Genomics-Driven Precision Oncology in Rare Cancers

Lessons From DKTK MASTER

Daniela Richter, NCT Heidelberg

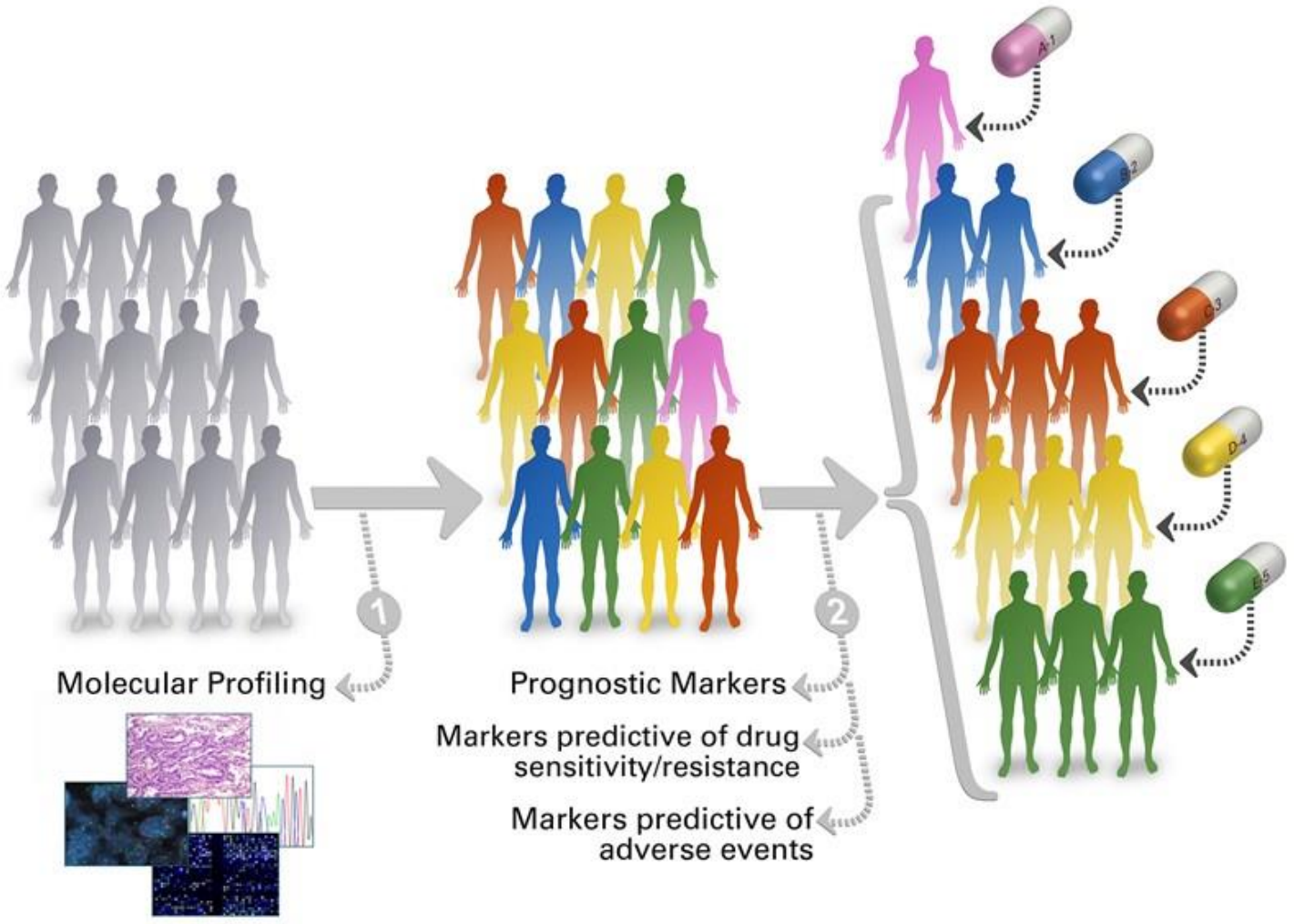
TMF Workshop | Omics in Medical Research

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION
Research for a Life without Cancer

UniversitätsKlinikum Heidelberg

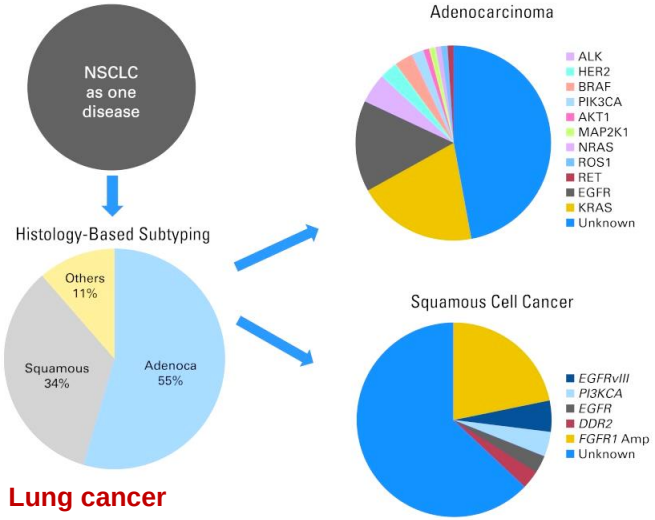
NCT NATIONAL CENTER FOR TUMOR DISEASES HEIDELBERG

Precision Oncology



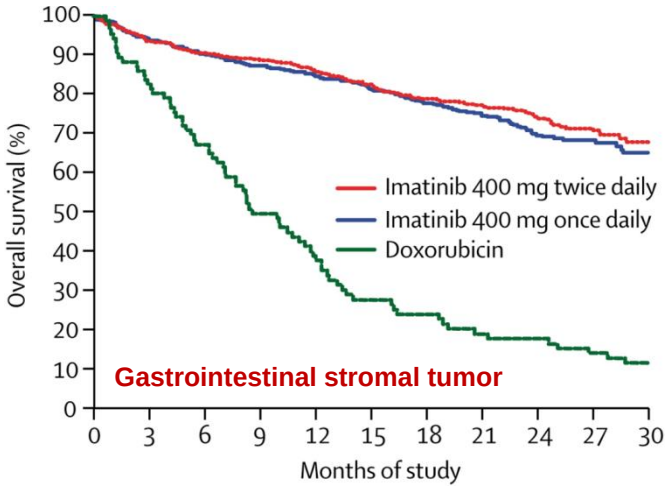
MD Anderson Cancer Center
Institute for Personalized Cancer Therapy
https://pct.mdanderson.org

Clinical Impact of Cancer Genomics



Common cancers as multiple rare diseases of the same organ, demanding unique therapies

Li et al. J Clin Oncol 2013



Improved clinical outcome through genotype-directed therapy

Verwej et al. Lancet 2004

Distinct mutations shared across multiple cancers

$BRAF^{V600E/K}$ in melanoma; thyroid, lung, colorectal, ovarian, gastric, esophageal, head and neck cancer; gastrointestinal stromal tumor; glioma; hairy-cell leukemia; multiple myeloma; etc.

