Challenges in Personalized Cancer Medicine

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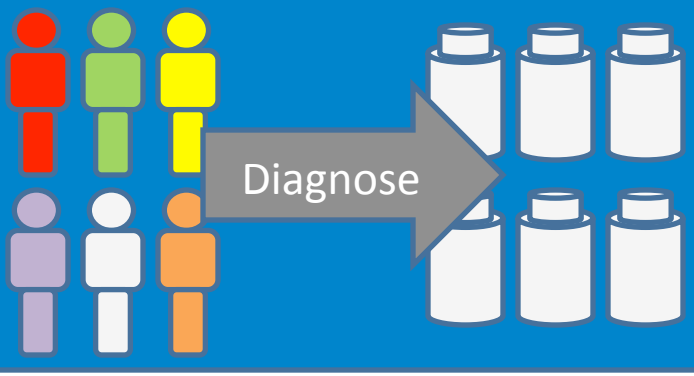
Personalized Cancer Medicine
Expectations and Reality

- **Expectations and Marketing**
  - **Highly effective cancer therapy**
  - **Neglectable side effects**
  - **Higher cost effectiveness**
  - **Reduced attrition rate in clinical development**
- **Reality**
  - **Molecular or immunological targeted therapy is feasible (= personalized medicine?)**
    - **At least in some tumor entities or tumor subpopulations**
  - **Side effects changed in quality but are still an issue**
  - **Complexity of cancer genetics and other "-omics"**
  - **New challenges in translation and clinical development**
  - **Moderate improvement in cancer therapy associated with massively increasing costs**

Zukunftsmarkt
Personalisierte und zielgerichtete Medizin

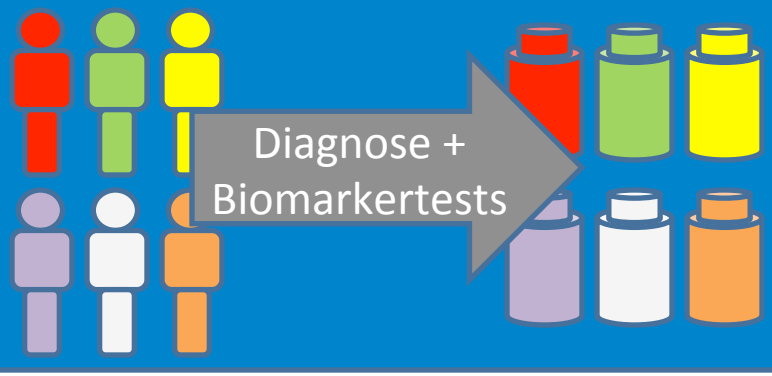
Symptombasierte Medizin

- „one fits all“/Blockbuster-Ansatz,
- geringe Wirksamkeit (nur 40-60%)
- hohe Nebenwirkungsraten
- hohe „Attrition Rates“
- lange Entwicklungszeiten
- hohe Kosten der Medikamentenentwicklung



Personalisierte Medizin

- auf Patientengruppen zugeschnittene Medizin
- effektivere Medikamente
- sicherere Medikamente
- niedrigere Ausfallraten
- bis zu 10 mal kleinere klinische Studien
- geringere Kosten für klinische Studien



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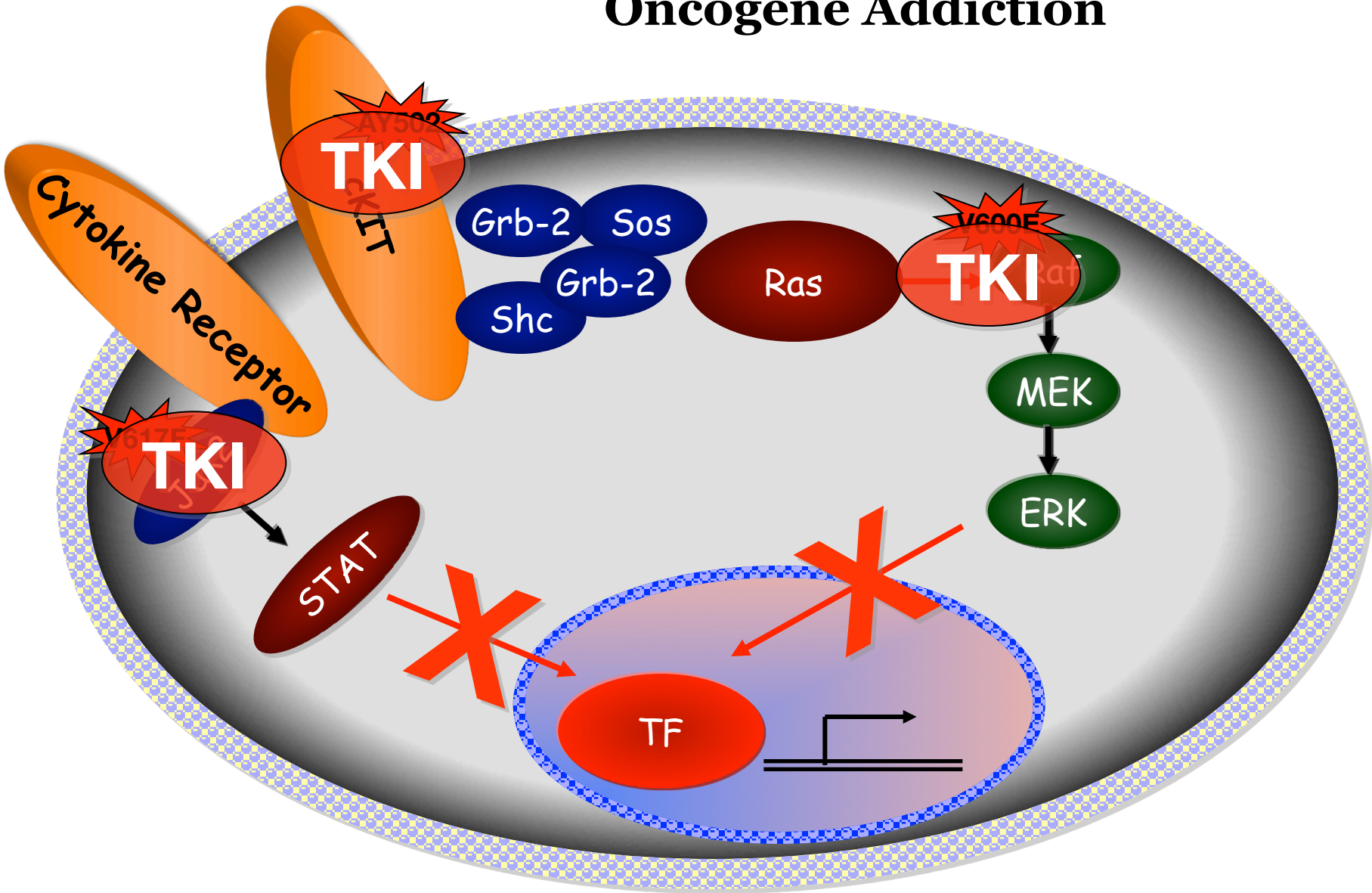
Definition and Rationale

(Tran et al JCO 2012)

- **The US National Cancer Institute defines personalized medicine as „a form of medicine that uses information about a person‘s genes, proteins, and environment to prevent, diagnose, and treat disease“.**
  - **Genetic aberrations exist in human malignancies**
  - **A subset of these aberrations drives oncogenesis and tumor biology**
  - **These aberrations are actionable**
  - **Highly specific anticancer agents are available that effectively modulate these targets (druggable)**
- **Mission and Goals to facilitate PCM**
  - **Enhance the understanding of the molecular mechanisms of cancer**
  - **Accelerate genomic science and technology development**
  - **Translate genomic data to improve cancer prevention, early detection, diagnosis and treatment**

Activating Mutations: Constitutive (Oncogenic) Signal Transduction = Oncogene Addiction



