COMPREHENSIVE CANCER CENTER VIENNA

EINE EINRICHTUNG VON MEDUNI WIEN UND AKH WIEN

Präzisionsmedizin in der Klinik

Christoph Zielinski
Comprehensive Cancer Center Wien, Austria
www.ccc.ac.at

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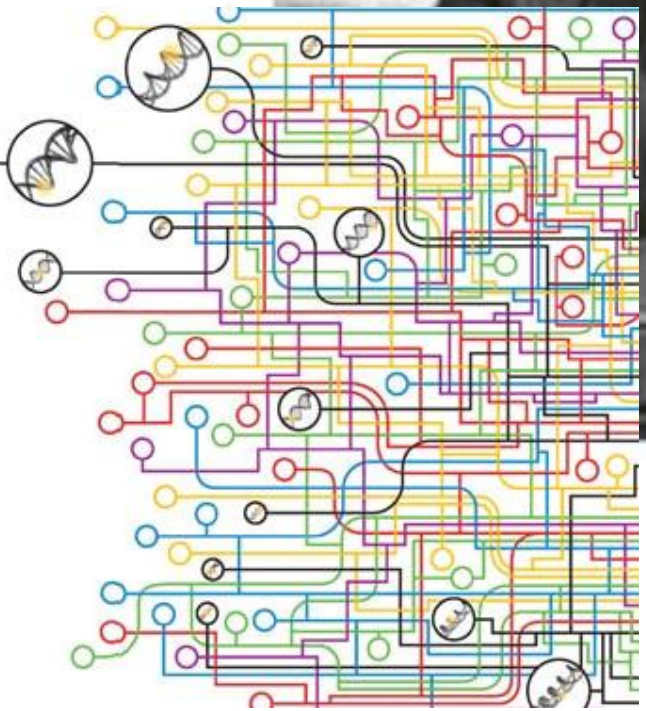
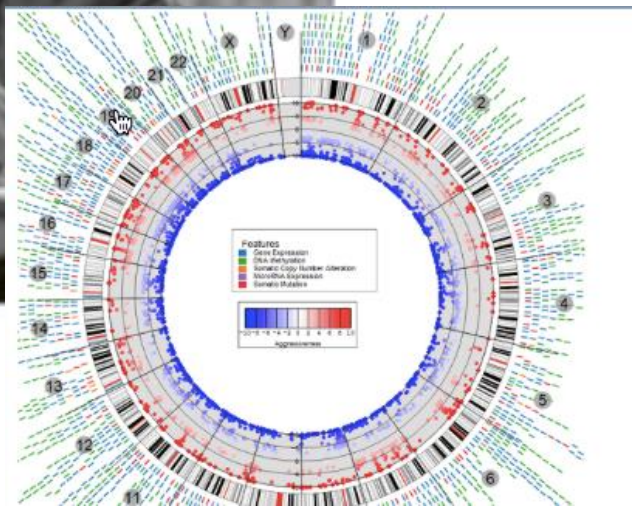
Nixon Signs $1.6 Billion Cancer Bill, Names Man to Head Fight

NIH

THE CANCER GENOME ATLAS

National Cancer Institute
National Human Genome Research Institute





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Molecular Drivers of Cancers

ERBB

ABL

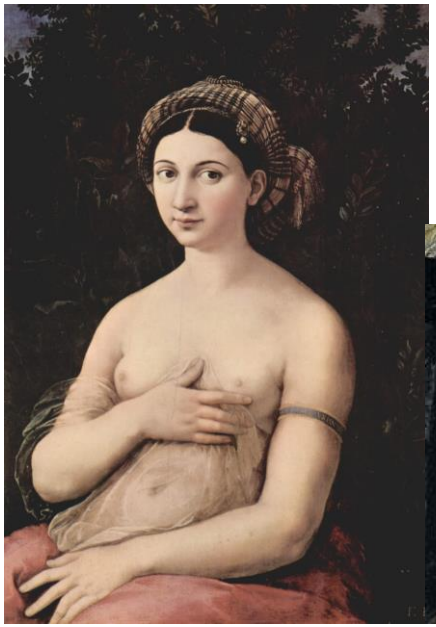
RAF

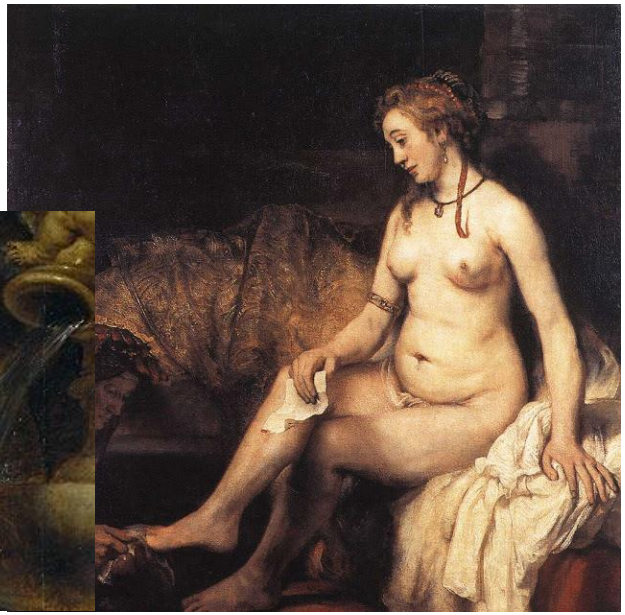
RAS

Breast Cancer Survival in the Arts:

Tumour Heterogeneity 1.0

R. Gross, Breast Cancer Res Treat 84: 293, 2004





Rafael: La Fornarina
Margherita Luti

Rubens: The Three Graces
Helene Fourment

Rembrandt: Bathsheba
Hendrickje Stoeffels

Survival after the Painting:

at least >2yrs.

>30 yrs.

9 yrs.

Tumour Heterogeneity 2.0: Molecular Concepts

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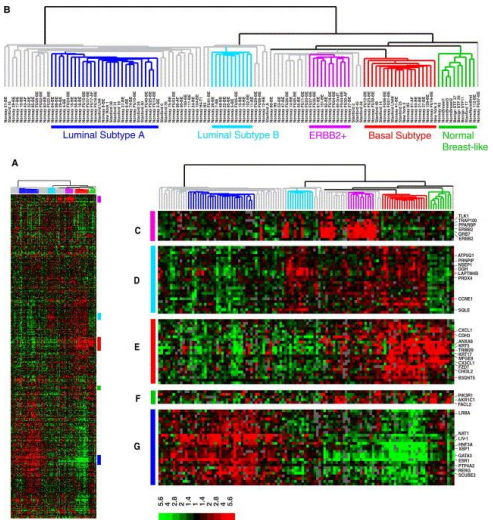
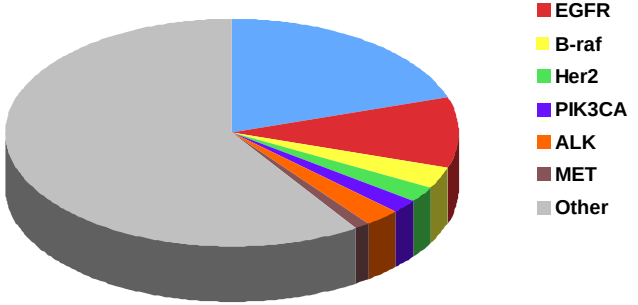
- **Homogeneicity of Signal Transduction across Anatomic Borders**

- **Macro- and Micro-Heterogeneity of Tumours**





Consequences of Molecular Research and Analyses in Oncology

- ***Heterogeneity of Previous "Entities"***

  (Examples: Breast Cancer, NSCLC, Colon Cancer, Stomach Cancer, Bile Duct Cancer)

- ***Identification of New "Entities" Based on Molecular Characteristics***

- ***Biological Similarities Across Anatomic Borders According to Signaling Pathway Activation***