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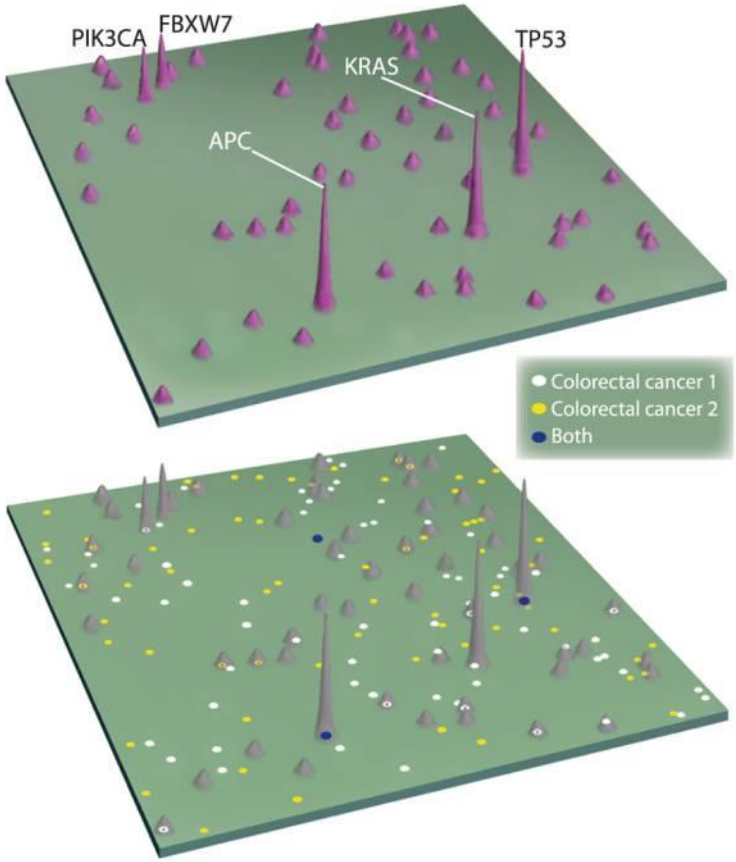
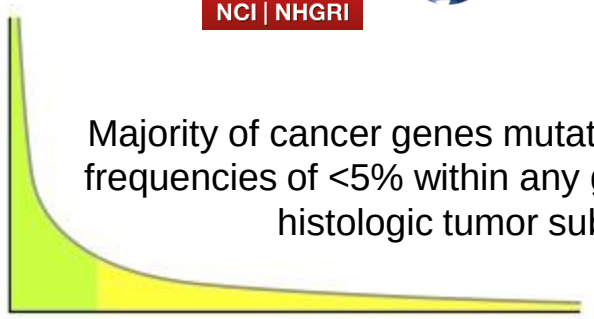
Genomic Landscape of Cancer



Gene “mountains” and “hills”
Wood et al. Science 2007

TCGA
NCI | NHGRI
ICGC



Majority of cancer genes mutated at frequencies of <5% within any given histologic tumor subtype

“Long tail” pattern of actionable cancer gene alterations
TCGA Pan-Cancer Analysis
Lawrence et al. Nature 2013

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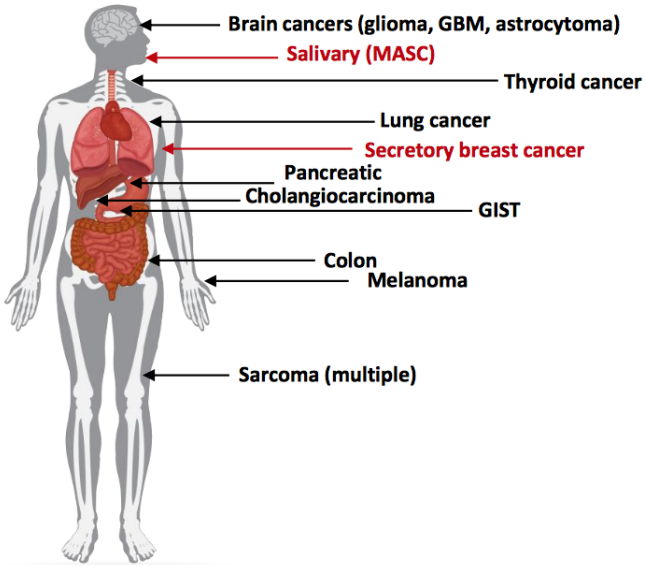
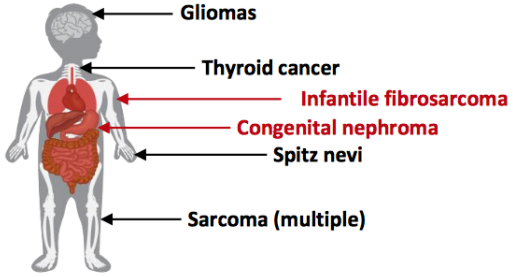
Rare Driver Mutations | NTRK Fusions

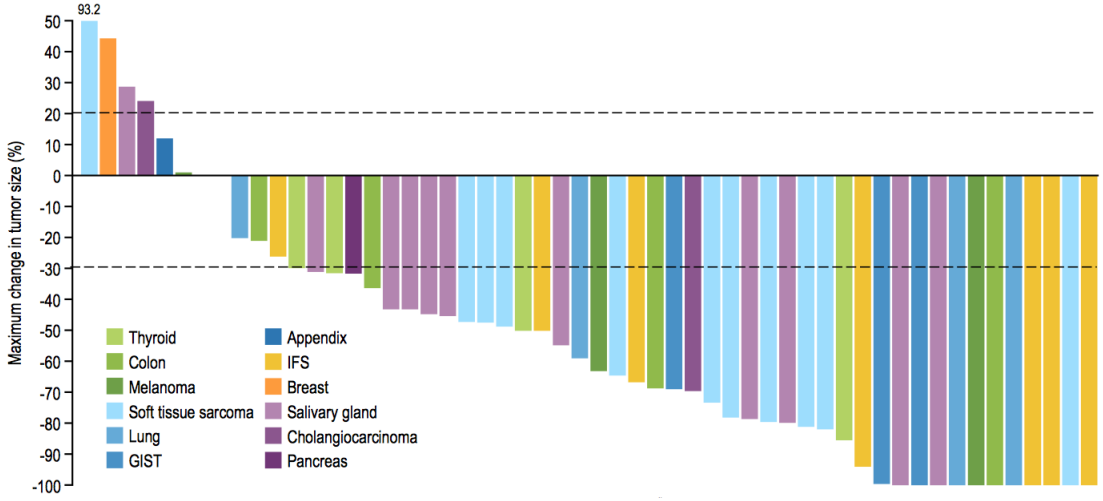


■ Common cancer with low TRK fusion frequency

■ Rare cancer with high TRK fusion frequency



- Estimated 1,500-5,000 NTRK fusion-positive cancers in the US annually
- Constitutively active receptor tyrosine kinases
- Small-molecule inhibitors
  - Larotrectinib
  - Entrectinib



- Pooled analysis of 3 larotrectinib basket trials
- 55 NTRK fusion-positive patients (pediatric, adult)
- Overall response rate, 76%
  - Complete, 12%
  - Partial, 64%
- Efficacy across age groups and histologies
- Median response duration not reached (median follow-up, 5.8 months)