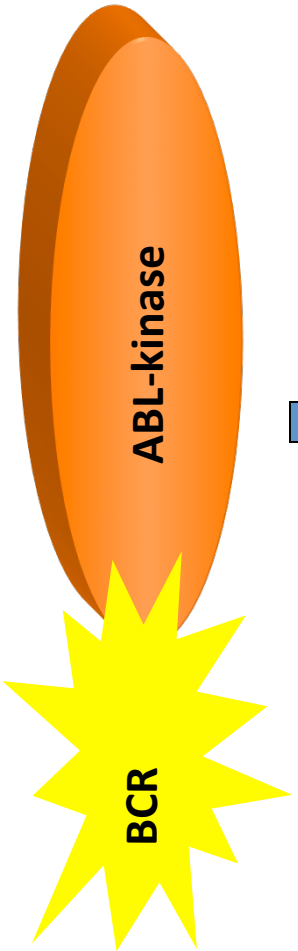
Kinase Inhibitors in Clinical Use

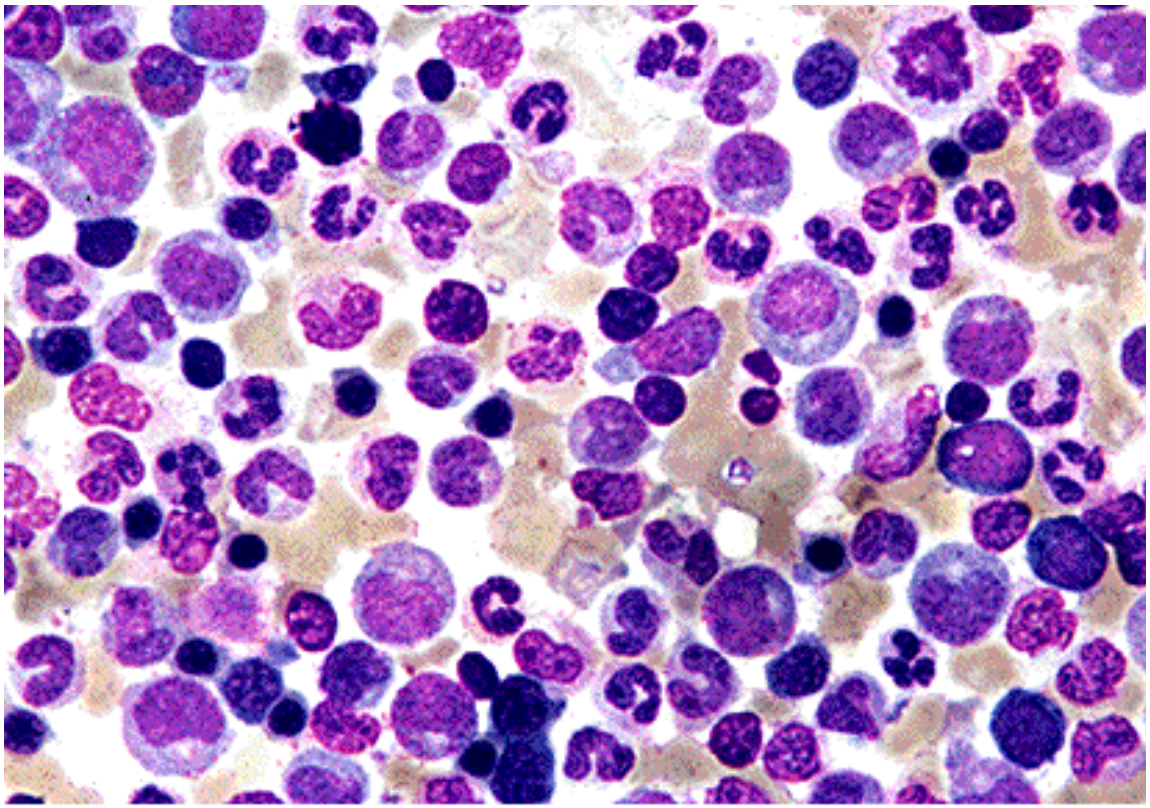
AML	FLT3/ITD	→ AC220, PKC412, MLN518, CEP-701, su5416, Sorafenib, Sunitinib
CEL	FIP-PDGFRA	→ **Imatinib**, Nilotinib, Dasatinib, Sorafenib
CML	Bcr-Abl	→ **Imatinib**,**Dasatinib**,**Nilotinib**, Bosutinib
GIST	cKit,PDGFRA	→ **Imatinib**, **Sunitinib**, Nilotinib, Dasatinib
IMF/PV/ET	JAK1/2	→ **Ruxolitinib**, Pacritinib, CYT387, TG101
Liver	VEGFR	→ **Sorafenib**
Lung	EGFR	→ **Erlotinib**, **Gefitinib**
	ALK	→ **Crizotinib**
Mamma	HER-2	→ **Lapatinib**
Melanoma	B-RAF	→ **Vemurafenib**
Kidney	VEGFR	→ **Sunitinib**, **Sorafenib**, **Pazopanib**
	mTOR	→ **Temsirolimus**, **Everolimus**
Pancreas	EGFR	→ **Erlotinib**
PNET	mTOR	→ **Temsirolimus**
Thyroid	VEGFR,EGFR, RET	→ **Vandetanib**

green = licensed

Chronic Myeloid Leukemia (CML)

Bcr-Abl = constitutively activated signal transduction



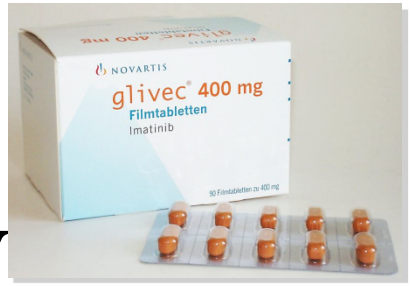


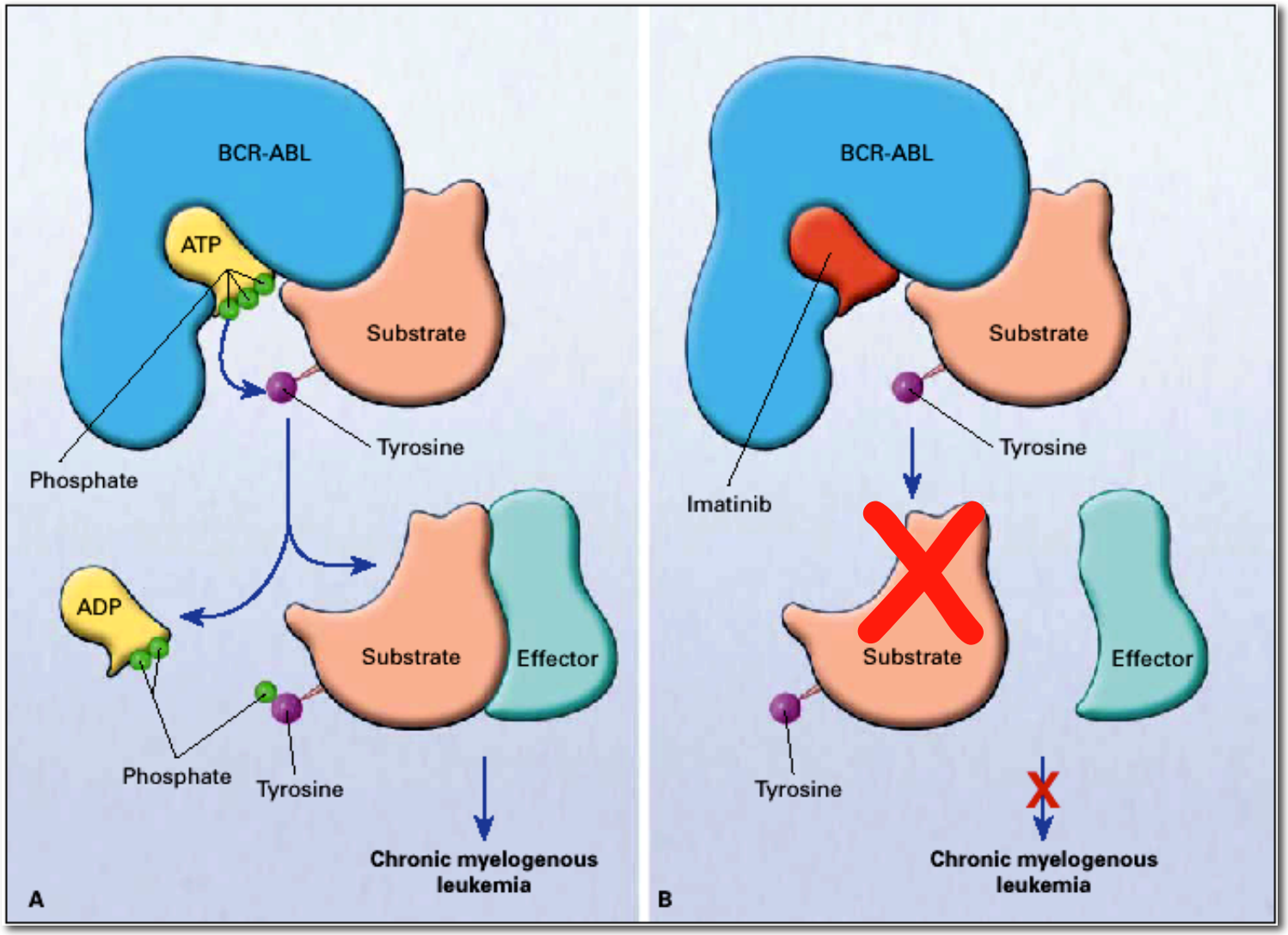
Chronic myelogenous leukemia Bone marrow aspirate

Bcr-Abl sufficient for induction of leukemia:

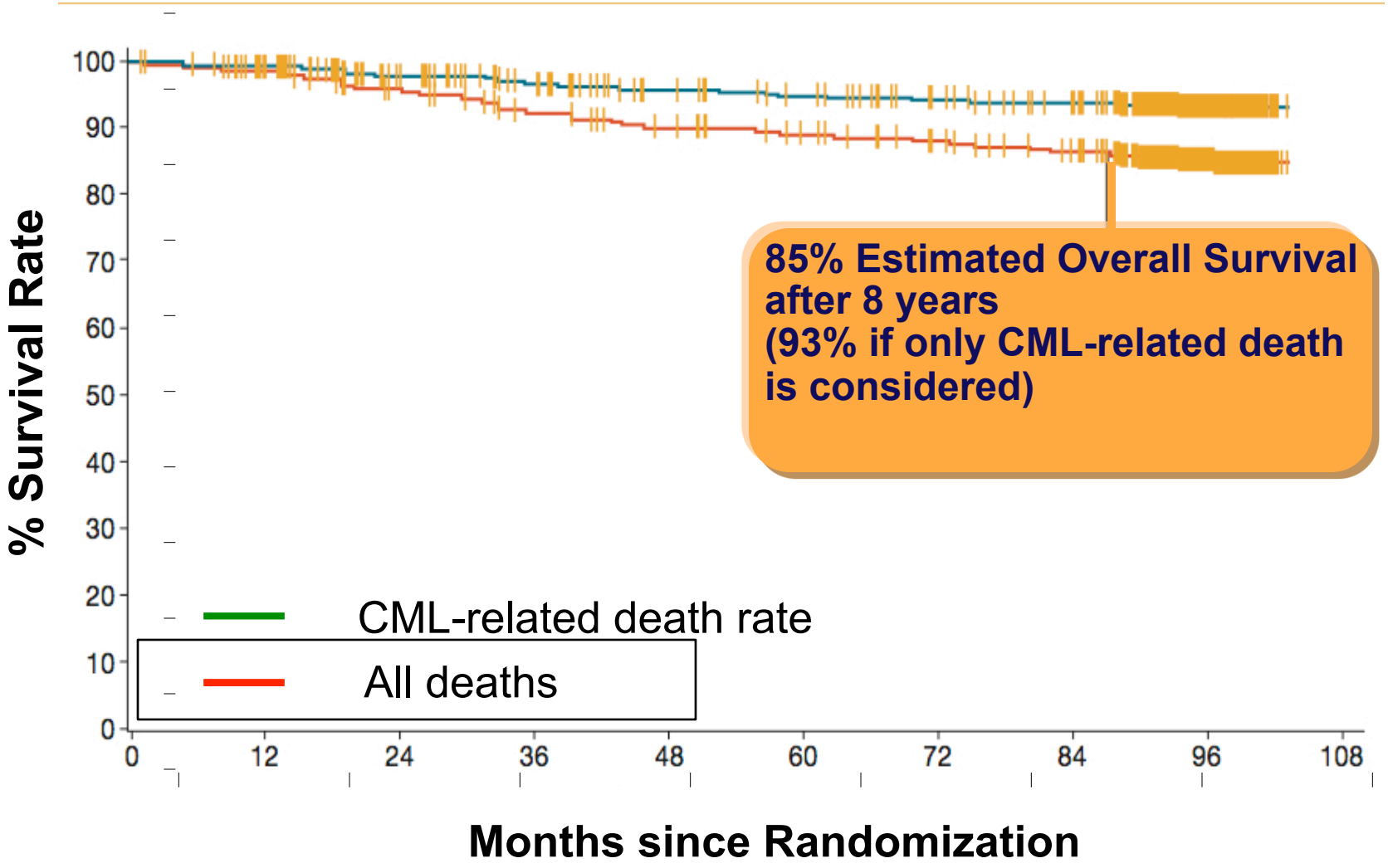
„single hit oncogene“

Imatinib (Glivec): ATP-competitor, disables kinase activity



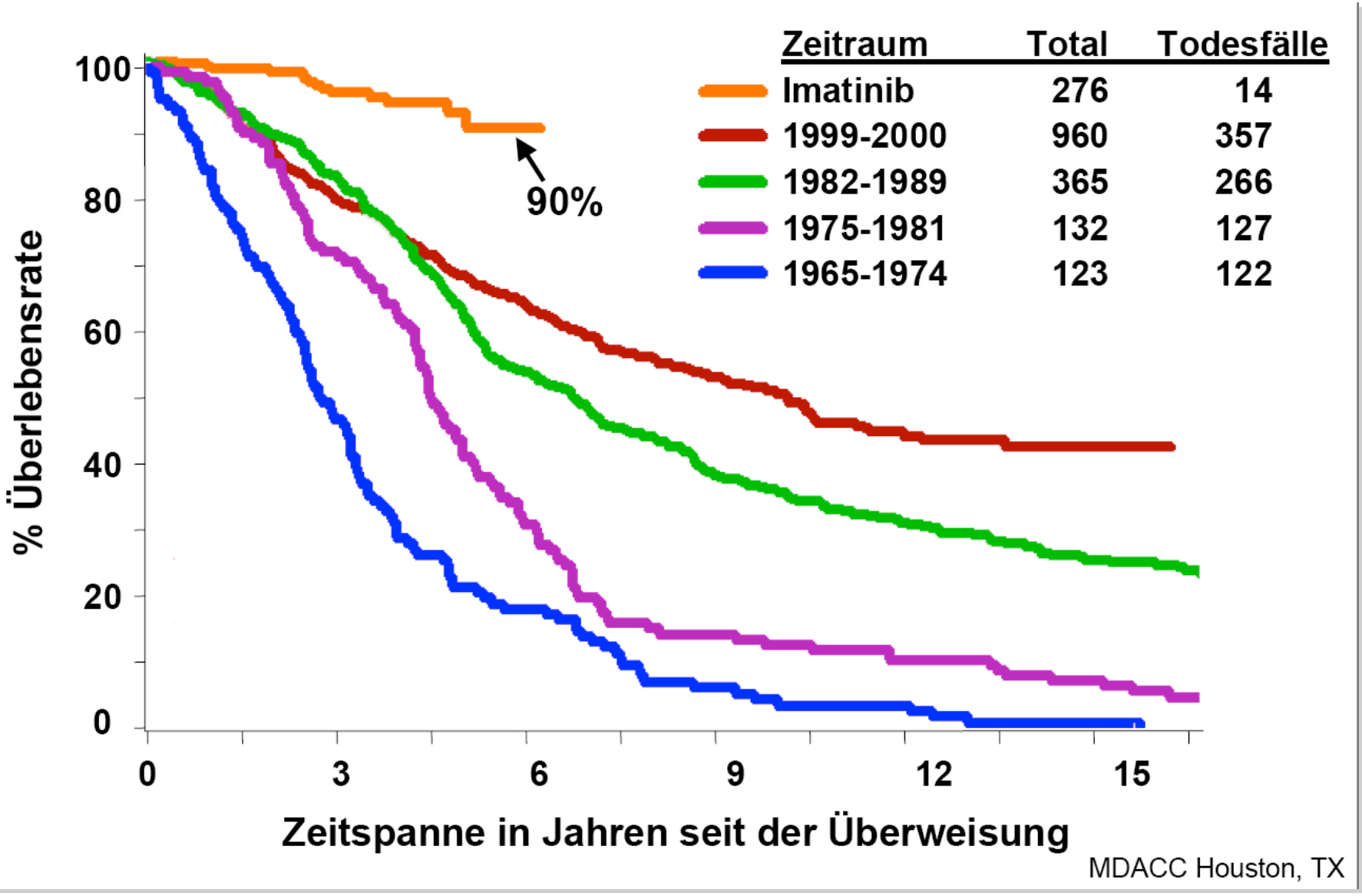


IRIS 8 Years Update: Overall Survival Rate (ITT)