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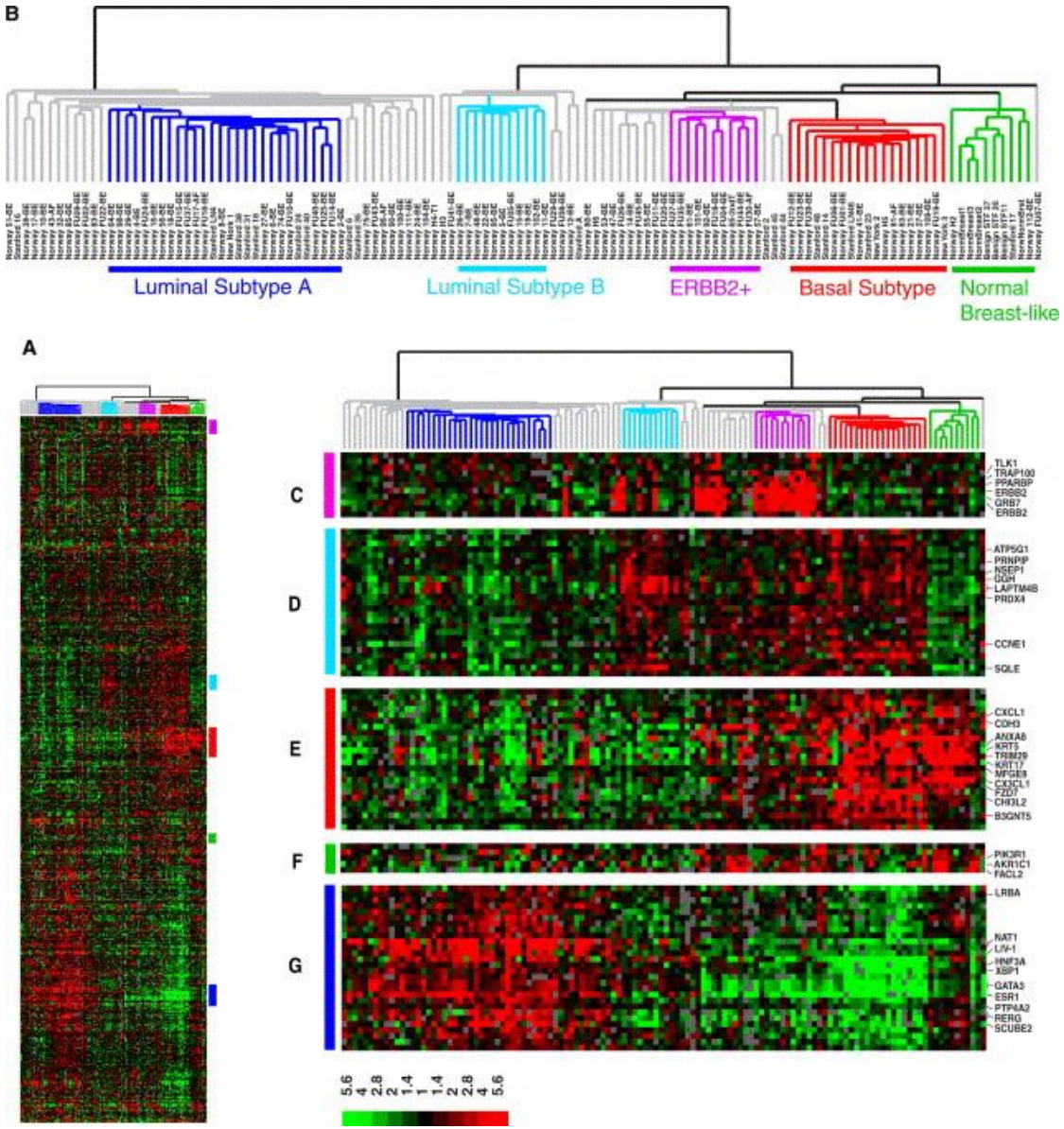
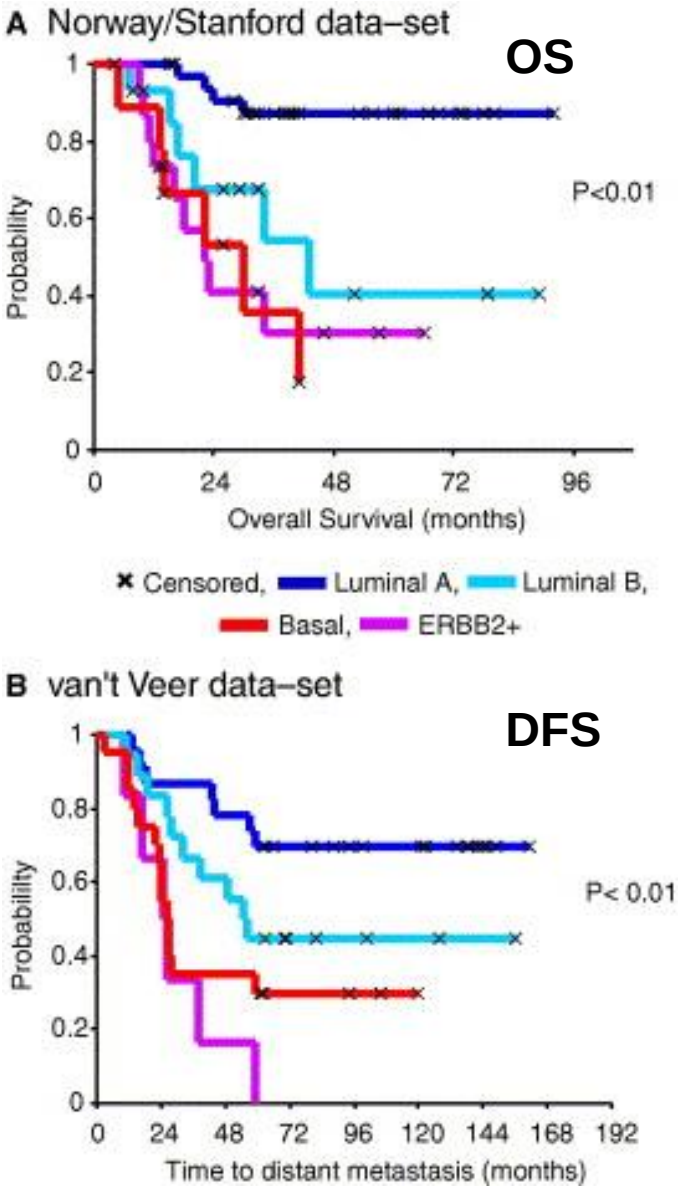
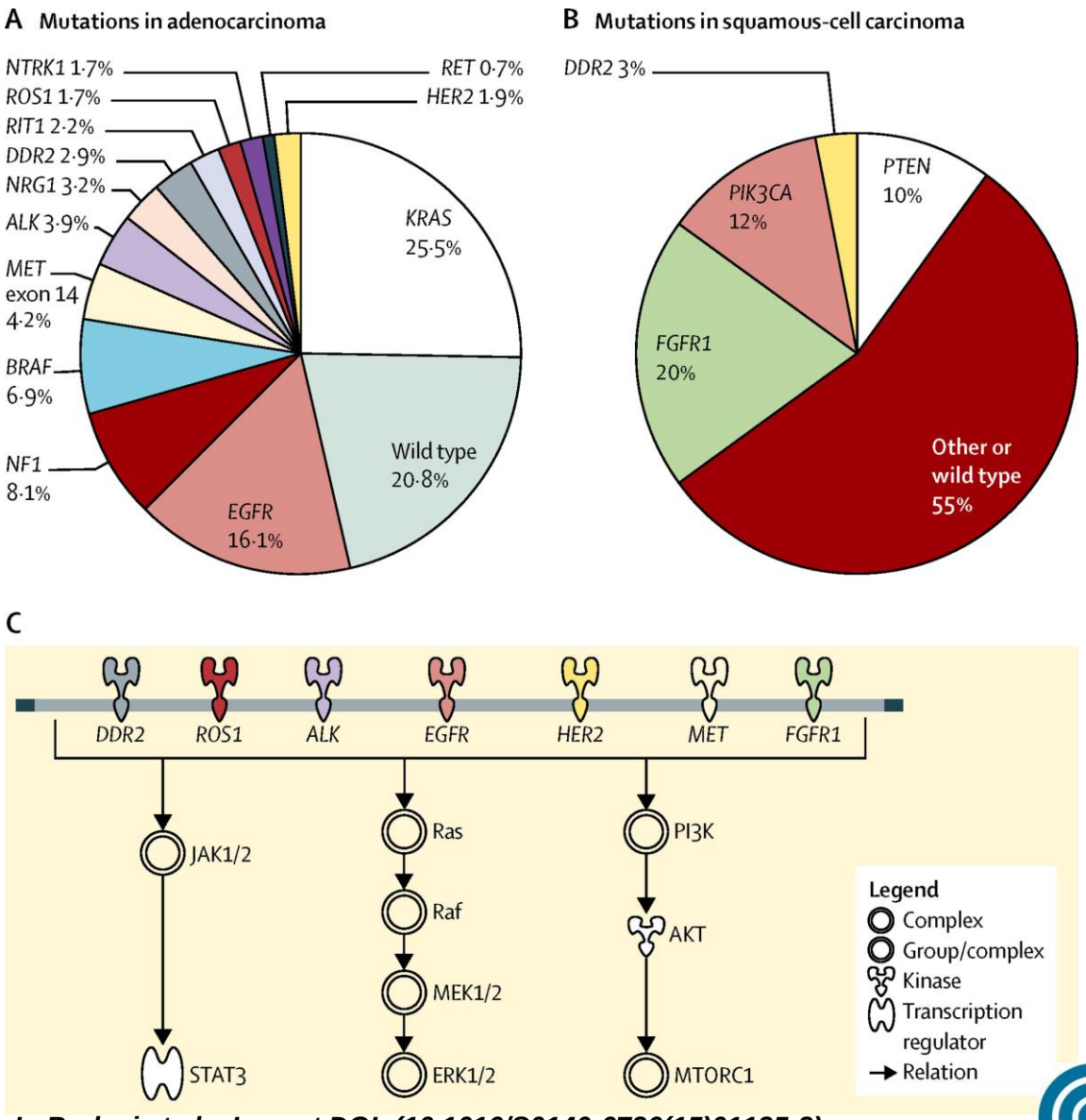
Breast Cancer is a Heterogeneous Group of Diseases





Large Scale Screening for Somatic Mutations in Lung Cancer



L. Barlesi et al., Lancet DOI: (10.1016/S0140-6736(15)01125-3)

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Identification of New Entities According to Molecular Characteristics

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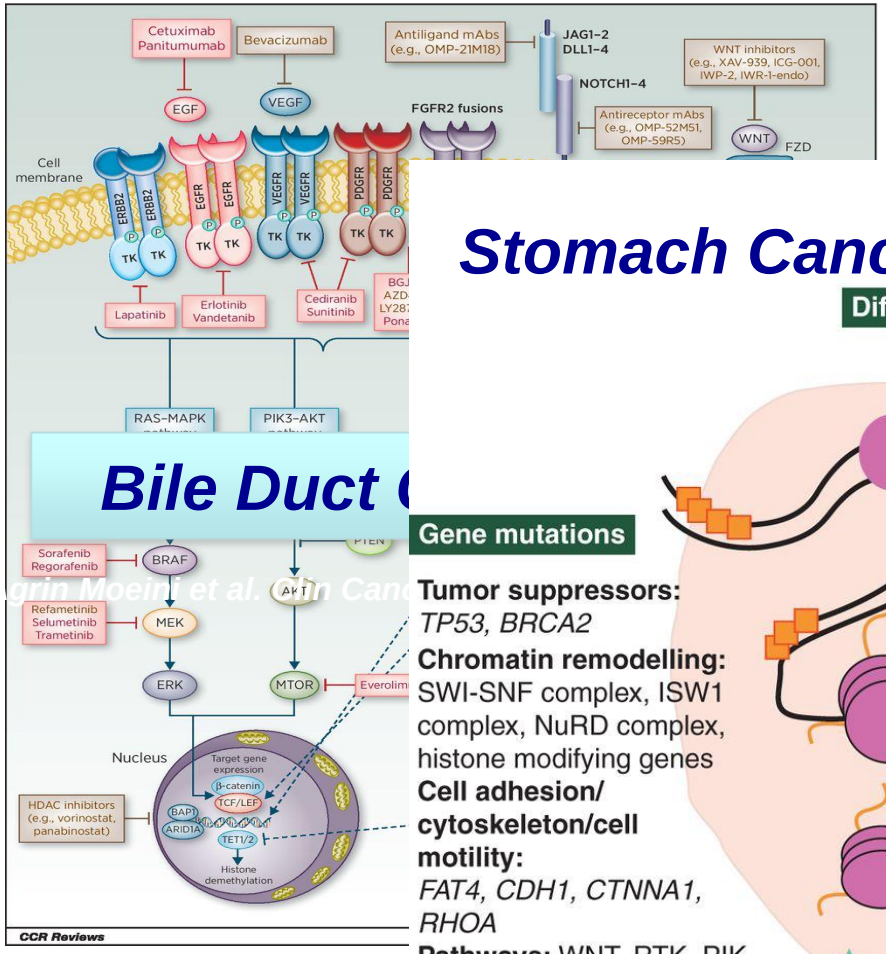

Bile Duct C

Stomach Cancer

Differential gene expression

Subtypes
- G-INT, G-DIF
- Proliferative, metabolic, mesenchymal
- Mesenchymal-like, TP53-active, TP53-inactive, MSI-H

Pathway: AMPKα-HNF4α-WNT5A

Gene mutations

Tumor suppressors: *TP53, BRCA2*
Chromatin remodelling: SWI-SNF complex, ISW1 complex, NuRD complex, histone modifying genes
Cell adhesion/ cytoskeleton/cell motility: *FAT4, CDH1, CTNNA1, RHOA*
Pathways: WNT, RTK, PIK

Subtype: HiC, Loc

DNA/histone methylations

Subtypes: MSI-H, MSI-L, CIMP+ H3K27 methylation

SCNAs

AMplifications: *ERBB2, EGFR, MET, FGFR2, RAS, CCND1, CCNE1, CDK6 KLF5, GATA4, GATA6*
LOH: *APC, TP53, NME1*
Fusion: *SLC1A2-CD44, SLC34A2-ROS1, CLDN18-ARHGAP26*
Subtypes: Genomically stable, CIN

Subtype: EBV+

Examples for Biological Similarities Across Anatomical Borders with Varying Biologic Importance

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EGFR	**Colon, ENT, NSCLC**
Her-2/neu	**Breast, Stomach, Bladder**
ckit	**CML, GIST, Dermatofibrosarcoma**
AKT	**NSCLC, NHL, Inflammatory Myofibroblastic Tumor**
BRAF	**Melanoma, Colon, Thyroid, CCC**