Hyman et al. ASCO Annual Meeting 2017

Complex Biomarkers | Benefit from Immunotherapy

Overall mutational load and neoantigen burden

Snyder et al. N Engl J Med 2014, Van Allen et al. Science 2015, Rizvi et al. Science 2015, Le et al. N Engl J Med 2015

Neoantigen intratumoral heterogeneity

McGranahan et al. Science 2016

Immunogenic insertion/deletion mutations

Turajlic et al. Lancet Oncol 2017

PDL1 amplification and/or overexpression

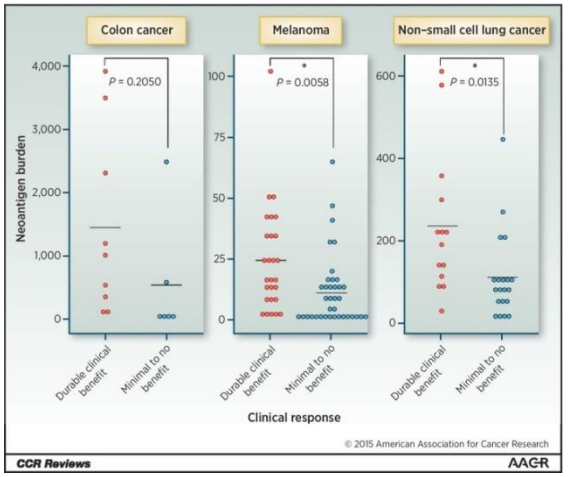
Ansell et al. N Engl J Med 2015

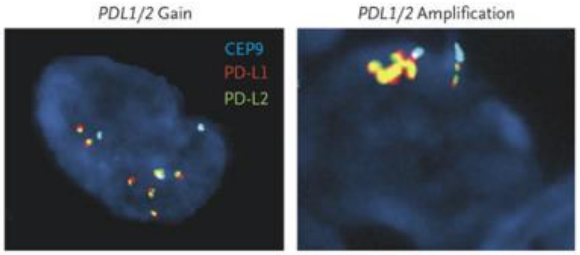
Structural rearrangements of *PDL1/2* and *CIITA*

Steidl et al. Nature 2011, Chong et al. Blood 2016

Disruption of *PDL1* 3' untranslated region

Kataoka et al. Nature 2016





Innate and acquired resistance to PD1 blockade due to inactivating mutations in JAK family members and B2M

Zaretsky et al. N Engl J Med 2016, Shin et al. Cancer Discov 2016, Marabelle et al. Cancer Discov 2017

Association of MDM2/4 amplification with hyperprogression after PD1/PDL1 blockade

Kato et al. Clin Cancer Res 2017, Champiat et al. Clin Cancer Res 2017, Forschner et al. Clin Cancer Res 2017 (DKTK MASTER Program)

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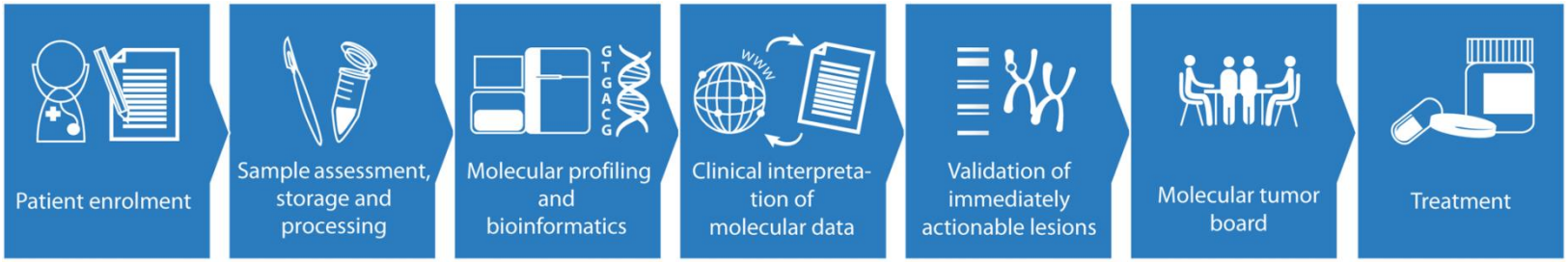
Molecularly Aided Stratification for Tumor Eradication Research



Biopsy, shipping, frozen section, DNA/RNA isolation, QC

Variable

DNA/RNA sequencing, data processing and annotation

15-18 days

Validation, clinical interpretation, treatment recommendation

Variable

- Young adults with advanced-stage cancer
- Patients with rare tumors
- ~100 external partners, including all DKTK sites

Start: 06/2013
Fast-track exome and RNA sequencing

Since 10/2016:
Genome sequencing (60-80x) and RNA sequencing

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Genomics-Driven Oncology Within DKTK

DKTK German Cancer Consortium

Joint DKTK activity since March 2016

Institutional Review Board approval
8 Partner Sites (11 Comprehensive Cancer Centers)

Internet-based clinical data repository
8 Partner Sites (11 Comprehensive Cancer Centers)

Access to sequencing data
8 Partner Sites (11 Comprehensive Cancer Centers)

DKTK MASTER Molecular Tumor Board
Weekly videoconference

DKTK MASTER Scientific Board
Monthly videoconference

Joint publications
Forschner et al. Clin Cancer Res 2017
Ugurel et al. Eur J Cancer 2017
Czink et al. Cold Spring Harb Mol Case Stud 2017
Dieter, Heining et al. Ann Oncol 2017
Chudasama et al. Clin Cancer Res 2017
Gröschel, Bommer et al. Cold Spring Harb Mol Case Stud 2016
Bochtler et al. Cold Spring Harb Mol Case Stud 2016
Czink et al. Z Gastroenterol 2016
Kordes, Röring, Heining et al. Leukemia 2016

