACR Annual Meeting. Abstract 1469

Activity of 5T4 ADC in High Expressing PDX

RNASeq
+
Proteomics
+
5T4 IHC



9 PDX models with
2+ / 3+ expression of 5T4

Modified from Rosfjord et al., (2015) AACR Annual Meeting. Abstract 1469

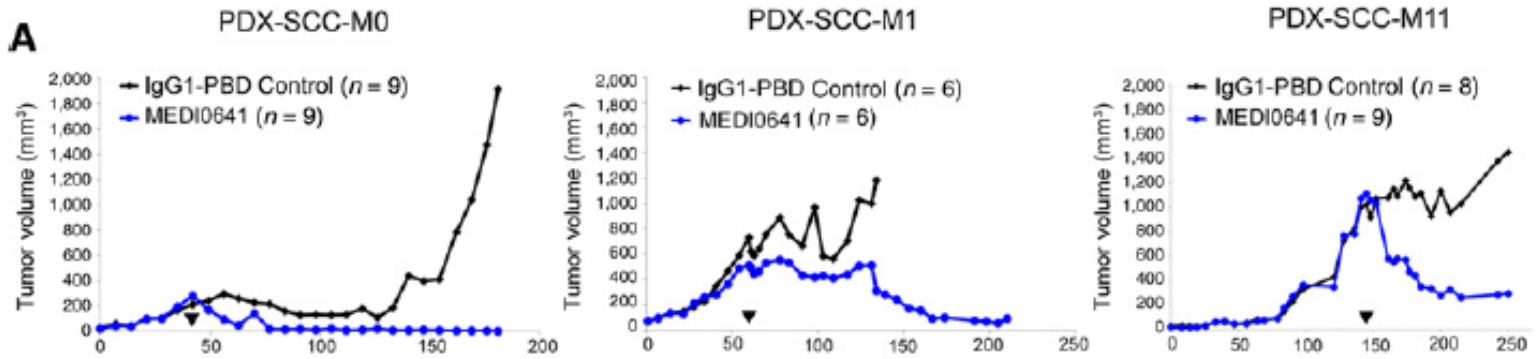
5T4 expression correlates with worse prognosis
MedImmune 5T4 ADC has efficacy in Head and Neck PDX

Cancer Therapy: Preclinical

Clinical Cancer Research

5T4-Targeted Therapy Ablates Cancer Stem Cells and Prevents Recurrence of Head and Neck Squamous Cell Carcinoma

Samuel A. Kerk[1], Kelsey A. Finkel[1], Alexander T. Pearson[1,2,3], Kristy A. Warner[1], Zhaocheng Zhang[1], Felipe Nör[1,4], Vivian P. Wagner[4,5], Pablo A. Vargas[6], Max S. Wicha[2,3], Elaine M. Hurt[7], Robert E. Hollingsworth[7], David A. Tice[7], and Jacques E. Nör[1,3,8,9]



- **MEDI0641 (MedImmune) is a PBD conjugated ADC to 5T4.**
- **Treatment of head and neck PDX that express 5T4 with MEDI0641 resulted in durable tumour regression.**