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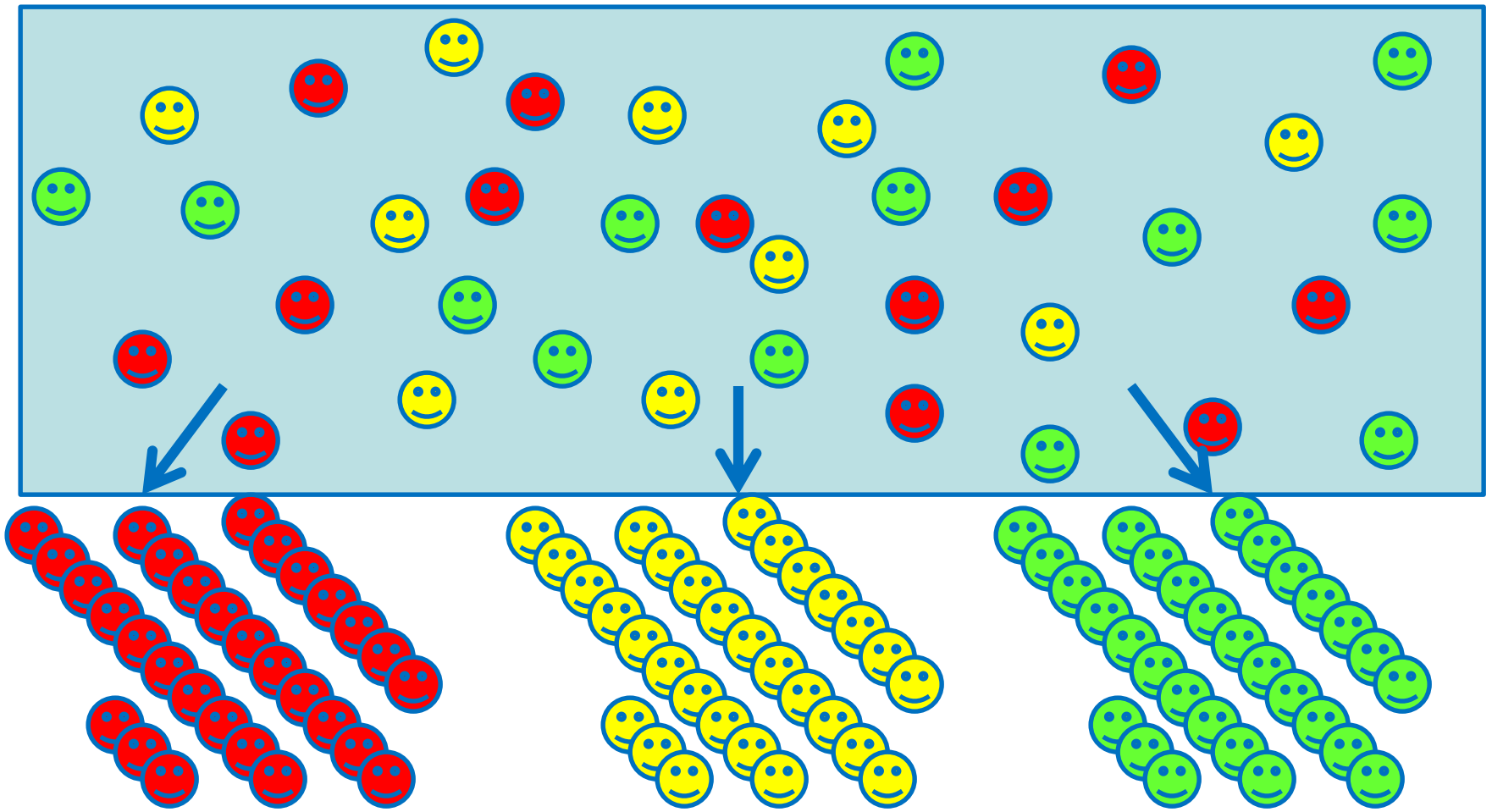
Individualized Medicine in Cancer Treatment: The Vision



Predicted poor or no response to drug

Increased likelihood of toxicity of drug

Predicted good response to drug

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2017

Search of somatic gene alterations for actionable information has become routine practice in clinical oncology

BRAF

ALK

EGFR

RAS

HER2

PD-L1

Colorectal cancer: Identifying Patient Benefit from anti-EGFR

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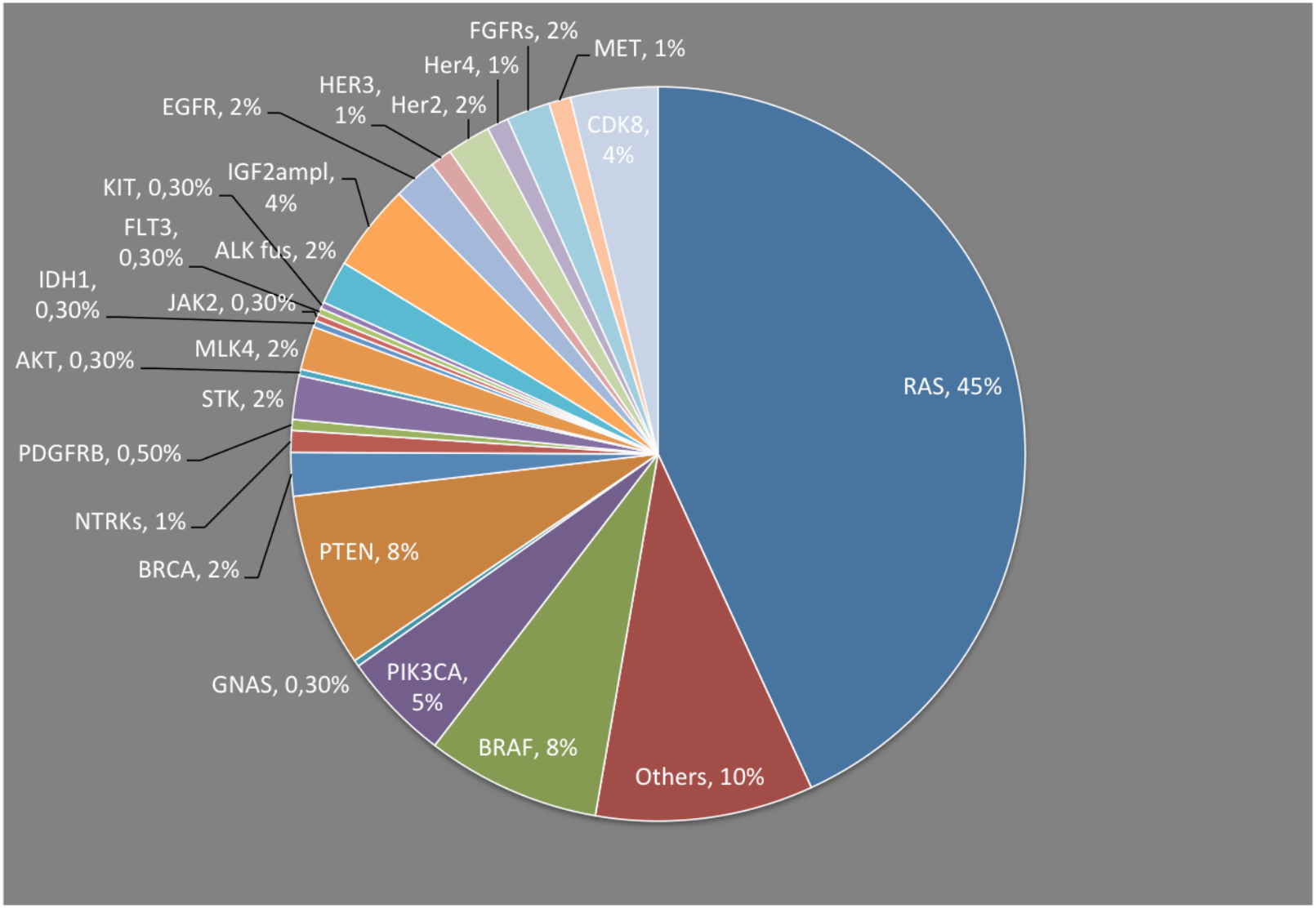
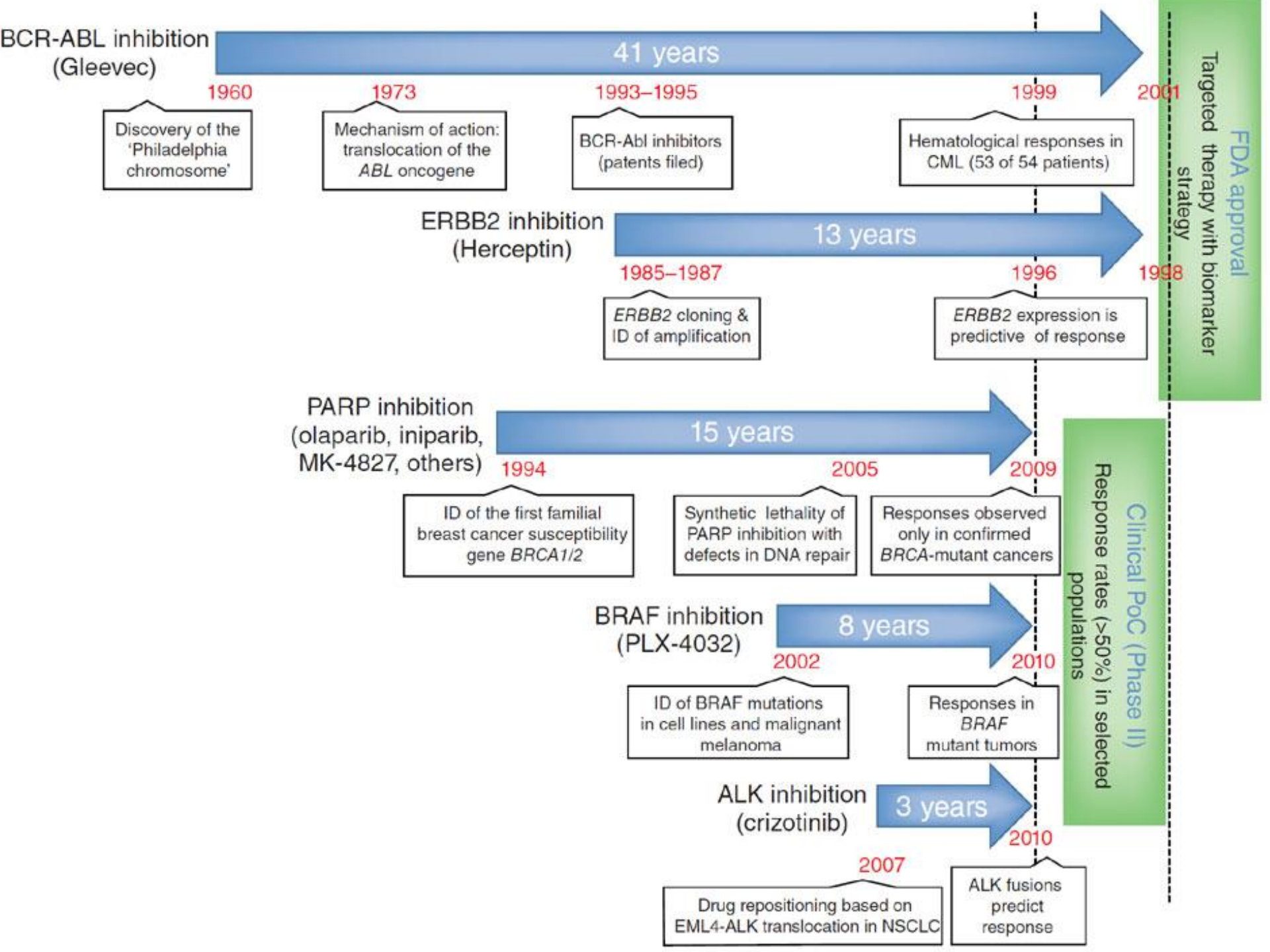
Actionable Targets in CRC




BCR-ABL inhibition (Gleevec)
41 years
1960
Discovery of the 'Philadelphia chromosome'
1973
Mechanism of action: translocation of the ABL oncogene
1993–1995
BCR-Abl inhibitors (patents filed)
1999
Hematological responses in CML (53 of 54 patients)
2001
ERBB2 inhibition (Herceptin)
13 years
1985–1987
ERBB2 cloning & ID of amplification
1996
ERBB2 expression is predictive of response
1998
FDA approval
Targeted therapy with biomarker strategy
PARP inhibition (olaparib, iniparib, MK-4827, others)
15 years
1994
ID of the first familial breast cancer susceptibility gene BRCA1/2
2005
Synthetic lethality of PARP inhibition with defects in DNA repair
2009
Responses observed only in confirmed BRCA-mutant cancers
Clinical PoC (Phase II)
Response rates (>50%) in selected populations
BRAF inhibition (PLX-4032)
8 years
2002
ID of BRAF mutations in cell lines and malignant melanoma
2010
Responses in BRAF mutant tumors
ALK inhibition (crizotinib)
3 years
2010
2007
Drug repositioning based on EML4-ALK translocation in NSCLC
ALK fusions predict response