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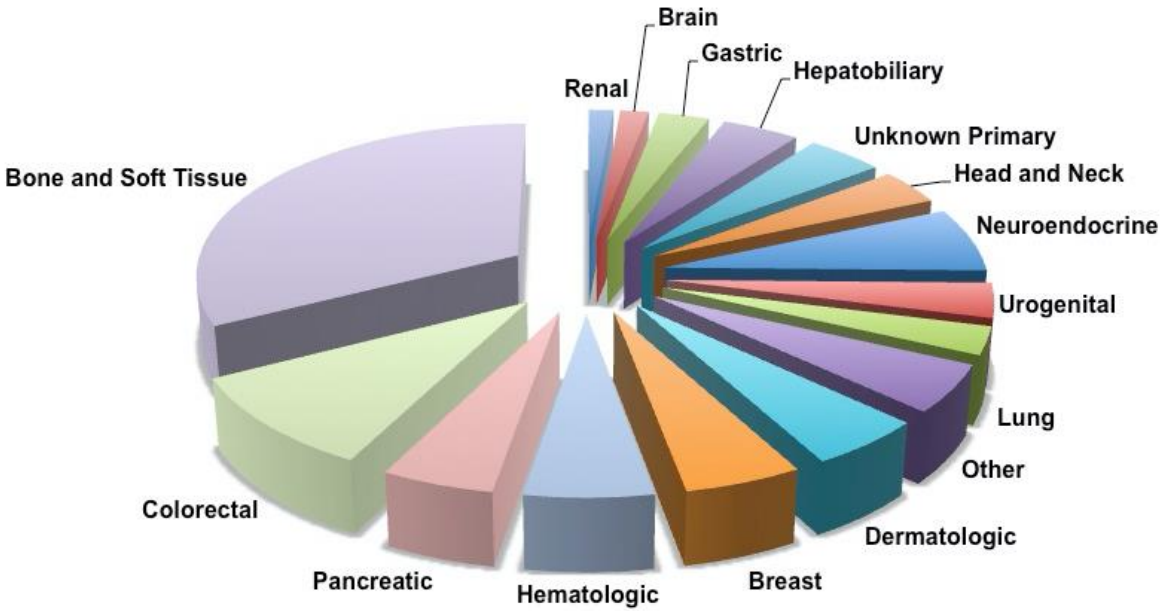
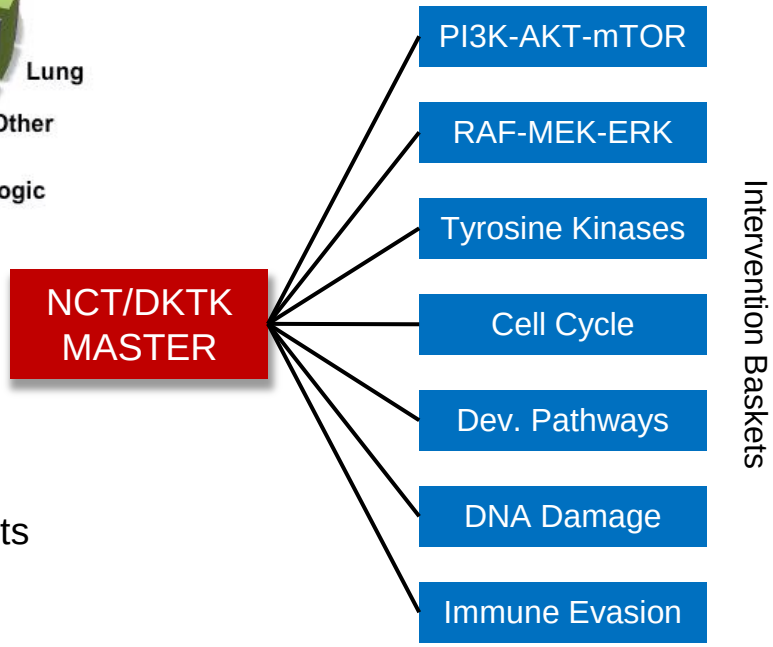
Workflow, Patient Accrual, and Current Results





October 25, 2017

Molecular tumor board	751 patients
Reevaluation of clinical diagnosis	~5%
Management recommendation (Level 1-4)	~83%
Genomics-guided clinical management	~24%

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Diagnostic Implications and Germline Predisposition

Reevaluation of clinical diagnosis in ~5% of cases

Diagnosis	Mutation(s)	Differential Diagnosis	Potential Clinical Action
Sarcoma NOS	CDK4/MDM2 amplification	Liposarcoma	→ CDK4/MDM2 inhibition
	MYOD1 p.V125L/p.L122R	Rhabdomyosarcoma	→ CWS Guidance
	PDGFRA p.D842V	GIST	→ Crenolanib*, BLU-285*
	COL1A1-PDGFB	DFSP	→ Imatinib*
	TPM3-ALK	IMT	→ Crizotinib*
Carcinoma of unknown primary site	EWSR1-WT1	DSRCT	→ EWING 2008
	NUTM1-NSD3	NUT midline carcinoma	→ BET inhibitor
Thymic carcinoma	NUTM1-BRD3	NUT midline carcinoma	→ BET inhibitor
Urothelial carcinoma	NUTM1-BRD4	NUT midline carcinoma	→ BET inhibitor

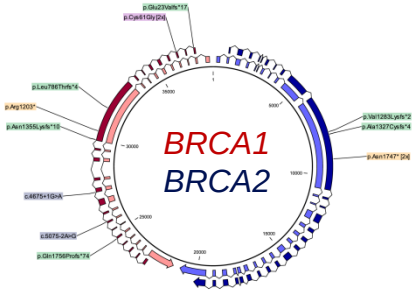
**Not approved for this indication in Germany*

Clinically actionable germline alterations

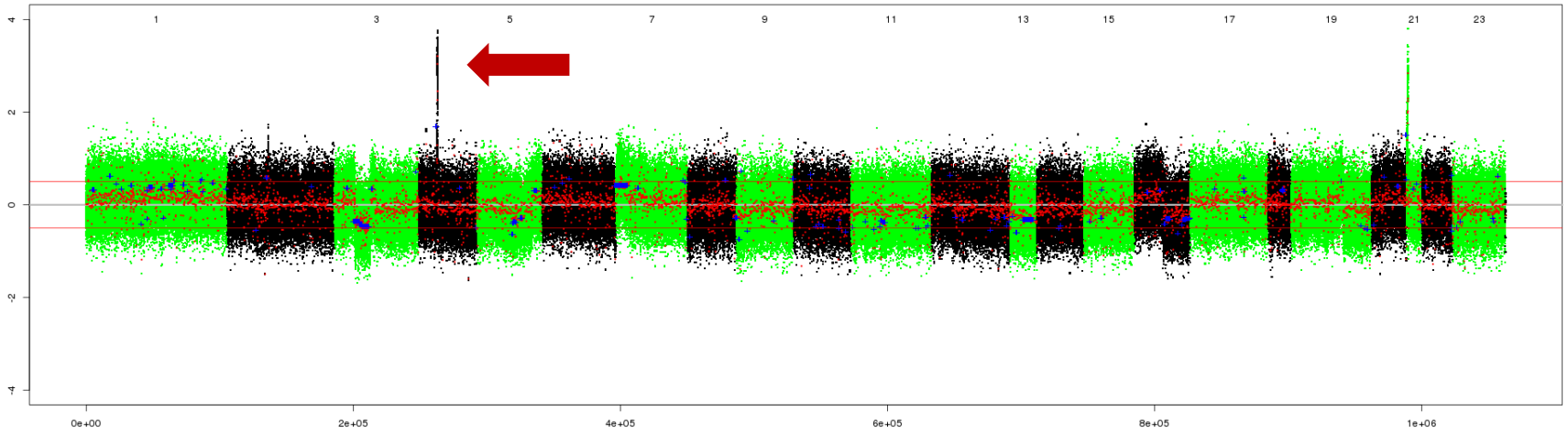
- Pathogenic variants in 23 tumor predisposition genes (*BRCA1/2*, *PALB2*, *ATM*, *NF1*, *MEN1*, *RB1*, *APC*, *SDHB*, *PTEN*, *CDH1*, *MSH2*, etc.) in 11% of cases
- Carrier status for autosomal recessive disorders (Fanconi anemia, Bloom syndrome, xeroderma pigmentosum, etc.) in 4% of cases

E. Schröck

B. Klink



Therapeutic Implications – single biomarker



Metastatic pulmonary epithelioid hemangioendothelioma

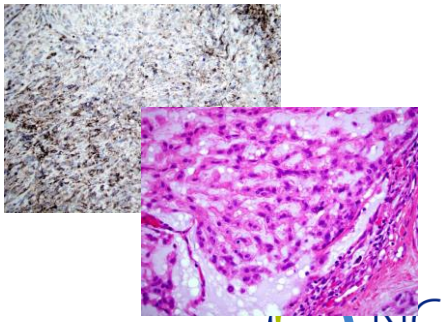
- Refractory to temozolomide/bevacizumab
- Refractory to lenalidomide