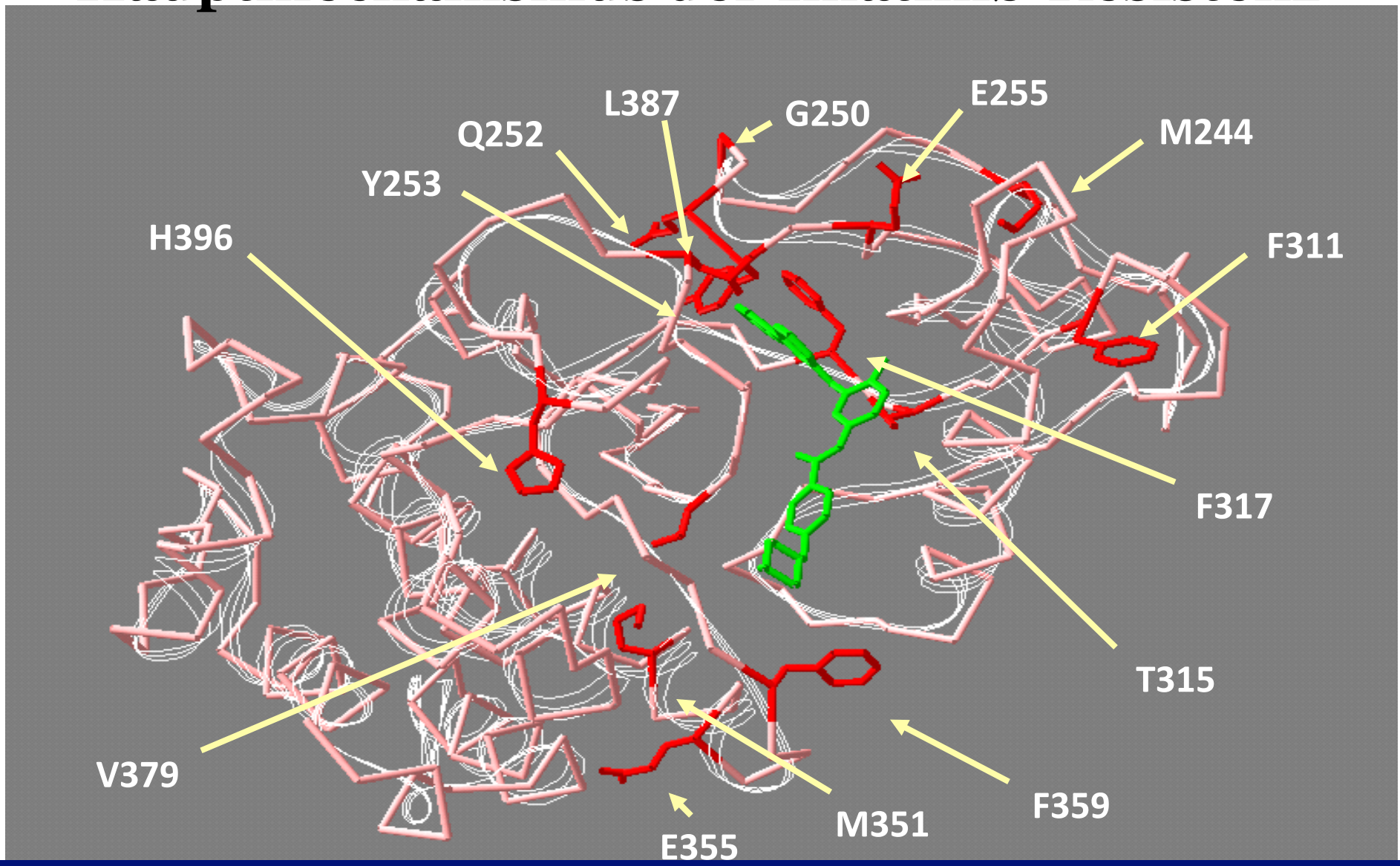


Deininger et al.; Poster Präsentation ASH 2009

Improved prognosis of CML



Bcr-Abl Punktmutationen: Hauptmechanismus der Imatinib-Resistenz



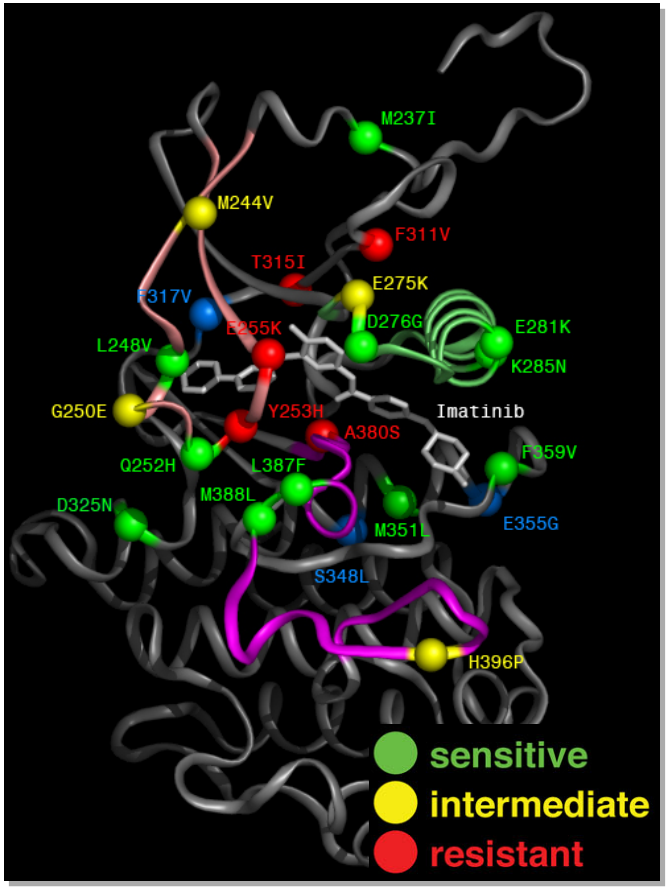
Gorre et al. 2001; von Bubnoff et al. 2002; Branford et al. 2002; Hochhaus et al. 2002; Hofmann et al. 2002; Roche-Lestienne et al. 2002; Shah et al. 2002

Novel BCR-ABL kinase inhibitors suppress all known imatinib resistant mutants

Mutation	Imatinib	Sprycel Dasatinib	Tasigna Nilotinib	SKI-606	INNO-406 NS-187	MK-0457 VX-680
G250E	✗	✓	✓	✓	✓	?
Y253F	✗	✓	✓	✓	✓	✓
Y253H	✗	✓	✓	✓	✗	?
E255K	✗	✓	✓	✓	✓	✓
E255V	✗	✓	✓	✓	✓	?
T315I	✗	✗	✗	✗	✗	✓
H396P	✗	✓	✓	✓	✓	✓

Gorre et al. Science 2001; von Bubnoff et al. Lancet 2002; Weisberg et al. Cancer Cell 2005; Shah et al. Science 2004; Golas et al. Cancer Research 2003; Soverini et al. EHA 2006; Kimura et al. Blood 2005; Tao et al. ASH 2006 #2179; Carter et al. PNAS 2005

Prediction of Resistance Pattern in Advance of Clinical Application?



?

?

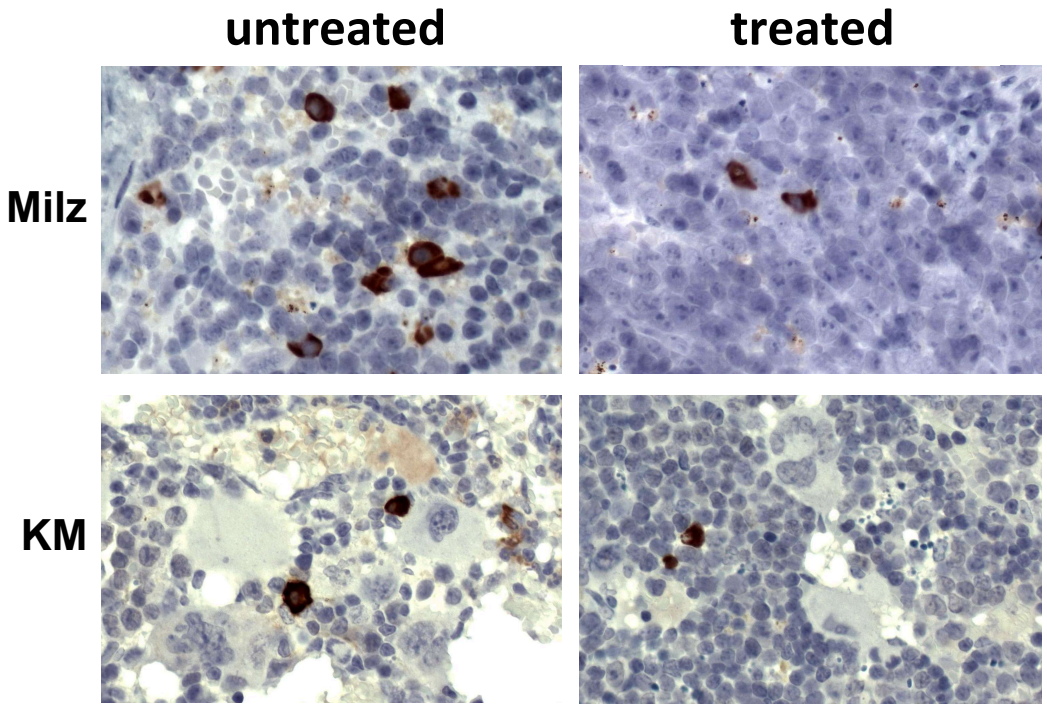
imatinib

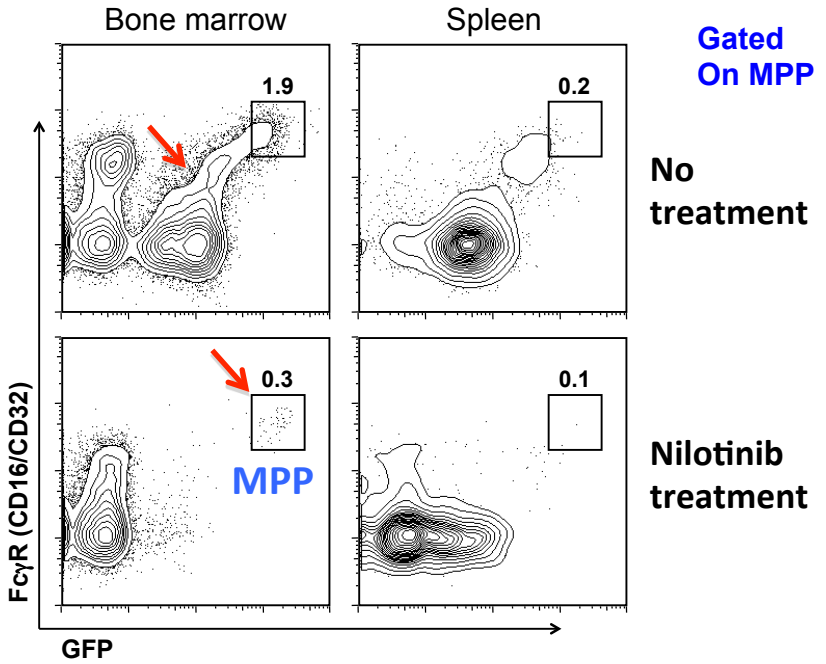
compound I

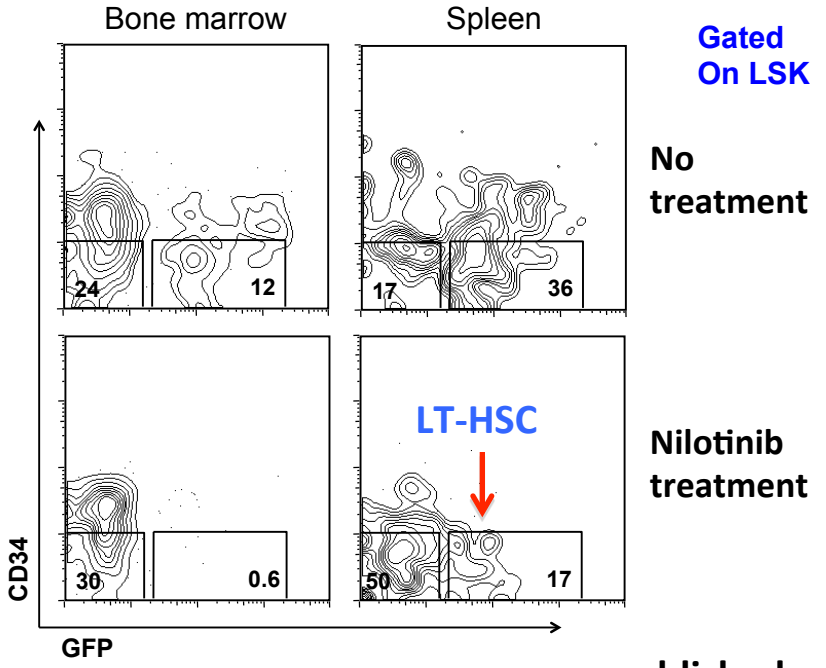
compound II

von Bubnoff et al.
Blood 2005

Persistance of CML Progenitors (LSC?) in CML Mouse Model







unpublished

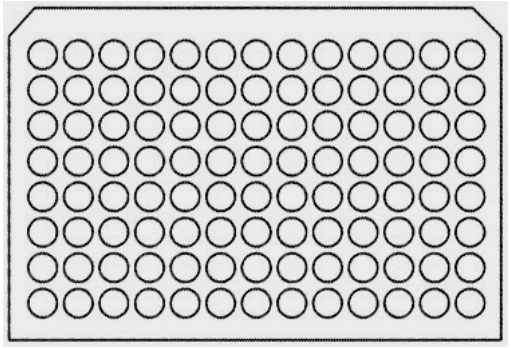
Zelllinien-basierte Methode zur Vorhersage von Resistenzmutationen gegenüber therapeutisch eingesetzten Kinaseinhibitoren