Scenarios of „Individualized“ Treatment

1. ***Drugable Target in a Defined Population with a Defined Disease (Abundant Examples)***

2. ***Targeting One Defined Mutation Across Anatomic Borders (Example: „BASKET Trial“)***

3. ***Moving Drugable Targets within an Individual Context Resulting in a Group Analysis according to Predefined Standards (Example: „EXACT Trial“)***

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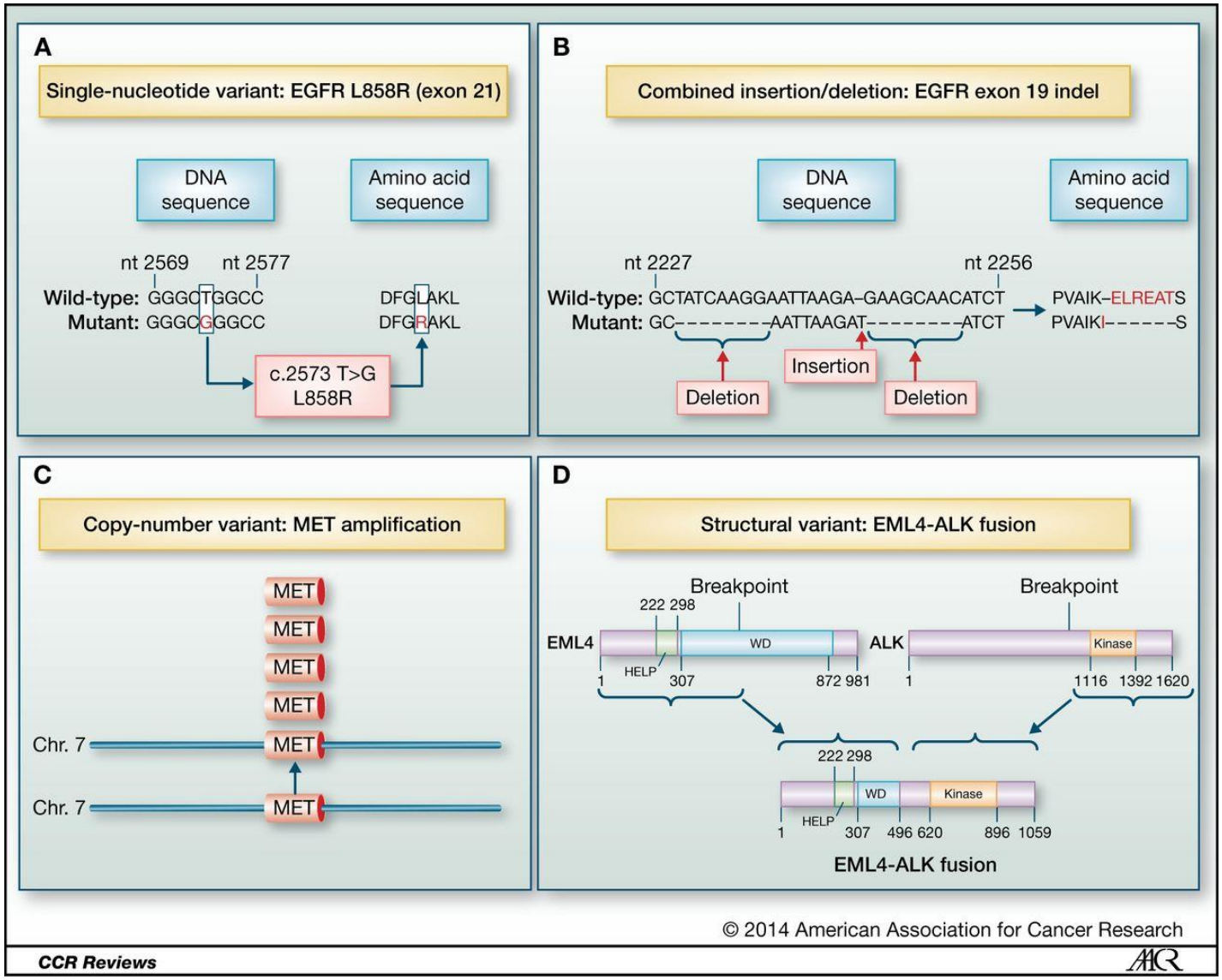
Examples of Types of "Driver" Genomic Alterations Found in Cancer



Meador C B et al. Clin Cancer Res 2014;20:2264-2275

Clinical Cancer Research

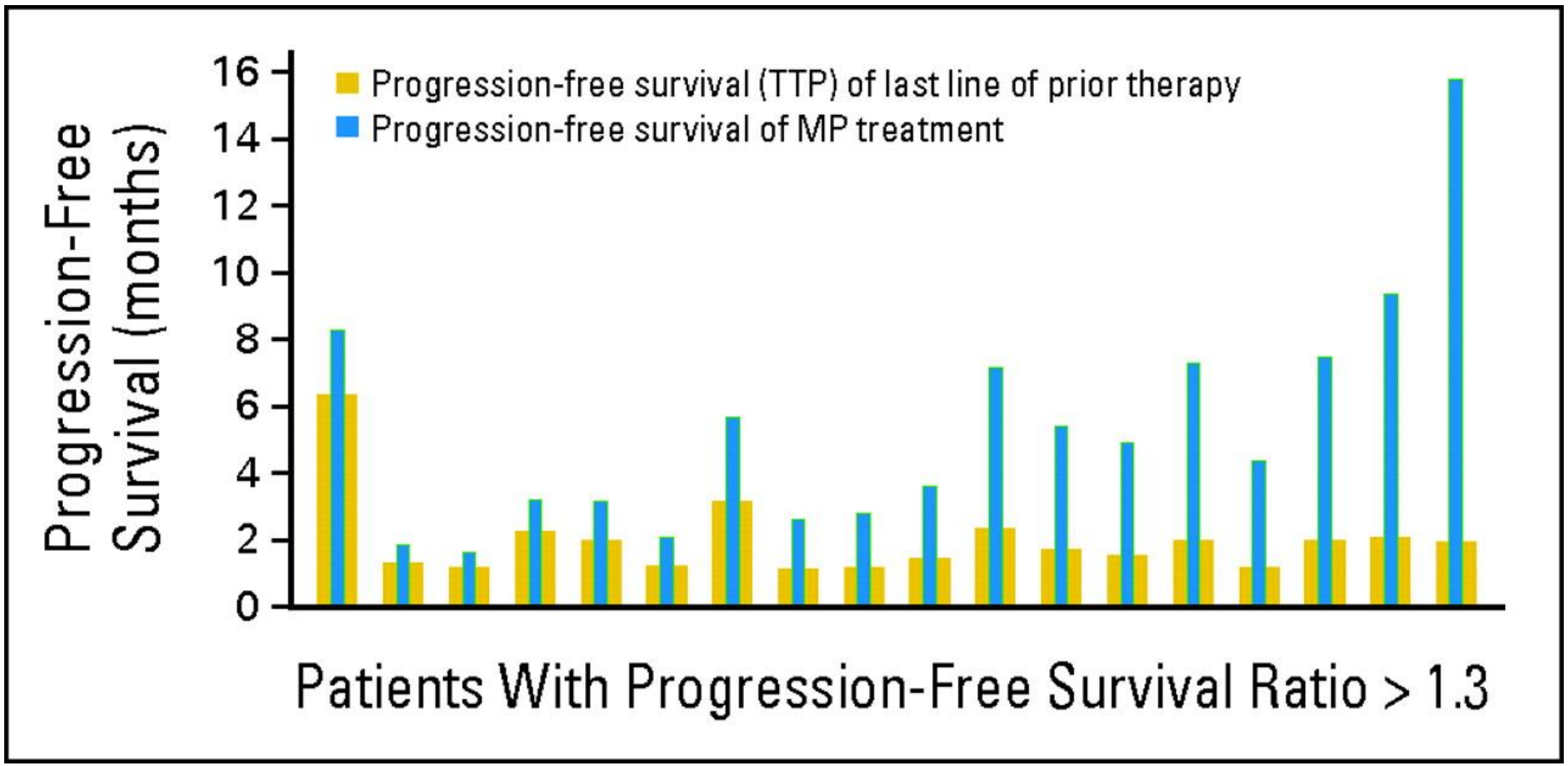
Scenarios of „Individualized“ Treatment

1. *Drugable Target in a Defined Population with a Defined Disease (Abundant Examples)*

2. ***Targeting One Defined Mutation Across Anatomic Borders (Example: „BASKET Trial“)***

3. ***Moving Drugable Targets within an Individual Context Resulting in a Group Analysis according to Predefined Standards (Example: „EXACT Trial“)***

Comparisons of PFS on Molecular Profiling Therapy vs. PFS on Prior Therapy for 18 out of 66 Patients with a PFS ≥ 1.3.



von Hoff DD et al. JCO 2010;28:4877

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The SHIVA Trial

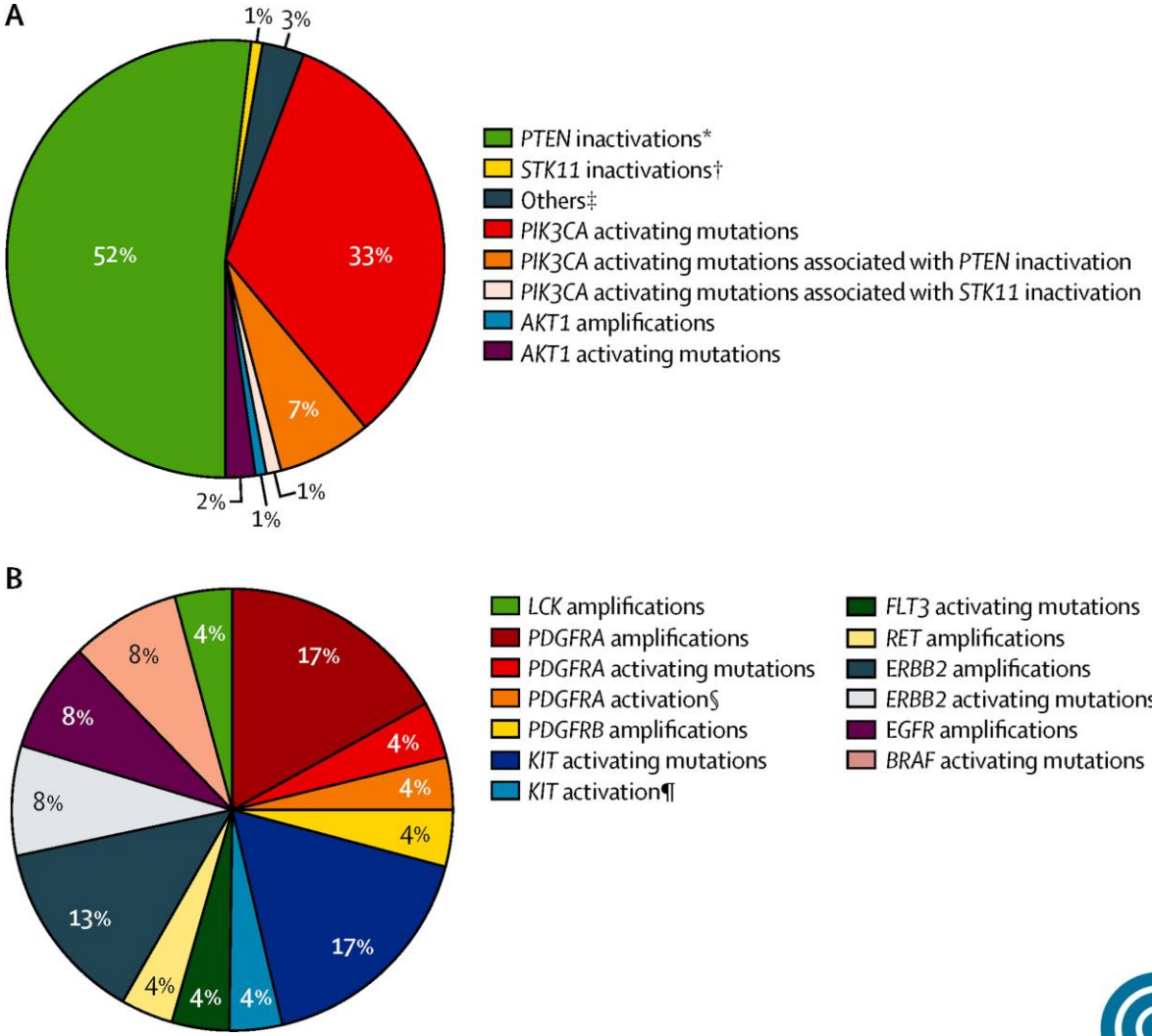
Christophe Le Tourneau et al., Lancet Oncol , Volume 16, Issue 13, 2015, 1324–1334