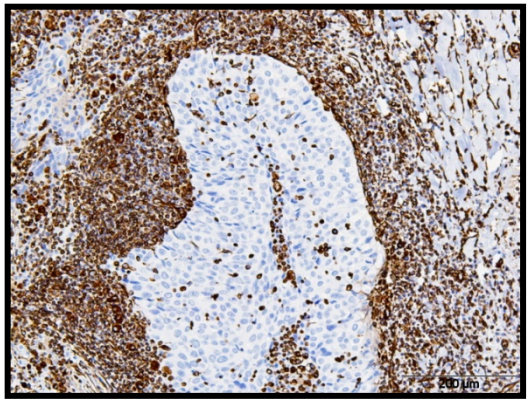
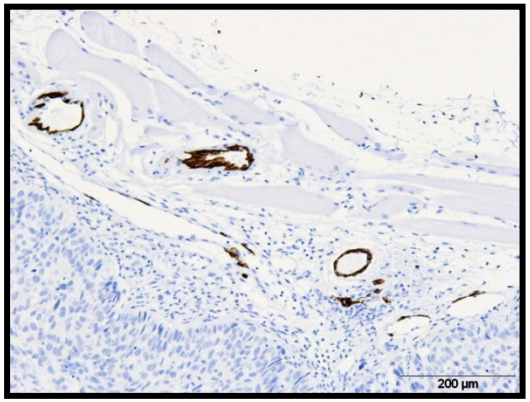
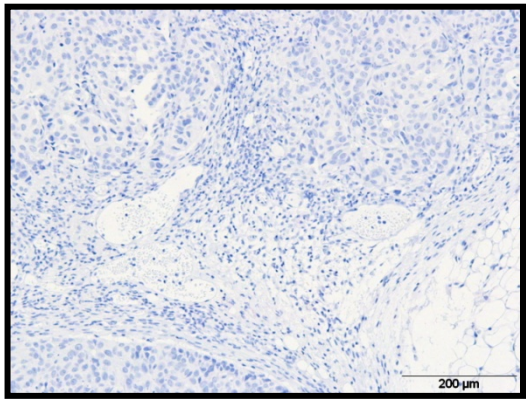
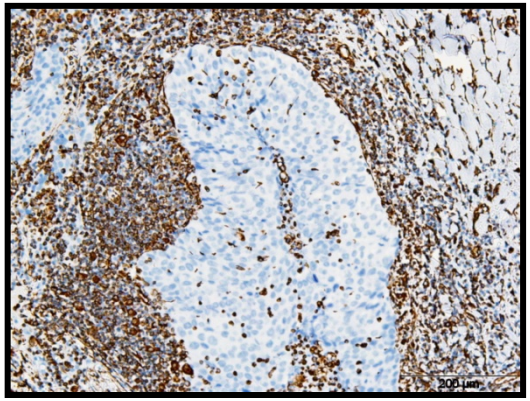
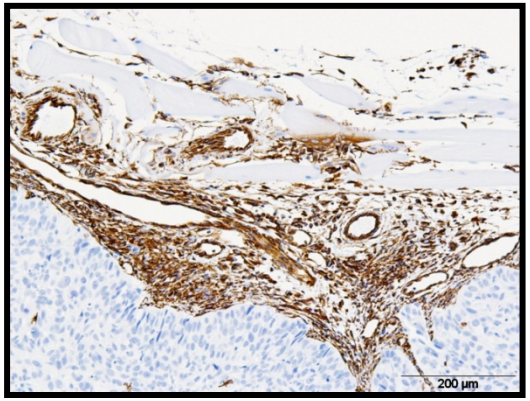
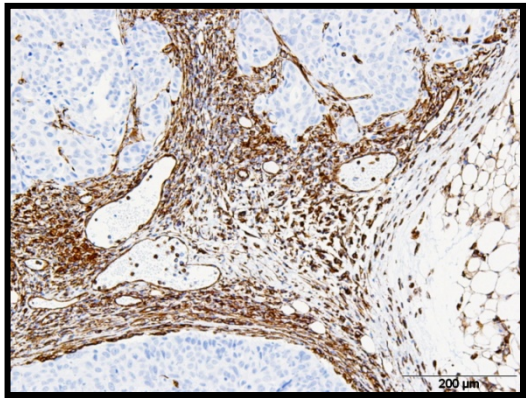
Kerk *et al.*, (2017) *Clin Cancer Research* 23: 2516-27