High-level amplification of chromosome 4q12, including *PDGFRA*

- Outlier *PDGFRA* mRNA expression
- PDGFRA protein expression by immunohistochemistry

Elevated *PDGFA* mRNA expression

Treatment with pazopanib, partial remission for >6 months



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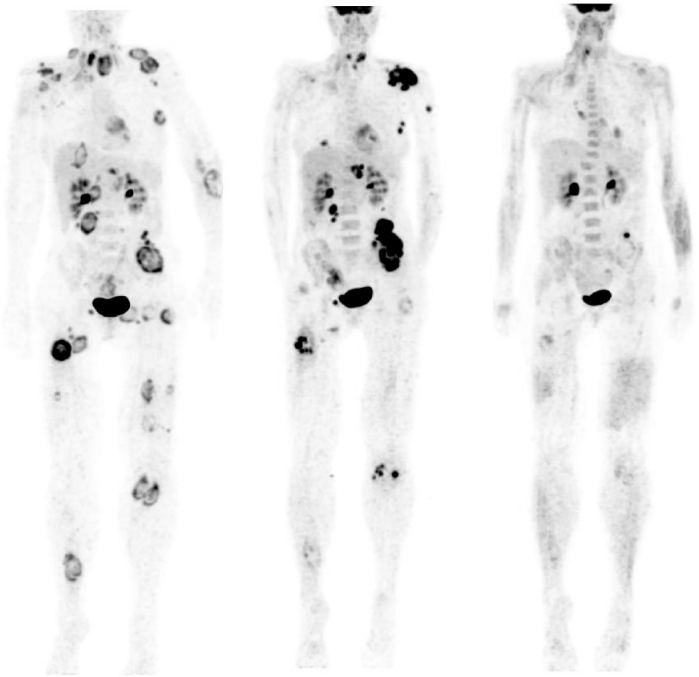
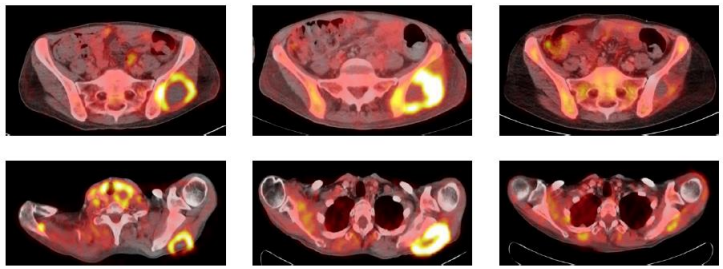
Therapeutic Implications – multifactorial biomarker





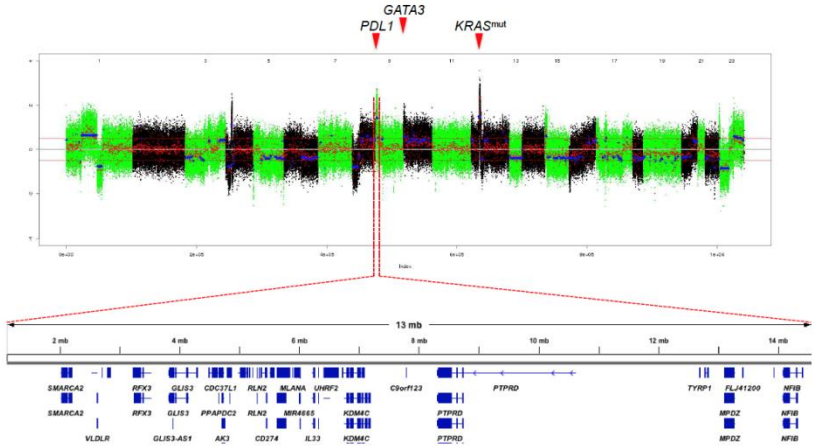
Baseline 2 months 6 months

Undifferentiated cancer of unknown primary

- Initially categorized as soft-tissue sarcoma, no response to doxorubicin/ifosfamide and trabectedin
- Histology and immunohistochemistry suggestive of triple-negative breast cancer

High mutational load and *PDL1* amplification

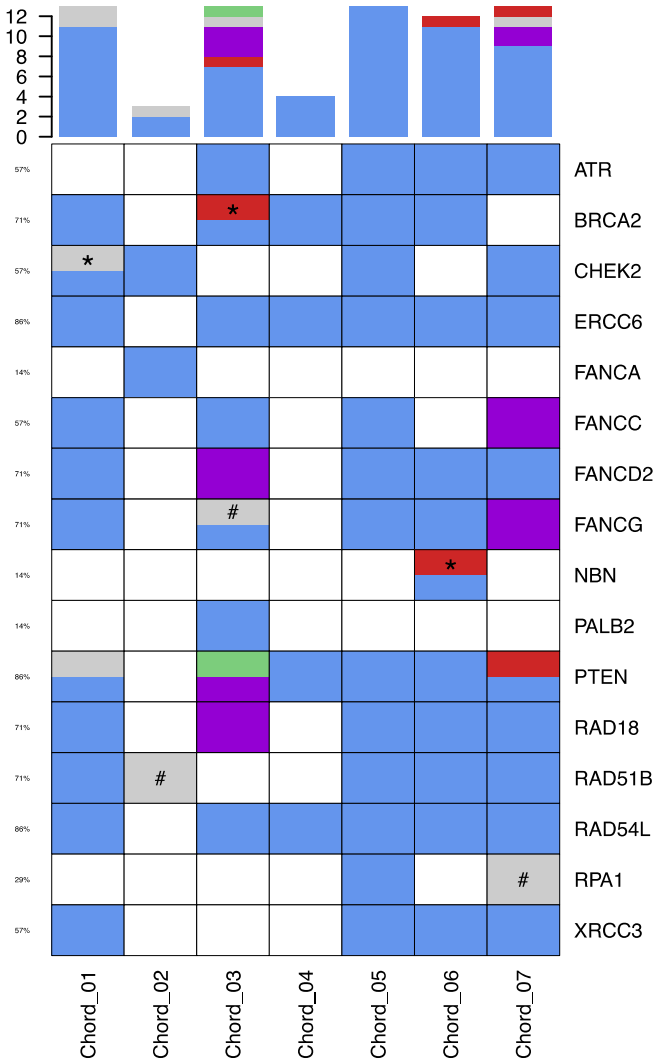
- 380 single-nucleotide variants and insertions/deletions
- Outlier *PDL1* mRNA expression
- PDL1 protein expression by immunohistochemistry
- Immune checkpoint blockade with pembrolizumab*
- Near-complete remission for >18 months