1. **Randomized Phase II Trial**
2. **Targeted Treatment vs. Physician Choice**
3. **Inclusion of 3 Molecular Pathways**
   (Hormone Receptors, PI3K/AKT/mTOR, RAF/MEK)
4. **10 Targeted Drugs**
5. **Primary Endpoint: PFS**

Molecularly Targeted Therapy Based on Tumour Molecular Profiling vs. Conventional Therapy for Advanced Cancer (SHIVA): a Randomised, Controlled Phase 2 Trial

C. Le Tourneau et al., The Lancet Oncology 2015 16, 1324-1334DOI: (10.1016/S1470-2045(15)00188-6)

Distribution of Molecular Alterations



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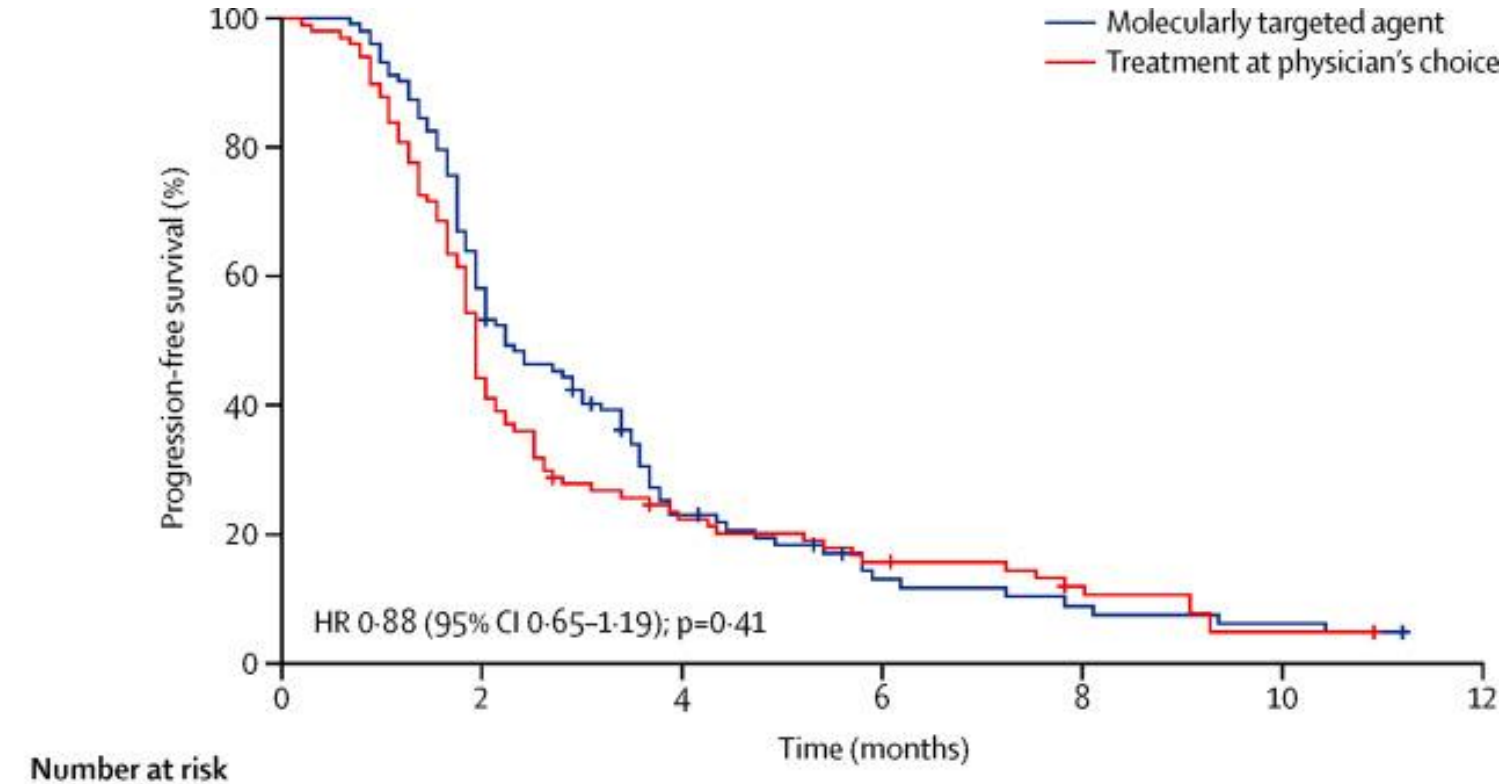
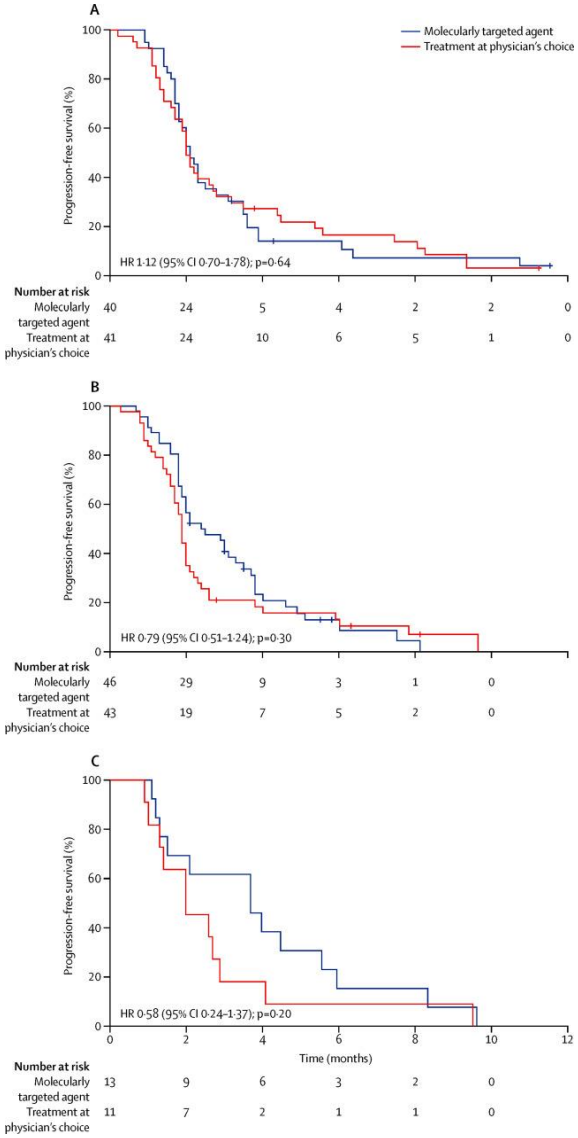
SHIVA Phase 2 Trial: PFS



Number at risk							
Molecularly targeted agent	99	62	20	10	5	2	0
Treatment at physician's choice	95*	50	19	12	8	1	0

Christophe Le Tourneau et al., Lancet Oncol , Volume 16, Issue 13, 2015, 1324–1334

SHIVA Trial: PFS in patients with molecular alterations in the hormone receptor pathway (A), PI3K/AKT/mTOR pathway (B), and RAF/MEK pathway (C).



Christophe Le Tourneau et al., Lancet Oncol , Volume 16, Issue 13, 2015, 1324–1334

Precision Medicine Protocols in Oncology at the Comprehensive Cancer Center of Medical Univ. Vienna

1. **EXtended Analysis for Cancer Treatment (EXACT) - controlled**
2. **Molecular Oncologic Diagnosis and Treatment Index (MONDTI) - observational**

Gerald Prager, Robert Mader, Stefan Kubicek,
Leonhard Müllauer, Fritz Wrba and Christoph Zielinski

- **patients with an incurable malignant disease**
- **refractory to standard therapy acc. to guidelines (ESMO, NCCN)**
- **informed consent (“HUMPHREY”-based protocol for profiling)**
- **real-time biopsy**

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Acknowledgements

Department of Medicine I
Medical University Vienna

Gerald Prager
Robert Mader
Matthias Unseld
Christiane Thallinger

CeMM

Stefan Kubicek

Department of Clinical Pathology
Medical University of Vienna

Peter Birner
Berthold Streubel
Fritz Wrba
Leonhard Müllauer

Department of Radiology

Fredrik Waneck

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Patients and Diagnoses included in the MONDTI Protocol

Characteristics	No. of pts (n=297)	%
Sex		
Female	128	43,1%
Male	169	56,9%
Age (years)	57 (46-66)	
Tested tissue		
Primary	142	47,8%
Metastatic	155	52,2%
Tumor types		
colon	35	11,8%
lymphoma	29	9,8%
head&neck	23	7,7%
CCC	19	6,4%
PDAC	19	6,4%
CNS	17	5,7%
HCC	13	4,4%
CUP	13	4,4%
ovarian	12	4,0%

NET	10	3,4%
adrenal	10	3,4%
cervical	8	2,7%
pleuramesothelioma	8	2,7%
thyroid	8	2,7%
soft tissue (sarcoma)	7	2,4%
breast	7	2,4%
gastric	7	2,4%
esophageal	6	2,0%
small intestines	5	1,7%
urothelial	4	1,3%
multiple myeloma	4	1,3%
N/A	4	1,3%
testis	4	1,3%
skin (non melanoma)	3	1,0%
NSCLC	3	1,0%
prostate	2	0,7%
GIST	2	0,7%
endometrial	2	0,7%
urachus	2	0,7%
melanoma	2	0,7%
hepatoid	1	0,3%
PECOM (renal)	1	0,3%
hematological	1	0,3%
appendix	1	0,3%
renal	1	0,3%
hemangioma	1	0,3%
adnexal	1	0,3%
vulva	1	0,3%
MPNST	1	0,3%

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DE GRUYTER DOI 10.1515/cclm-2013-0883 — Clin Chem Lab Med 2013; aop

Gregory J. Tsongalis*, Jason D. Peterson, Francine B. de Abreu, Christopher D. Tunkey, Torrey L. Gallagher, Linda D. Strausbaugh, Wendy A. Wells and Christopher I. Amos

Routine use of the Ion Torrent AmpliSeq™ Cancer Hotspot Panel for identification of clinically actionable somatic mutations

Target Genes

Ion AmpliSeq™ Cancer Hotspot Panel v2

(Ion Torrent™)