Ba/F3
Bcr-Abl

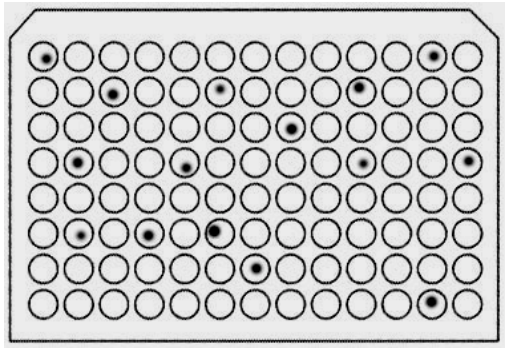
↓

Flüssigkultur
96-Lochplatte

Zugabe von Inhibitor

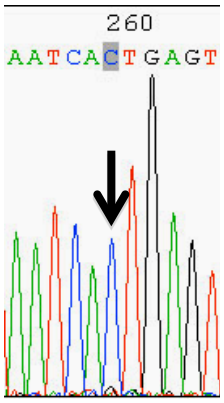


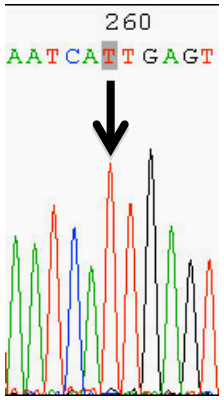
8-42 Tage ↓



Resistente Klone

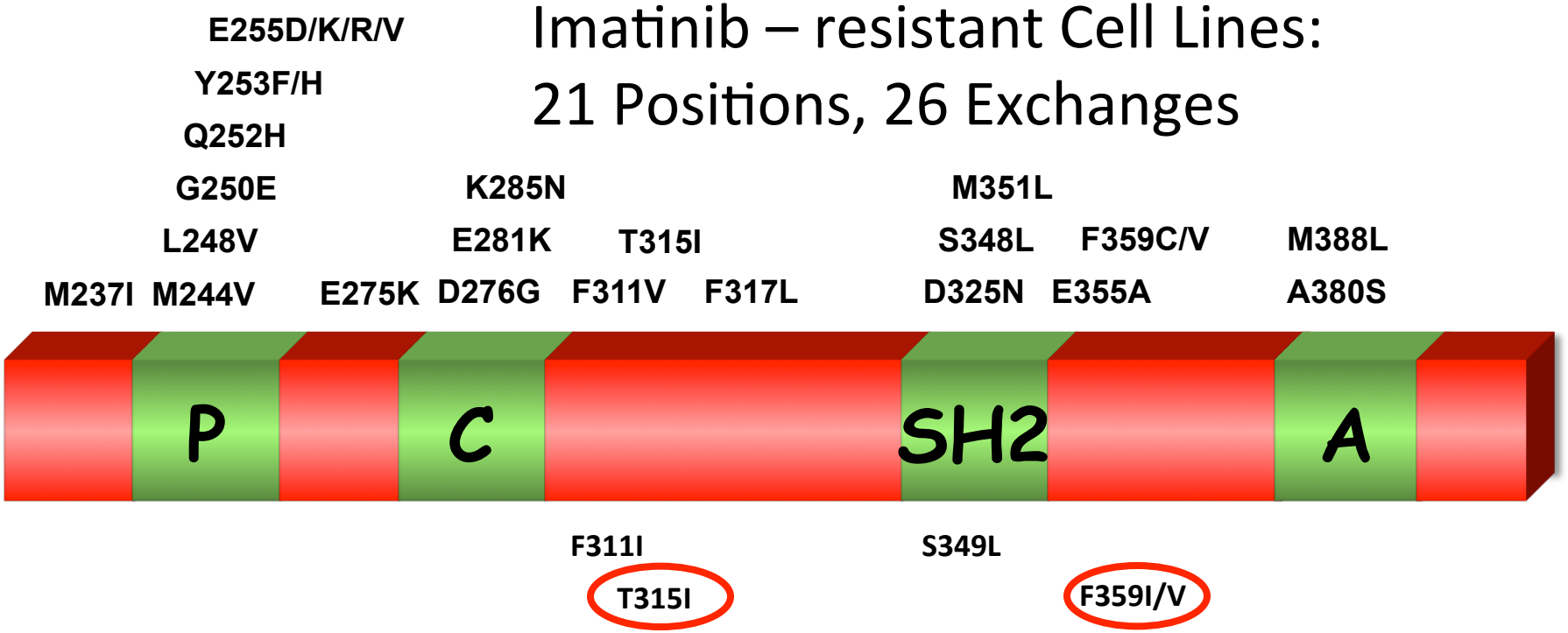
Sequenzieren Abl Kinasedomäne





von Bubnoff et al.
Cell Cycle 2005

CML: Bcr-Abl Resistance Spectrum



Imatinib – resistant Cell Lines:
21 Positions, 26 Exchanges

Q252H
Y253H
E255K/V

Nilotinib – resistant Cell Lines:
7 Positions, 8 Exchanges

von Bubnoff et al. Blood 2005, 2006

Nilotinib Efficacy According to Baseline BCR-ABL Mutations in CML-CP

Type of Newly Detectable Mutation During Nilotinib Therapy	
Imatinib-Resistant Patients	N = 202 n (%)
E255K/V	13 (6)
T315I	13 (6)
F359C/V	9 (4)
G250E	7 (3)
Y253H	7 (3)

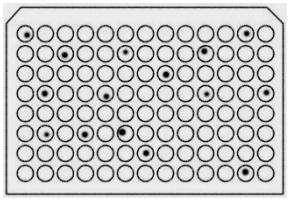
* Patients with multiple mutations are counted in each category

Hochhaus et al. Blood. 2008;112(11):Abstract 3216. Poster presentation at ASH 2008

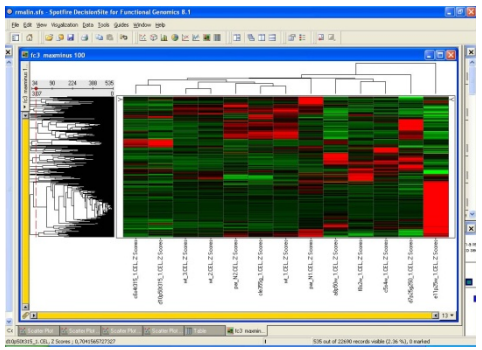
Andreas Hochhaus, Jena

Mechanismen der Behandlungsresistenz und Transformation bei malignen Erkrankungen