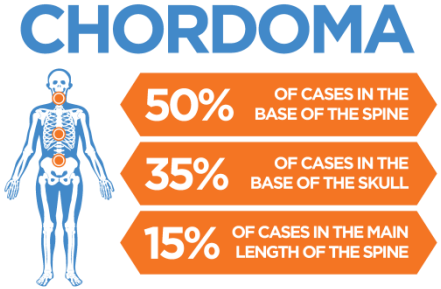


*Not approved for this indication in Germany

Gröschel, Bommer et al. Cold Spring Harb Mol Case Stud 2016

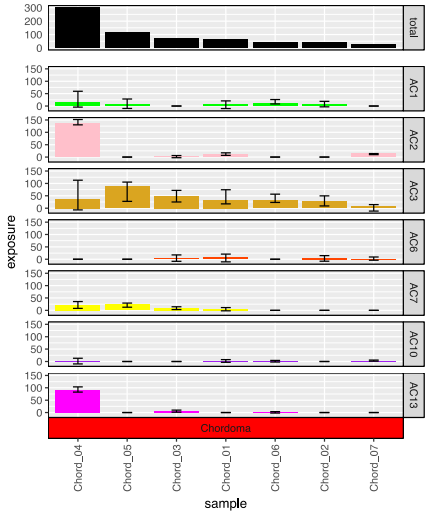
Therapeutic Implications – multifactorial biomarker

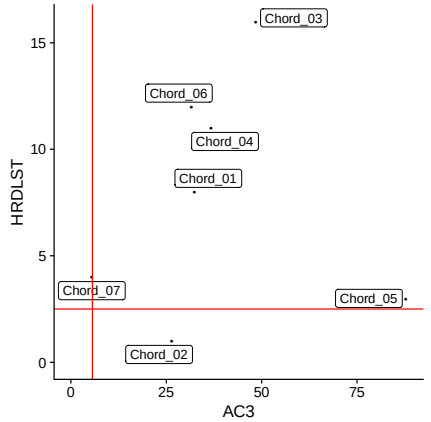




Locally recurrent and metastatic chordoma (*n* = 7)

- Prior irradiation in all cases
- Imprints of defective homologous recombination DNA repair (“BRCAness”) in all cases

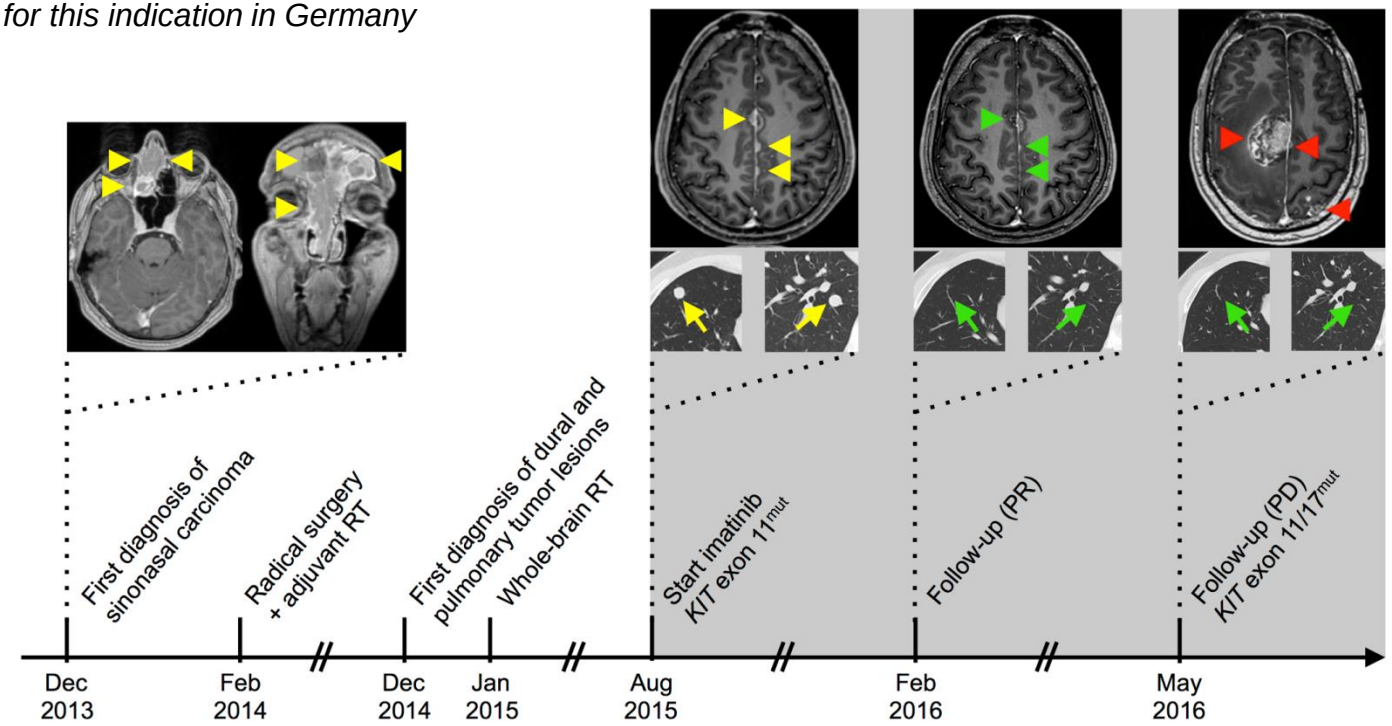




Gröschel, Hübschmann et al.

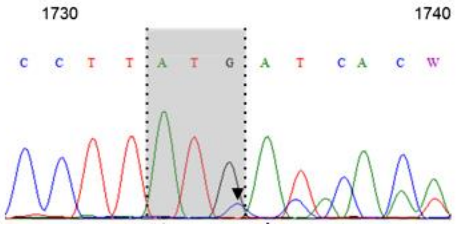
Therapeutic Implications – resistance marker

**Not approved for this indication in Germany*



Undifferentiated sinonasal carcinoma

- Pulmonary and dural metastases



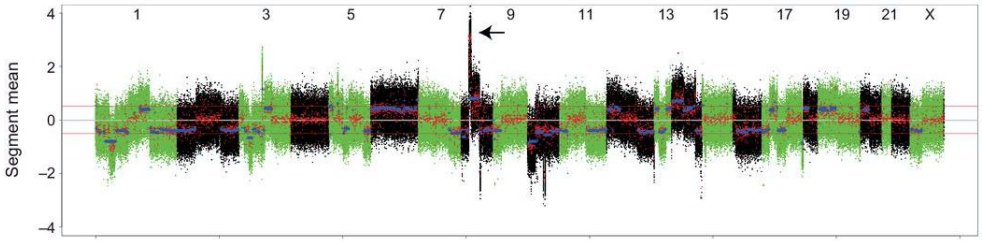
***KIT* exon 11 mutation (p.579del)**

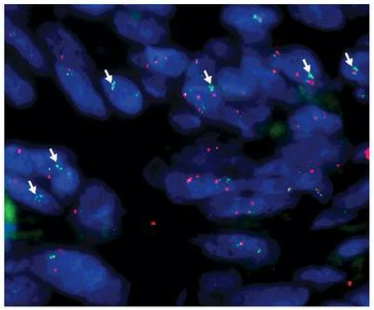
- Outlier *KIT* mRNA expression
- KIT protein expression by immunohistochemistry
- Imatinib* (400 mg/day) → complete/near-complete resolution of pulmonary and dural lesions
- Secondary resistance due to *KIT* exon 17 mutation (p.D820_S821delinsG)