ABL1	*EZH2*	*JAK3*	*PTEN*
AKT1	*FBXW7*	*IDH2*	*PTPN11*
ALK	*FGFR1*	*KDR*	*RB1*
APC	*FGFR2*	*KIT*	*RET*
ATM	*FGFR3*	*KRAS*	*SMAD4*
BRAF	*FLT3*	*MET*	*SMARCB1*
CDH1	*GNA11*	*MLH1*	*SMO*
CDKN2A	*GNAS*	*MPL*	*SRC*
CSF1R	*GNAQ*	*NOTCH1*	*STK11*
CTNNB1	*HNF1A*	*NPM1*	*TP53*
EGFR	*HRAS*	*NRAS*	*VHL*
ERBB2	*IDH1*	*PDGFRA*	
ERBB4	*JAK2*	*PIK3CA*	

Molecular Targets
ALK
MET/SE7
RET(10q11)
ROS1

Antibodies
CD30
c-kit
EGFR
HER2
HER2 SISH
MET
Östrogenrezeptor
Progesteronrezeptor
PDGFRalpha
PDGFRbeta
PTEN

FFPE / Native Tissue

Variant Caller
Ion Reporter Software
Ingenuity Variant Analysis

GROUP VON HAESELER | Populations, Adaptations & Evolution, Structural & Computational Biology
CIBIV - Center for Integrative Bioinformatics Vienna

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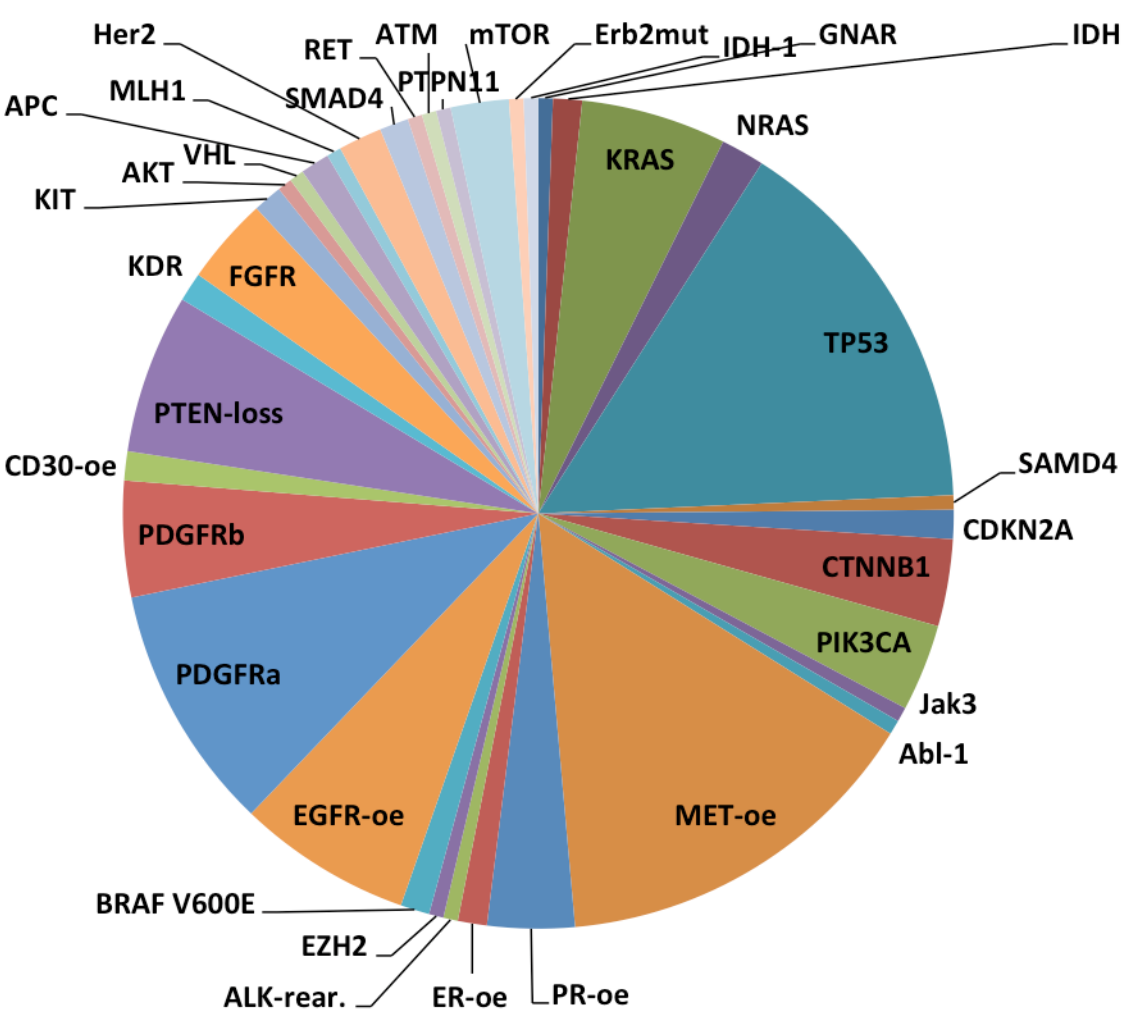
Molecular Alterations found in the Performance of the Molecular Diagnostics and Treatment (MONDTI) Protocol, CCC - Medical Univ. Vienna



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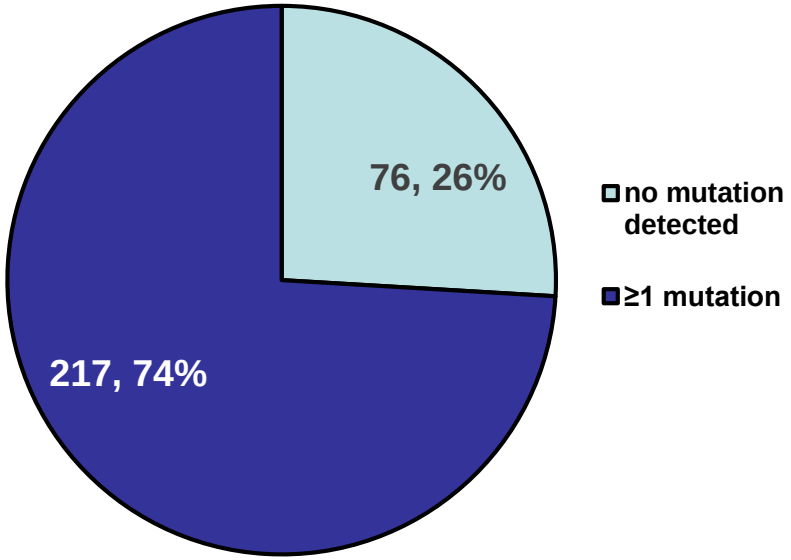
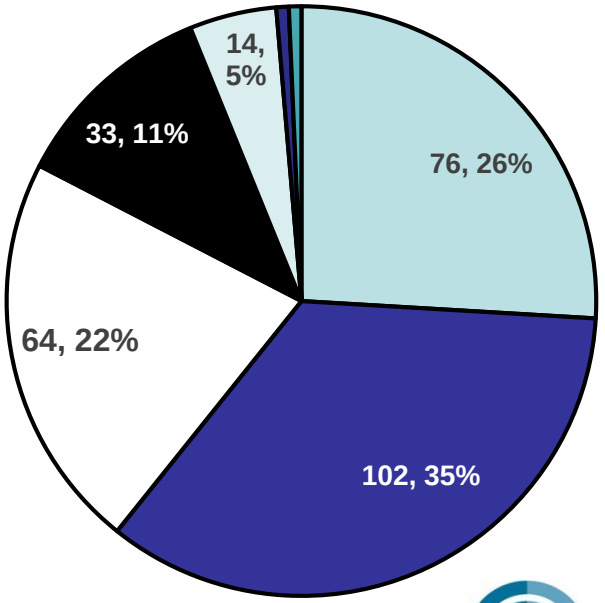
MONDTI: Detected Mutations

295 tumor samples,
293 NGS results available.



Distribution of the Amount of Detected Mutations

Results for 217 samples with ≥1 mutation



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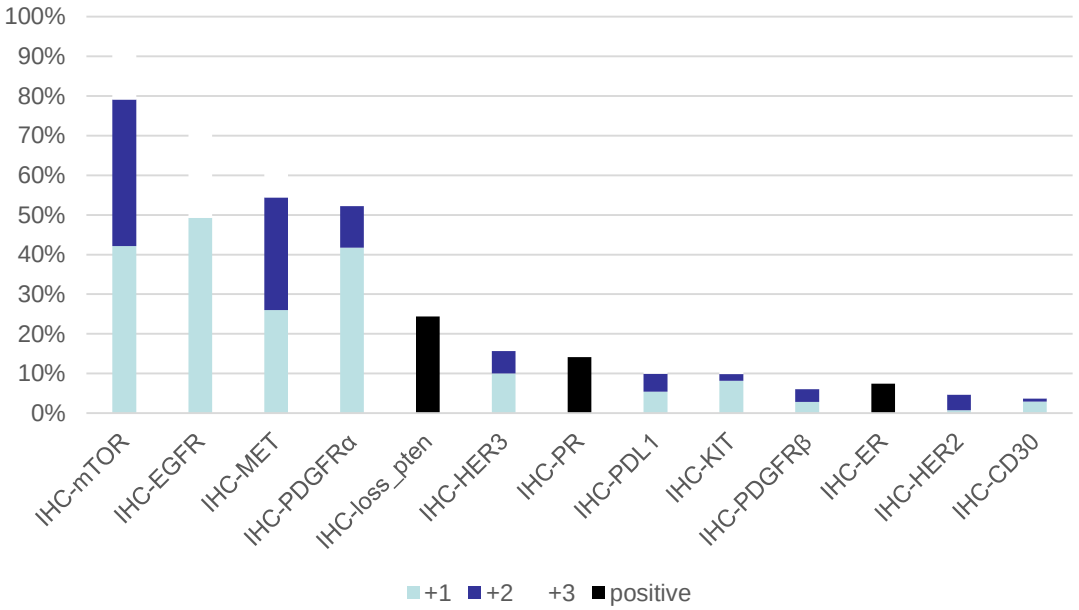
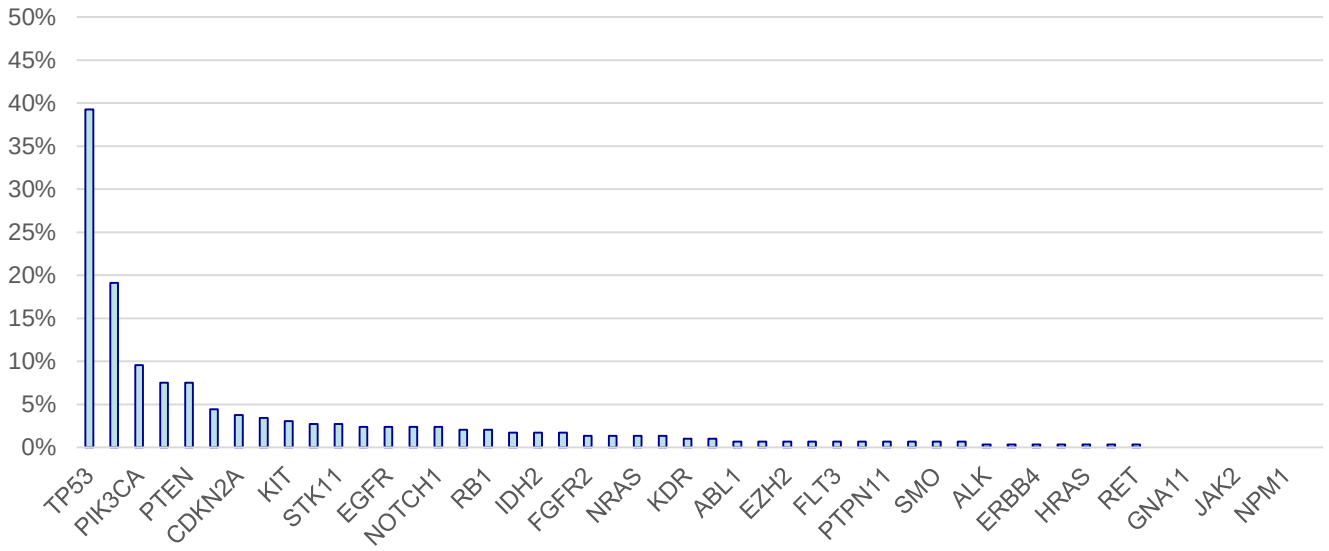
IHC-Results in Percent