Klinische Phase I/II Studie

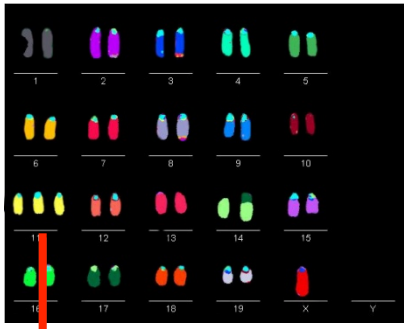


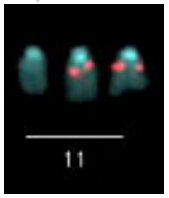
in vitro



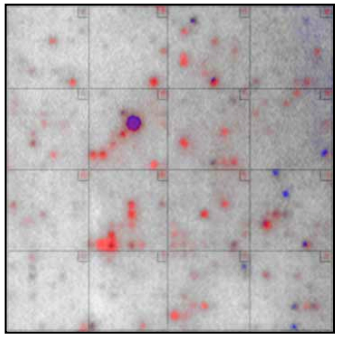
Maus-modell

- Genexpression
- Sequenzierung
- Phosphoproteom
- Zytogenetik

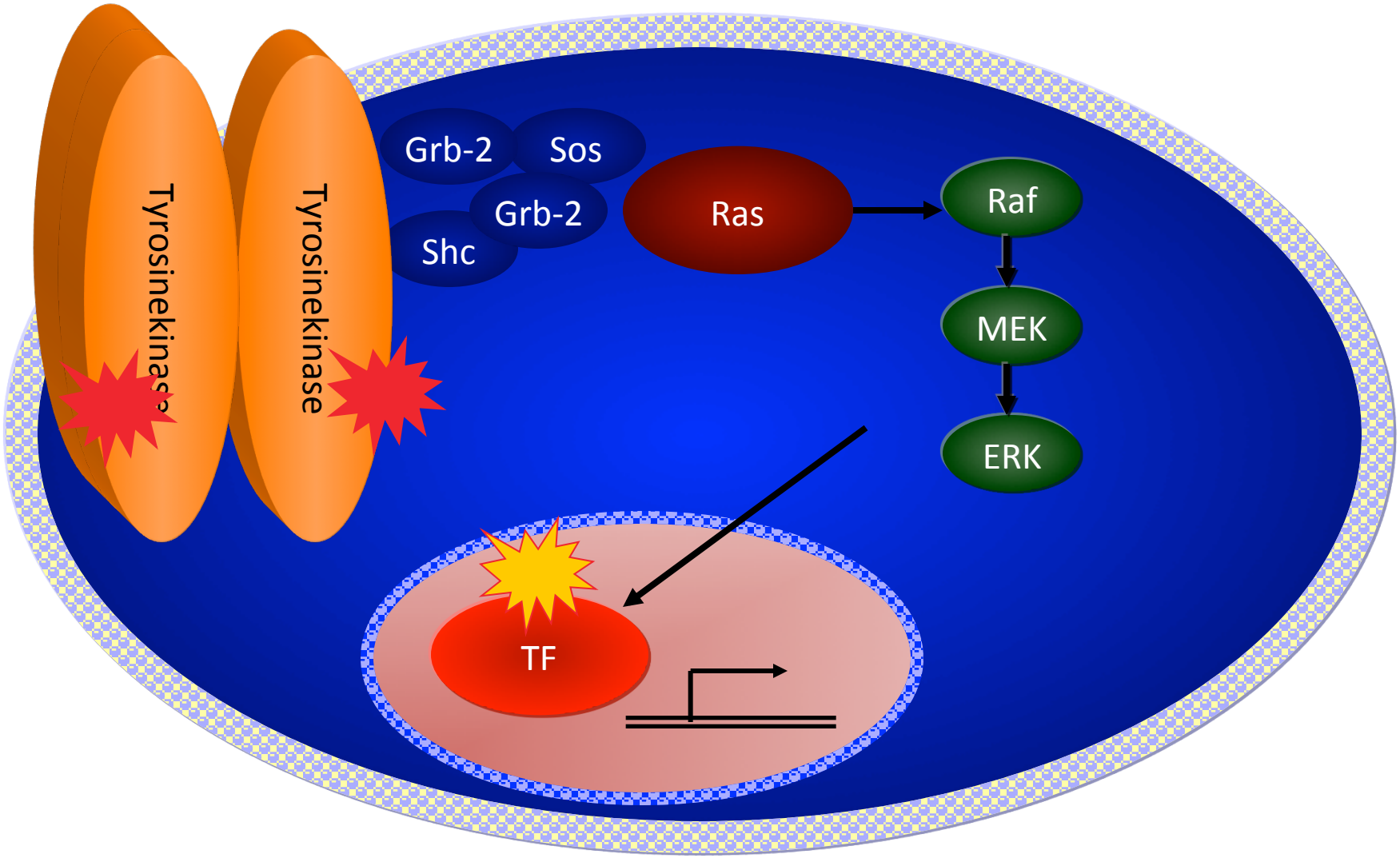




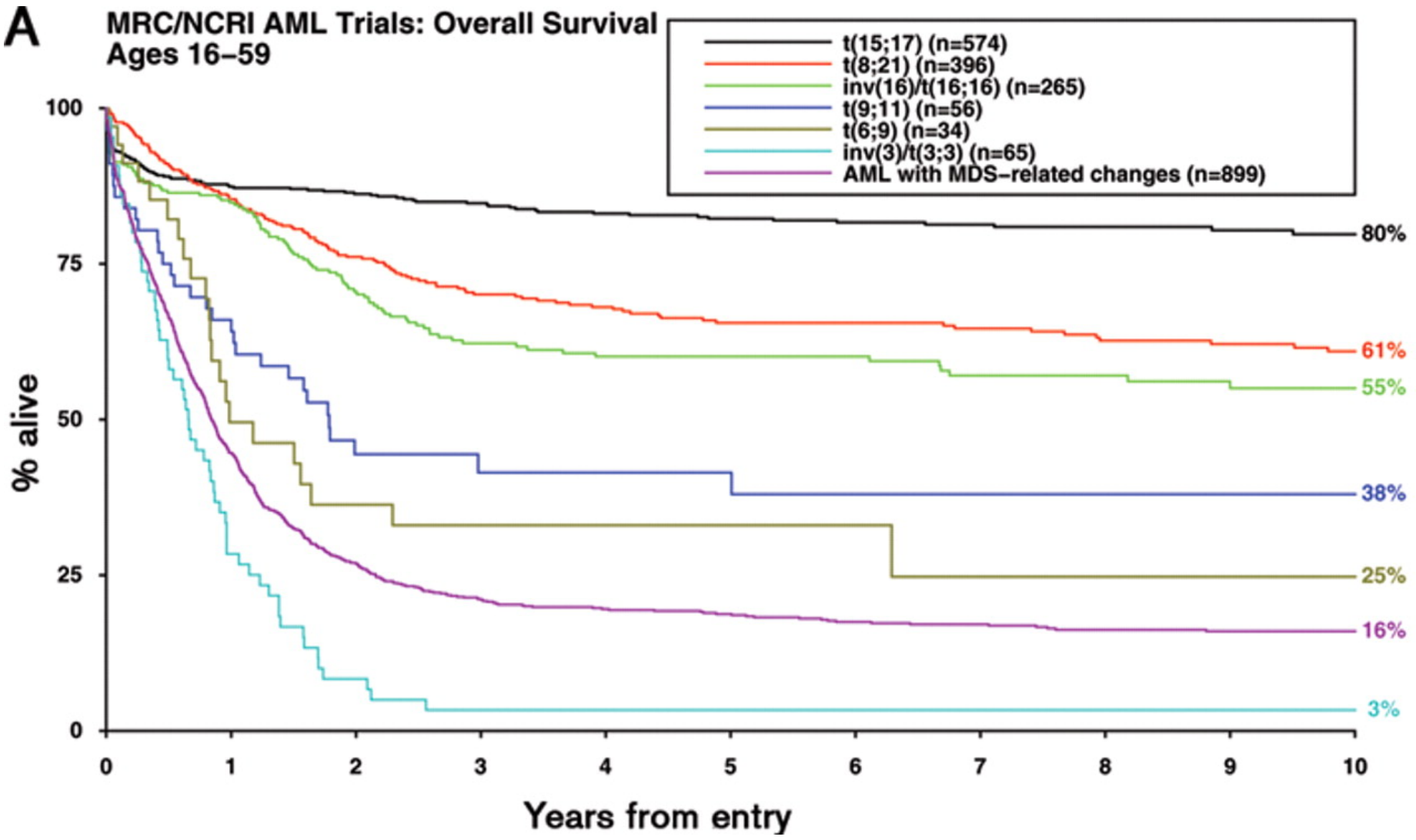
Klinische Samples



Oncogenic Mechanisms in Acute Myeloid Leukemia

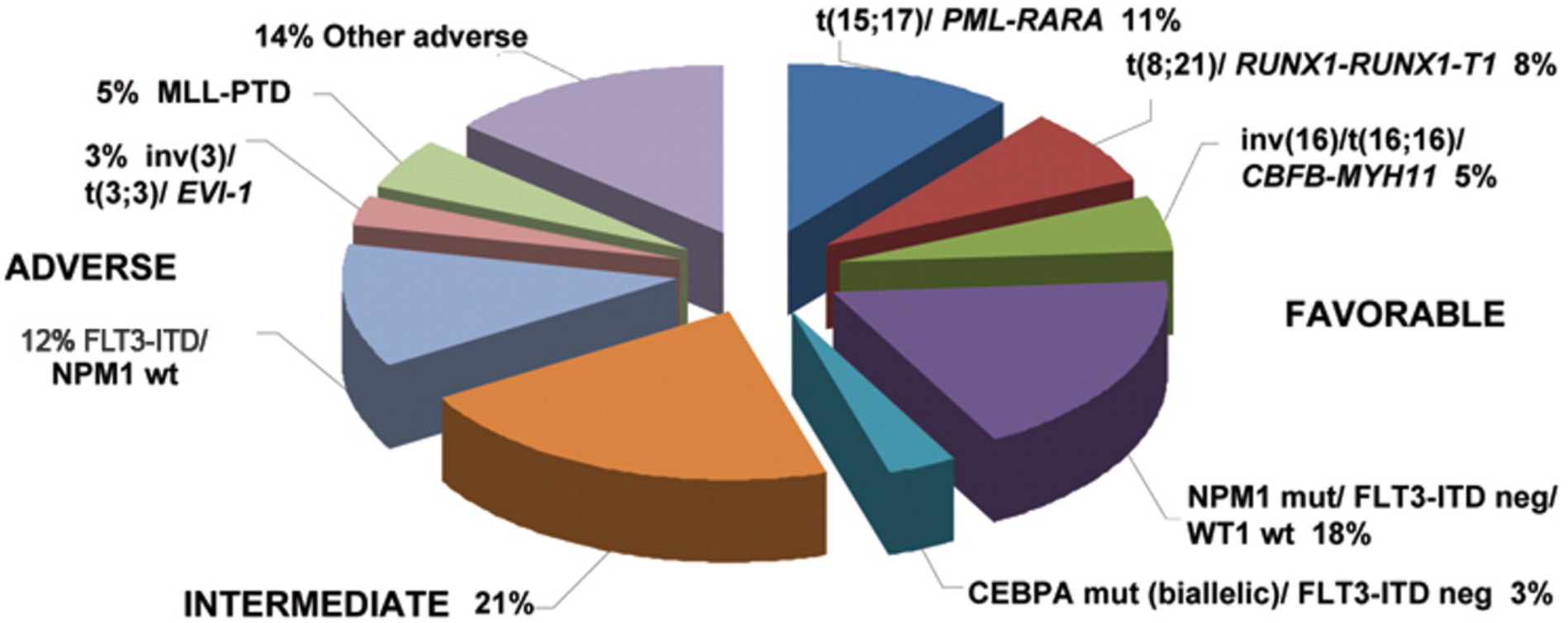


Impact of karyotype on outcome in younger adults with AML



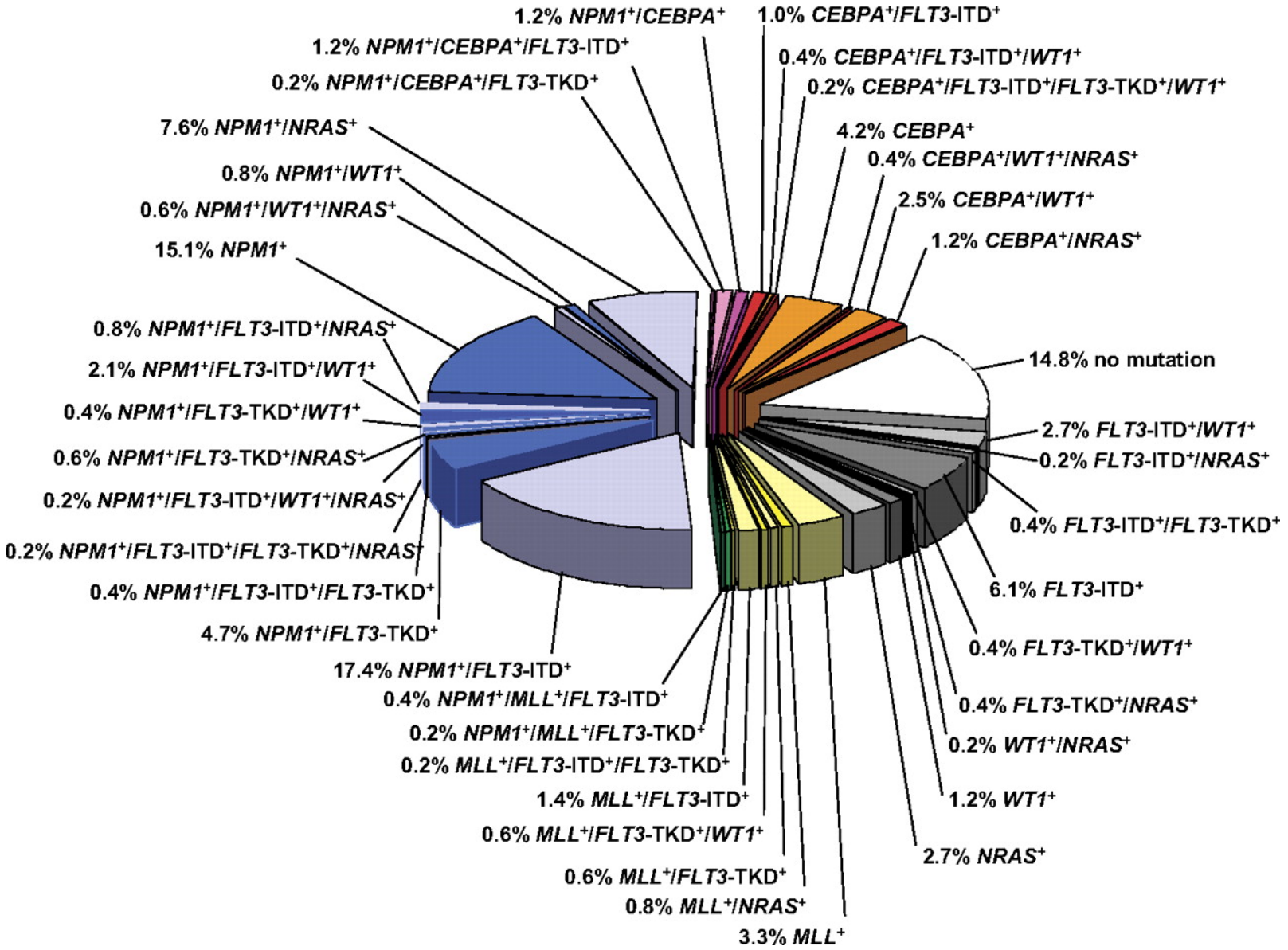
Grimwade, D. et al. Hematology 2009

Frequency of prognostically relevant molecular and cytogenetic subgroups of AML arising in younger adults



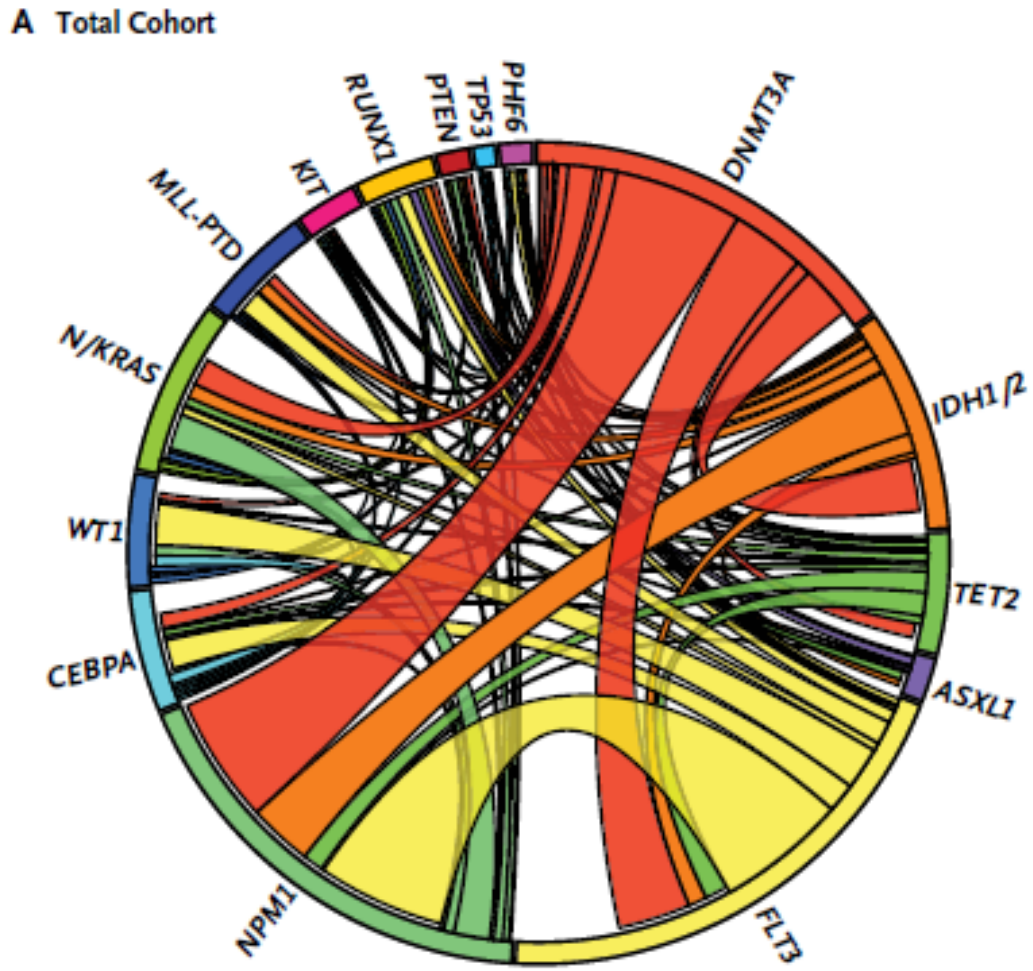
Grimwade, D. et al. Hematology 2009

Pie chart illustrating the molecular heterogeneity of cytogenetically normal AML based on mutations in the NPM1, CEBPA, MLL, FLT3 (ITD and TKD mutations at codons D835 and I836), NRAS, and WT1 genes



Dohner, H. et al. Blood 2010

Mutational Complexity of Acute Myeloid Leukemia (AML)



Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

Patel et al N Engl J Med 2012;366:1079-89

Mutational Complexity of AML

- Molecular profiling of AML led to significant advances in pathobiology
- Definition of prognostically relevant subgroups of AML patients
- Current therapeutic strategy still based on conventional chemotherapy and stem cell transplantation in high risk patients
- Multiple potentially druggable targets in small subpopulations
- Disappointing results of early clinical trials using single targeting agents
- Clinical trials with optimized compounds and in combination are in progress

Targeted Anticancer Therapies (Solid Tumors)

- **Molecular defined subpopulations:**
  - **HER2: Trastuzumab, Lapatinib and breast cancer, gastric cancer**
  - **EGFR: Erlotinib, Gefitinib in non-small cell lung cancer (activating EGFR-mutations)**
  - **Crizotinib and NSCLC (alk-translocation)**
  - **Vemurafenib and melanoma (b-raf mutation)**
  - **PARP inhibitors and BRCA mutations**
- **Targeting more common oncogenic mechanisms:**
  - **Cetuximab and CRC, SCCHN, NSCLC**
  - **Bevacizumab mCRC, ovarian cancer**
  - **Ipilimumab and melanoma**
  - **PI3K and mTOR inhibitors**