Dieter et al. Ann Oncol 2017

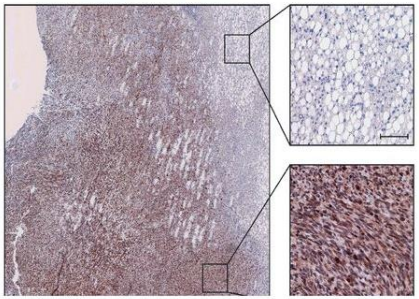
Therapeutic Implications – functional characterization

Whole-exome sequencing

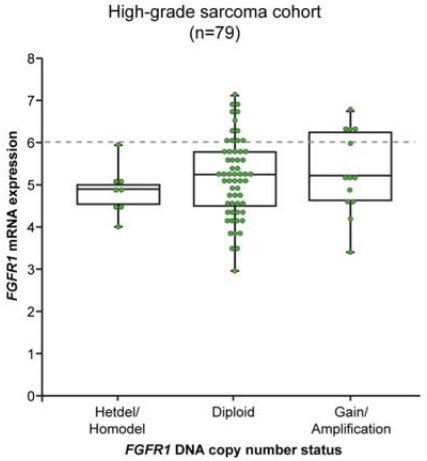


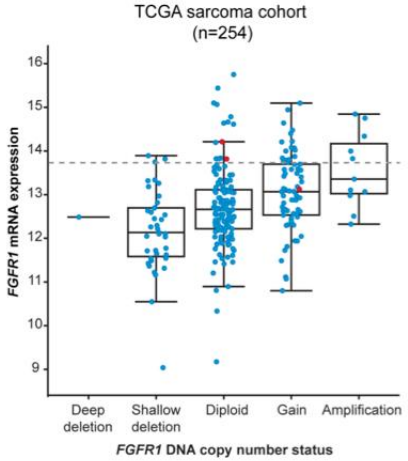


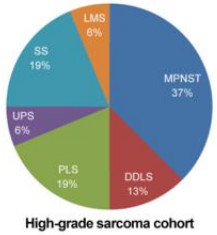
FISH

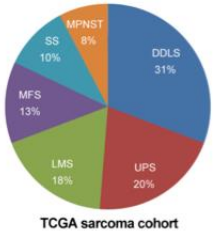


Immunohistochemistry









***FGFR1*-amplified leiomyosarcoma**

Clinical benefit from small-molecule FGFR inhibitors (BGJ398, nintedanib)* for >12 months

M. Scheffler & J. Wolf, Cologne

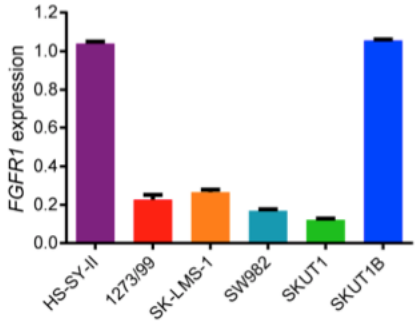
***FGFR1* amplification and/or overexpression in various soft-tissue sarcoma subtypes**

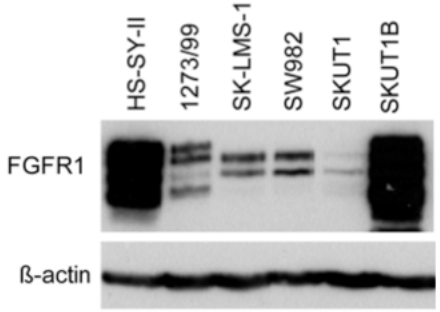
FISH, array-based CGH and transcriptome profiling, RNA sequencing

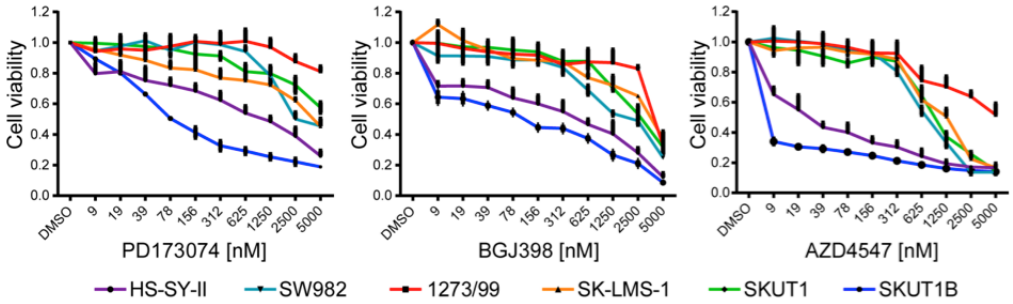
*Not approved for this indication in Germany

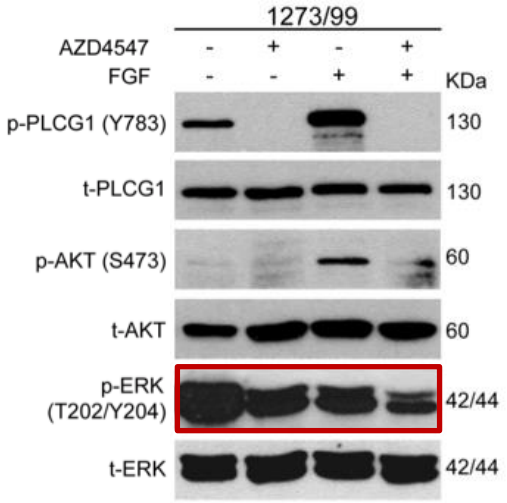
Chudasama et al. Clin Cancer Res 2017

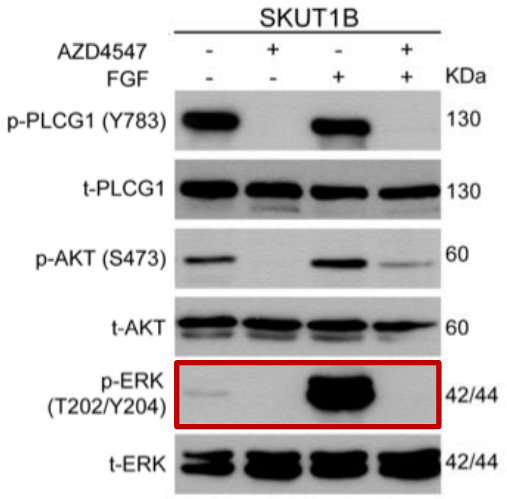
Therapeutic Implications – functional characterization