Percentage of Detected Mutations, n=293



Therapy Recommendations

160 therapy recommendations

81x targeting 1 genetic alteration:

- *11x IHC +1*
- *20x IHC +2*
- *27x IHC +3*
- *5x IHC (unspecified)*
- *15x somatic mutation*
- *3x MSI-high*

58x targeting 2 genetic alteration:

- *7x IHC (+1) + IHC (+1)*
- *2x IHC (+1) + IHC (unspecified)*
- *2x IHC (+1) + somatic mutation*
- *1x IHC (+1) + FISH detected alteration*
- *1x IHC (+2) + IHC (+1)*
- *2x IHC (+2) + IHC (+2)*
- *6x IHC (+2) + IHC (unspecified)*
- *2x IHC (+2) + somatic mutation*
- *5x IHC (+3) + IHC (+1)*
- *8x IHC (+3) + IHC (+2)*
- *4x IHC (+3) + IHC (+3)*
- *7x IHC (+3) + IHC (unspecified)*
- *5x IHC (+3) + somatic mutation*
- *1x IHC (+3) + FISH detected alteration*
- *1x IHC (unspecified) + IHC (unspecified)*
- *2x IHC (unspecified) + somatic mutation*
- *1x IHC (unspecified) + FISH detected alteration*
- *1x somatic mutations + somatic mutation*

20x targeting 3 genetic alteration:

- *1x IHC (+2) + IHC (+2) + IHC (+1)*
- *2x IHC (+3) + IHC (+2) + IHC (+1)*
- *1x IHC (+3) + IHC (+2) + IHC (+2)*
- *1x IHC (+3) + IHC (+3) + IHC (+2)*
- *3x IHC (+3) + IHC (+2) + IHC (unspecified)*
- *1x IHC (+2) + IHC (+1) + IHC (unspecified)*
- *1x IHC (+2) + IHC (+2) + IHC (unspecified)*
- *1x IHC (+1) + IHC (+1) + IHC (unspecified)*
- *1x IHC (+3) + IHC (+1) + somatic mutation*
- *1x IHC (+2) + IHC (unspecified) + somatic mutation*
- *1x IHC (+3) + IHC (unspecified) + somatic mutation*
- *3x IHC (+2) + IHC (unspecified) + FISH detected alteration*
- *1x IHC (+3) + IHC (unspecified) + FISH detected alteration*
- *1x IHC (+2) + IHC (+1) + FISH detected alteration*
- *1x IHC (unspecified) + somatic mutation + FISH detected alteration*

1x targeting 4 genetic alterations:

1x IHC (+3) + IHC (+2) + IHC (unspecified) + FISH detected genetic alteration

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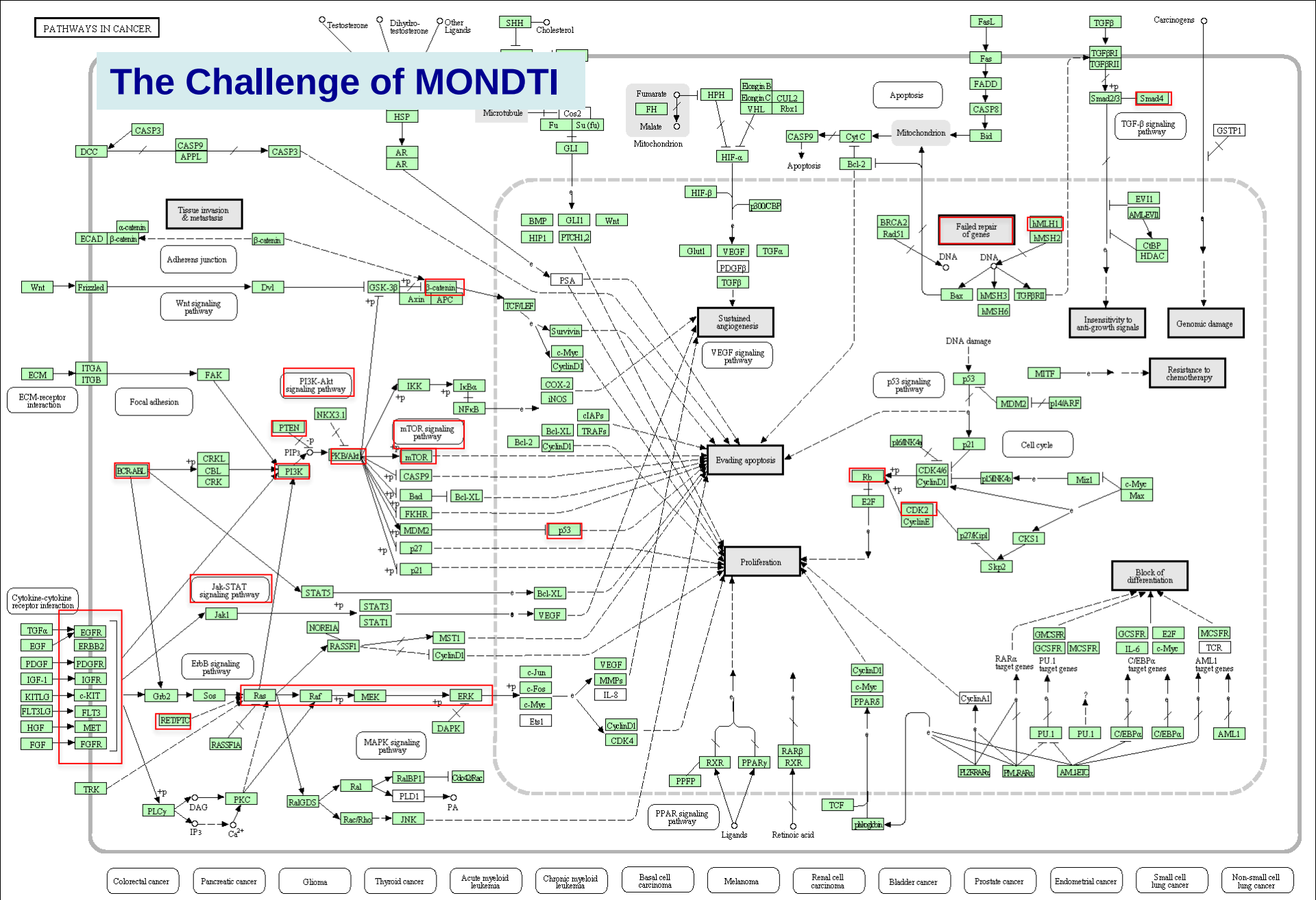
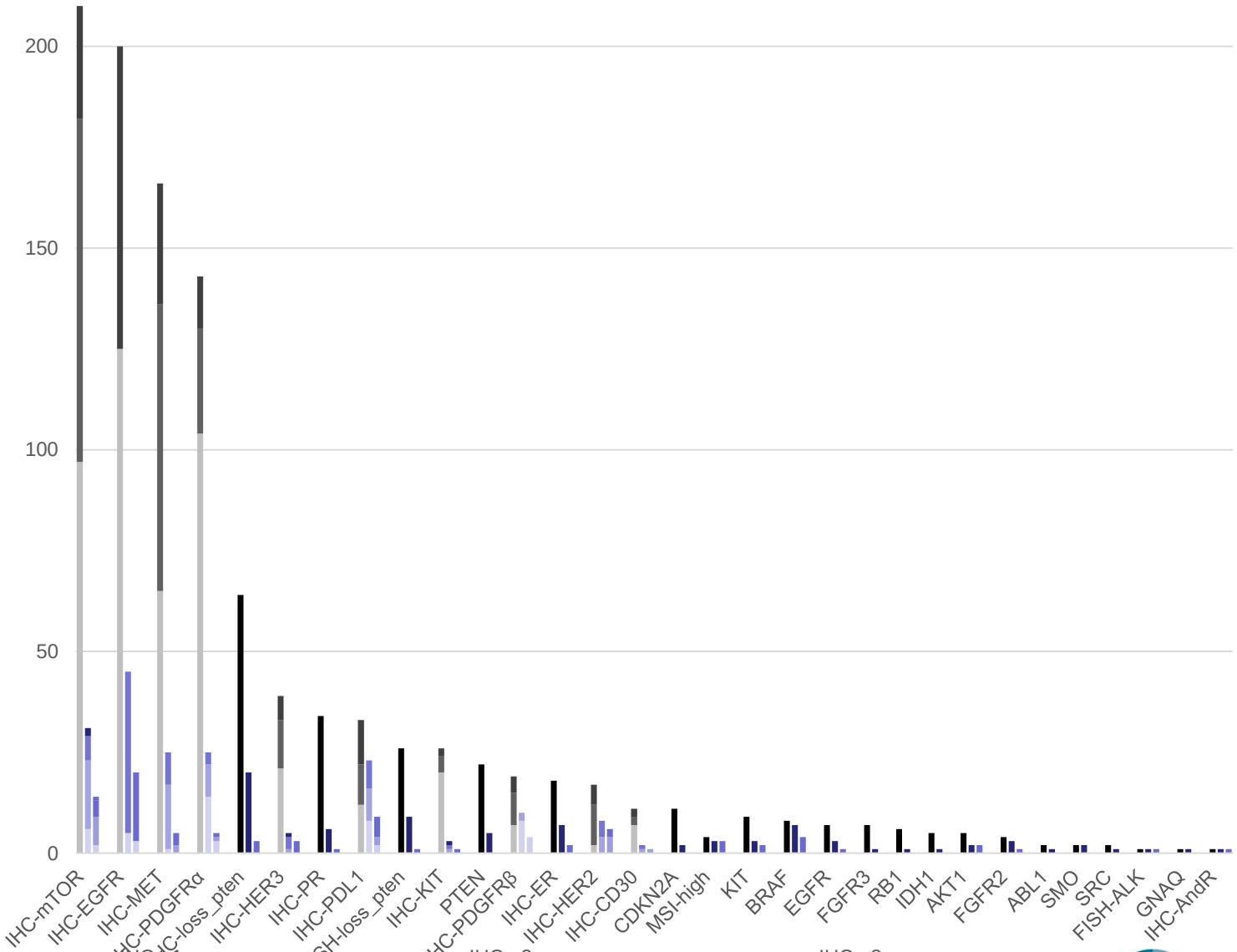
The Challenge of MONDTI



MONDTI: Results for Genetic Alterations with Number of Matched and Received Therapies