Summary

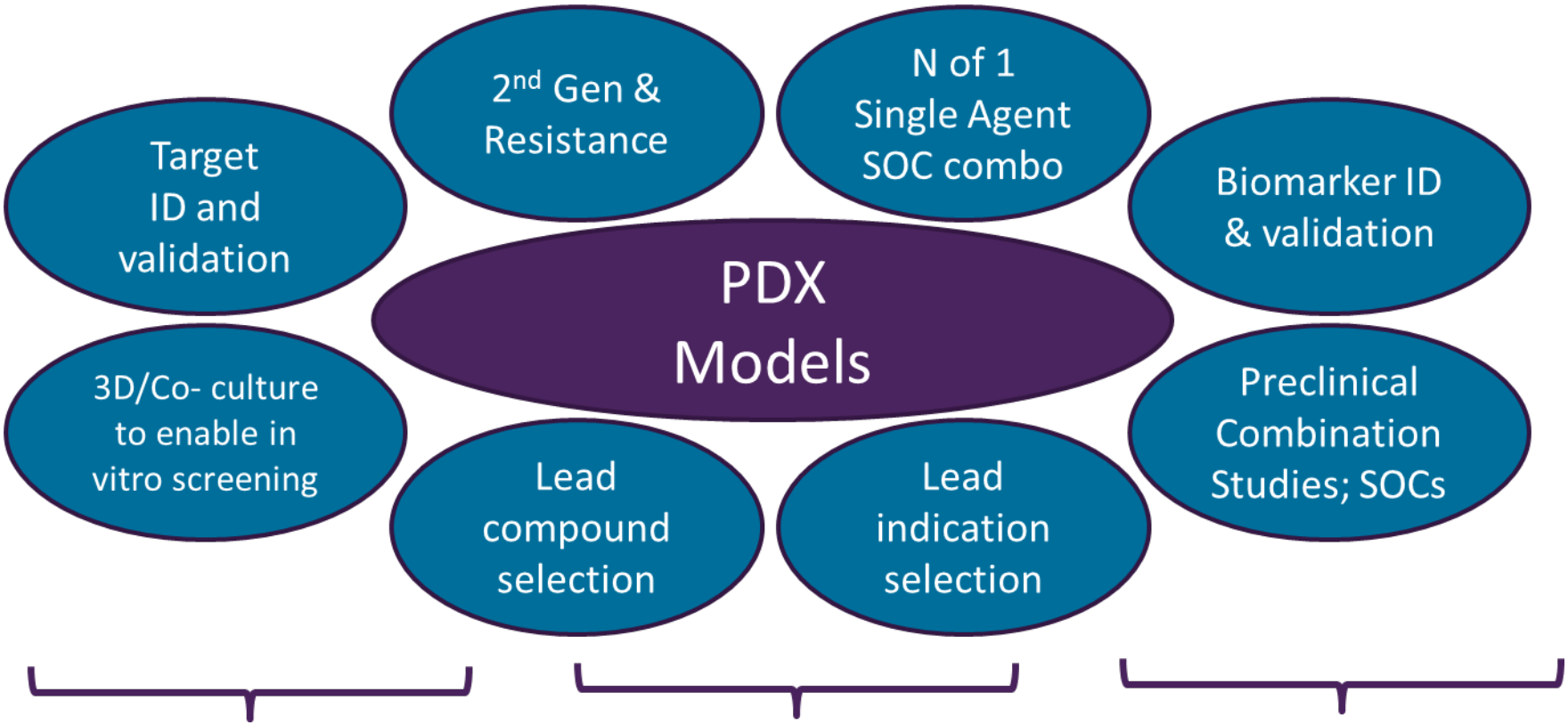
- PDX models can provide a diversity of preclinical models with a broad range of molecular drivers.
- Molecular analysis of PDX models may identify cancer indications that could benefit from targeted treatments.
- A panel of PDX models enables preclinical proof-of-concept studies that could be used histology agnostic patient selection strategies in the clinic.

Additional Slides

PDX Stroma Derived From Mouse

	NSX-11157 Patient Sample	NSX-11157 NSCLC PDX P0	NSX-11157 NSCLC PDX P1
Human Specific Vimentin			
Human/mouse Vimentin			

Utility of a PDX Collection in Oncology R&D



***Rosfjord, Lucas, Li, & Gerber (2014) Biochem Pharm*, 91:135-143**

Use of PDX Throughout Cancer Drug Discovery