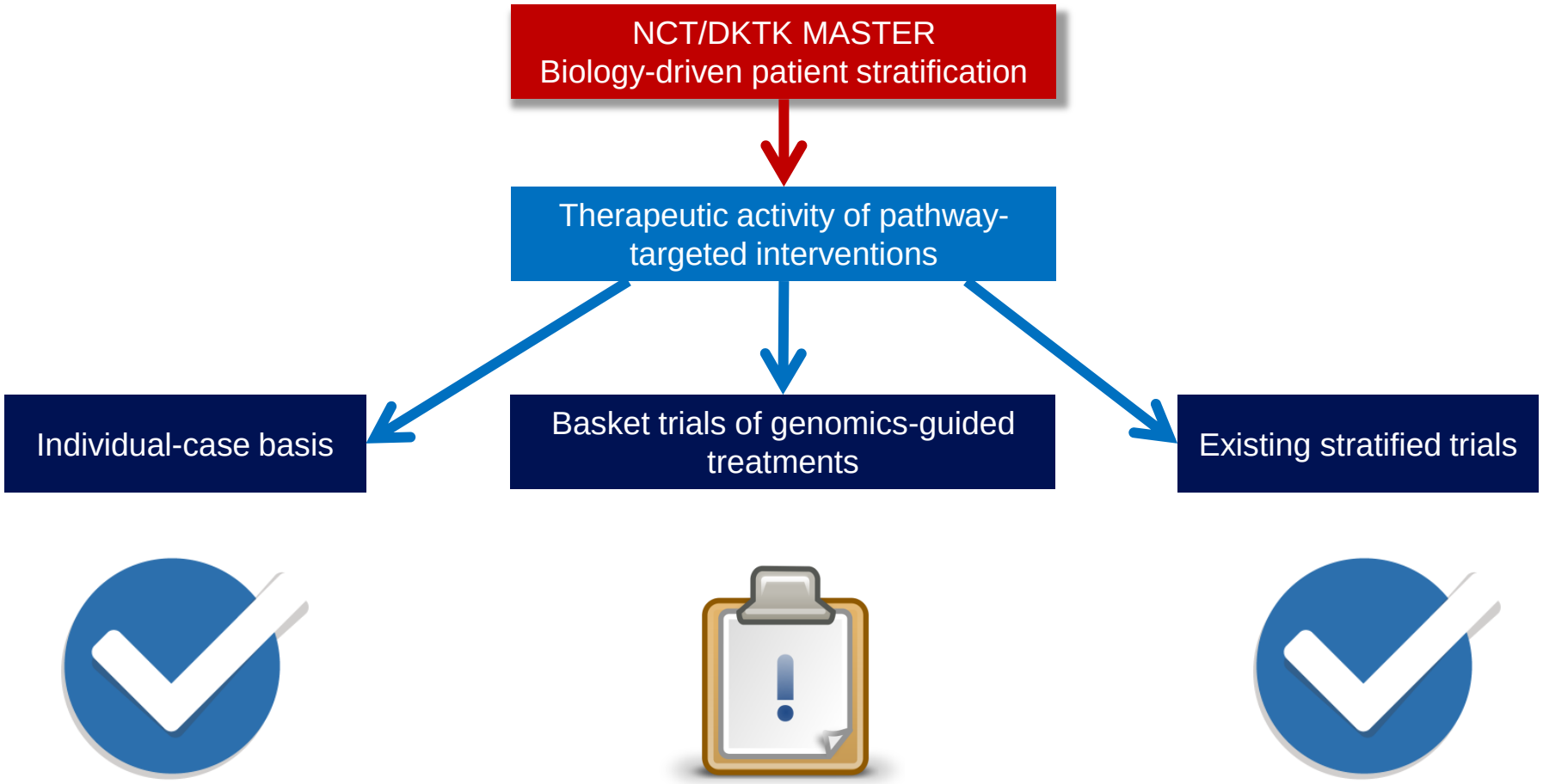


Determinants of response to FGFR inhibition

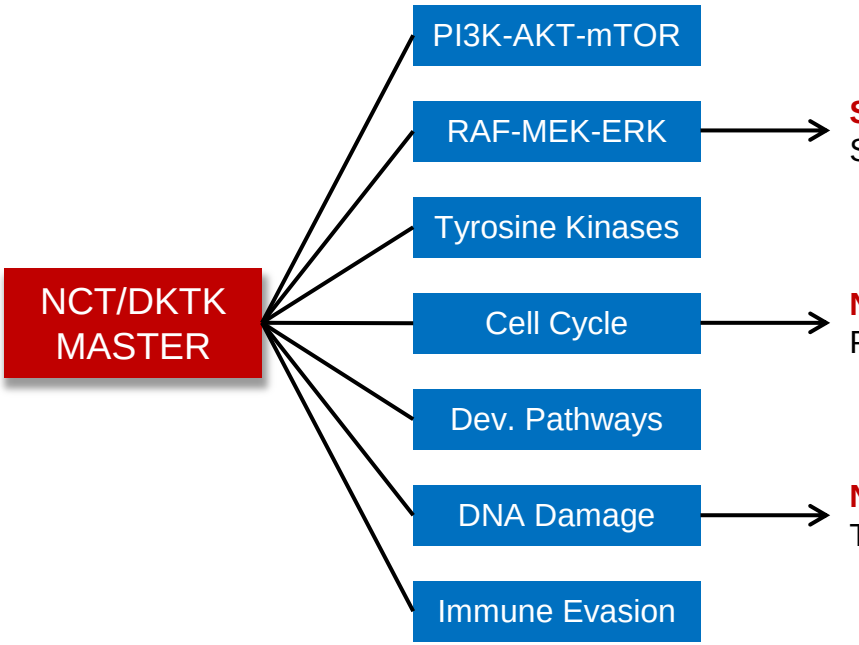
- FGFR1 overexpression with or without underlying *FGFR1* amplification
- Suppression of MAPK-ERK1/2 signaling

Chudasama et al. Clin Cancer Res 2017

Strategies for Clinical Translation



Genomics-Guided Basket Studies within DKTK



SoraTram (N. von Bubnoff [Freiburg], H. Glimm, S. Fröhling)
Sorafenib/trametinib in patients with non-V600 BRAF mutations

NCT PMO-1601 (S. Fröhling, C. Heilig, R. Schlenk)
Palbociclib in patients with CDKN2A/B-deficient chordoma

NCT PMO-1603 (S. Fröhling, S. Gröschel, R. Schlenk)
Trabectedin/olaparib in patients with DNA repair-deficient cancers

Eligibility

- Advanced-stage cancer
- Prior standard treatment
- Actionable molecular alteration, as determined by analysis within NCT/DKTK MASTER

DKTK German Cancer Consortium

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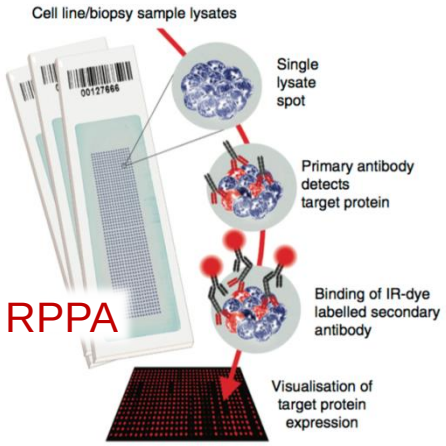
Conclusion and Outlook

Molecular profiling based on whole-exome/genome and RNA sequencing in a multi-institutional clinical setting

- ✓ Is feasible
- ✓ Provides important diagnostic information
- ✓ Creates therapeutic opportunities
  - Younger adults with advanced-stage cancer
  - Patients with rare tumors
- ✓ Needs to be evaluated within controlled clinical trials of genomics-guided therapies
- ✓ Should be complemented by additional layers of patient characterization and additional treatment modalities
  - Proteomics, functional imaging, DNA methylation analysis, immunomonitoring etc.
  - Radiotherapy, surgery, etc.



NCT MASTER Investigators

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DKFZ

High-Throughput Sequencing Unit
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