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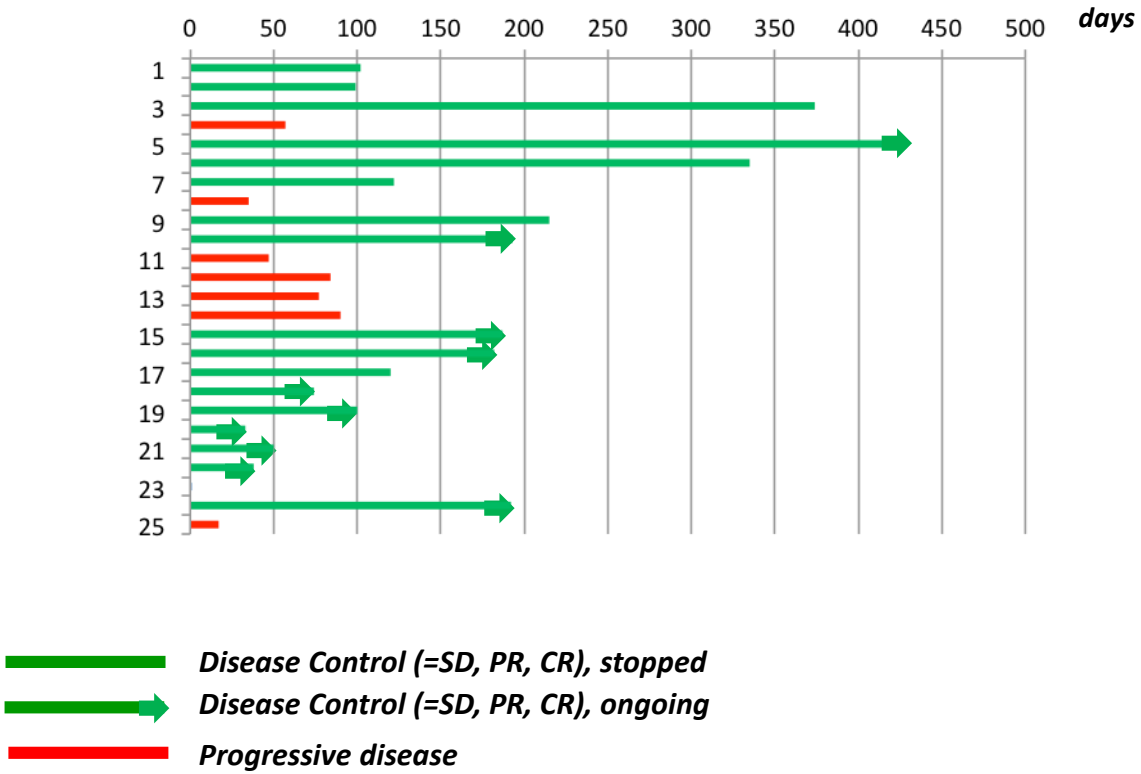
Targeted Therapy: Progression-Free Survival



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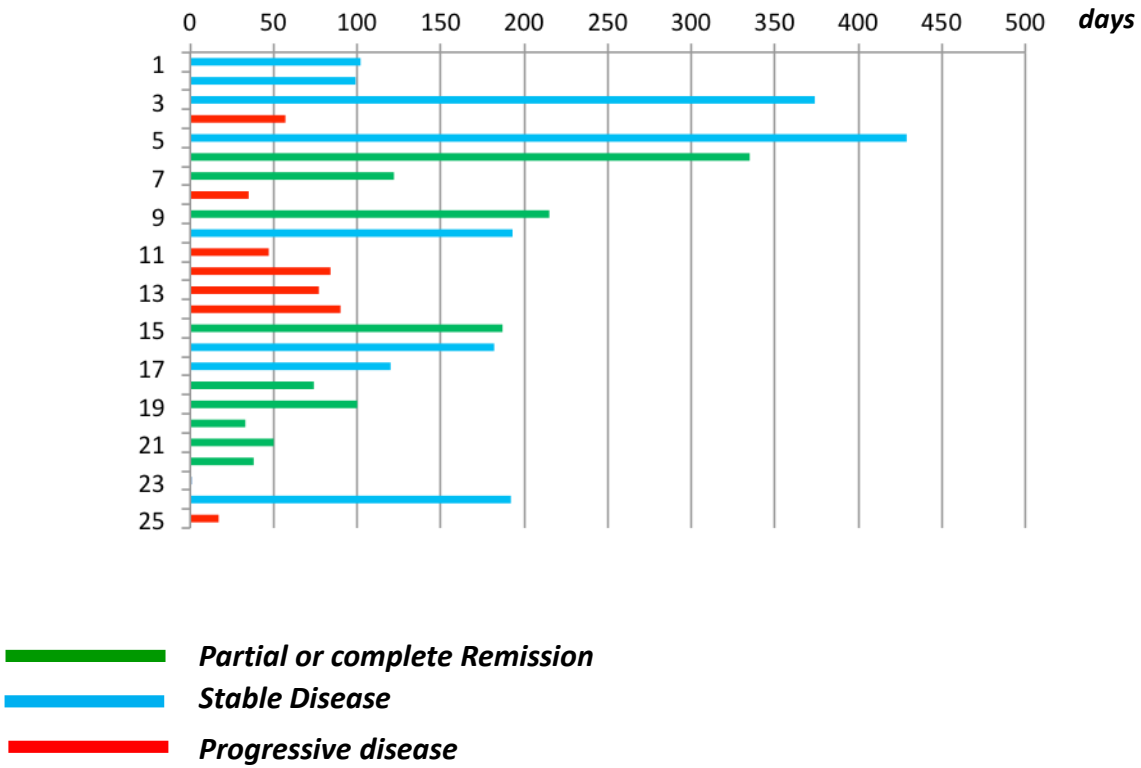
Targeted Therapy: Best Response and PFS



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Differences vs. Other Analyses on Personalized Treatment

- **difference re. disease distribution resulting in different outcomes**

  (e.g. ovarian, breast, renal cancers and sarcomas)

- **difference re. study set-up (e.g. time point of personalized treatment)**

J.J. Wheler et al., Cancer Res. 2016

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EXACT: Examples

Diagnosis	Age (y)	Sex	Target	Drug	Best Response*	PFS (m)
HCC	68	f	EGFR o.e.	Panitumumab	S.D.	13
Sertoli cell tumor	41	m	EGFR o.e. BRAF V600E	Cetuximab + Vemurafenib	S.D.	3.4
fibrolamellar HCC	30	m	EGFR o.e. PIK3CA mut	Cetuximab + Afinitor	S.D.	18
Hepatoides Karzinom	41	m	EGFR	Irinotecan + Cetuximab	P.R.	8.0
CUP	52	f	MET o.e. PR 2+ (IHC)	Crizotinib + tamoxifen	S.D.	4.2
anaplastic thyroid cancer	80	f	BRAF V600E MET o.e. EFGR o.e.	Vemurafenib	C.R.	12
CCC	66	m	EGFR	Cetuximab	S.D.	4.3
Gastric	64	m	Her-2 o.e.	Trastuzumab, Lapatinib	S.D.	16 (ongoing)
SCLC	69	m	EGFR exon 19 del.	Afatinib	P.R.	7 (ongoing)

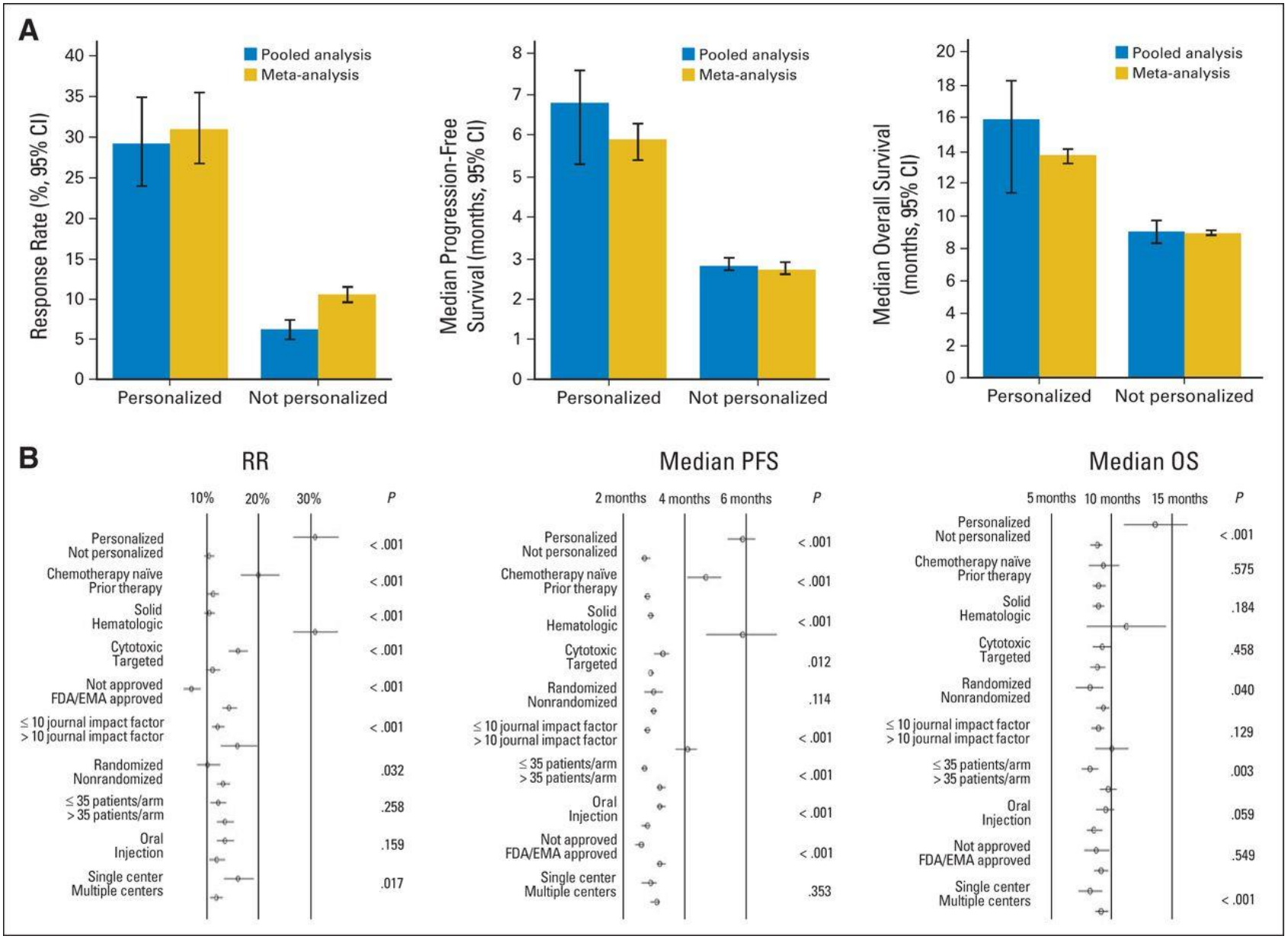
**** Response according to RECIST 1.1***

Challenges Posed by Individualized Medicine

- Common diseases are fragmenting
  - Every disease will be a molecular ‘orphan disease’
  - But many diseases share similar molecular ‘faults’, and will have common therapies
- Small populations of available patients
  - Trials have to find the ‘right’ patients
  - Diagnostics need to be available
  - Small safety datasets for approval
- Privacy and use of tumour samples / marker information
- The target keeps moving
  - Multiple, interdependent molecular pathways and the escape routes
- Science moves much faster than clinical trials
  - Trials slow, expensive, highly regulated, inflexible
- Often require large trials to find the small population who benefit
  - Small studies in selected population may miss those who benefit

Benefit of Personalized Therapy

Maria Schwaederle et al. JCO 2015;33:3817-3825



Further Development of Precision Medicine

- **ASCO: Targeted Agent and Profiling Utilization Registry (TAPUR) – Molecular Data plus Clinical Outcomes in Cancer**
- **AACR: Genomics Evidence Neoplasia Information Exchange (GENIE) – Registry from 7 Cancer –Research Centers**
- **Moffitt and Cancer Center, Tampa: Oncology Research Information Exchange Network (ORIEN) – similar to TAPUR and GENIE, yet clinical trial matching service**

Präzisionsmedizin in der Klinik: Zusammenfassung

- **Das Konzept über Entstehung und Entwicklung maligner Erkrankungen hat sich während des letzten Jahrzehnts radikal verändert.**
- **Molekulare Analysen von Tumoren haben nicht nur neue Targets und Therapieoptionen eröffnet, sondern auch zum Wandel des Konzepts von "Tumorentitäten" beigetragen.**
- **Erste Ergebnisse der Anwendung der Präzisionsmedizin in der Klink sind durchaus kontroversiell, und hängen vom Studiendesign ab.**
- **Die Ergebnisse des CCC Wien zur Präzisionsmedizin sind ermutigend und geben zur Entwicklung weiterer Studien Anlaß.**

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