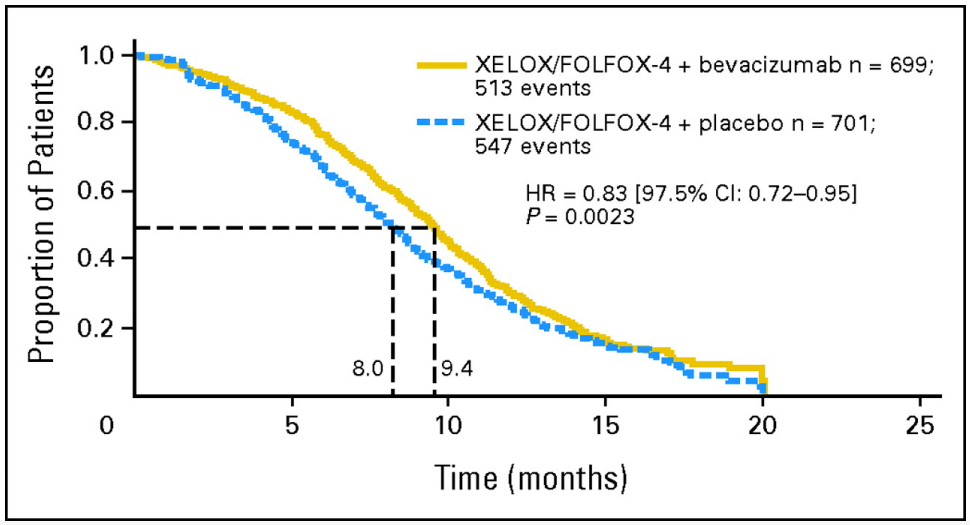
Well established targeted therapies and associated costs

Drug	Approximate cost per QALY
Trastuzumab	$ 50,000 – 70,000 in metastatic breast cancer
Bevacizumab	$ 100,000 in mCRC; 50,000 in NSCLC
Erlotinib	$ 37,000 in NSCLC
Sunitinib	$ 50,000 in mRCC
Rituximab	$ 50,000 in NHL
Imatinib	$ 45,000 in CML

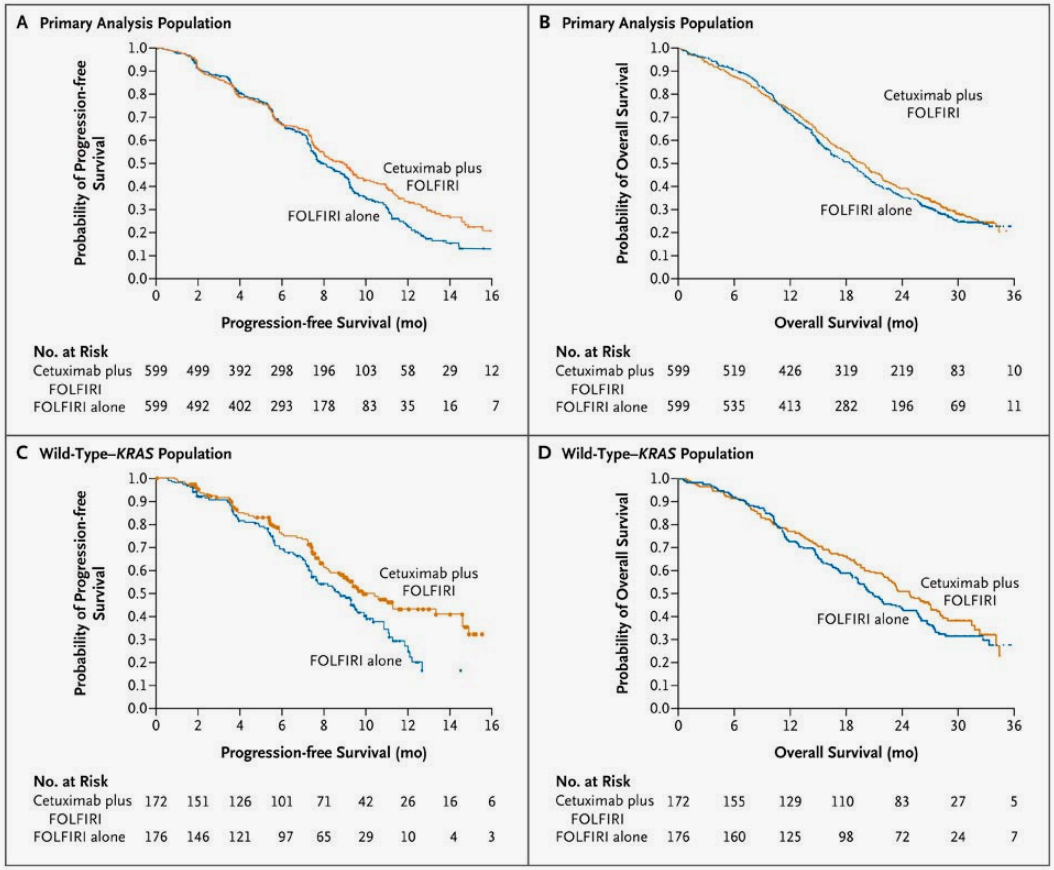
Nature Review Clinical Oncology 9:98, 2012

Predictive Biomarkers

- Prognostication of therapeutic success
- Negative predictive markers
  - Primary resistance
- Mechanisms of secondary resistance
  - Inhibition of drug binding/ interaction
  - Activation of alternative signaling pathways



Targeted Therapy (a-VEGF, a-EGFR) in Colorectal Carcinoma

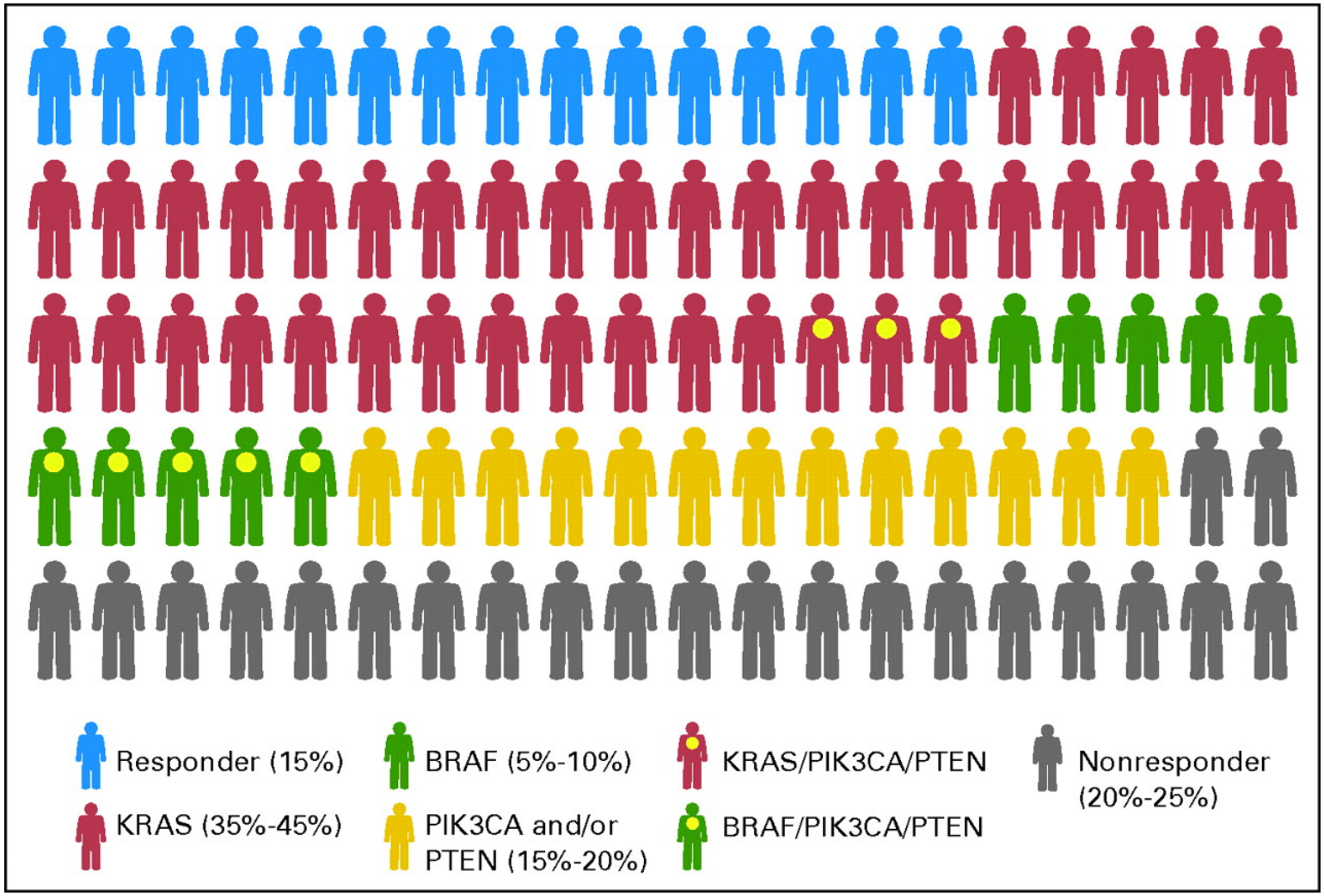


Predictive biomarkers:

For antiangiogenetic therapy not available

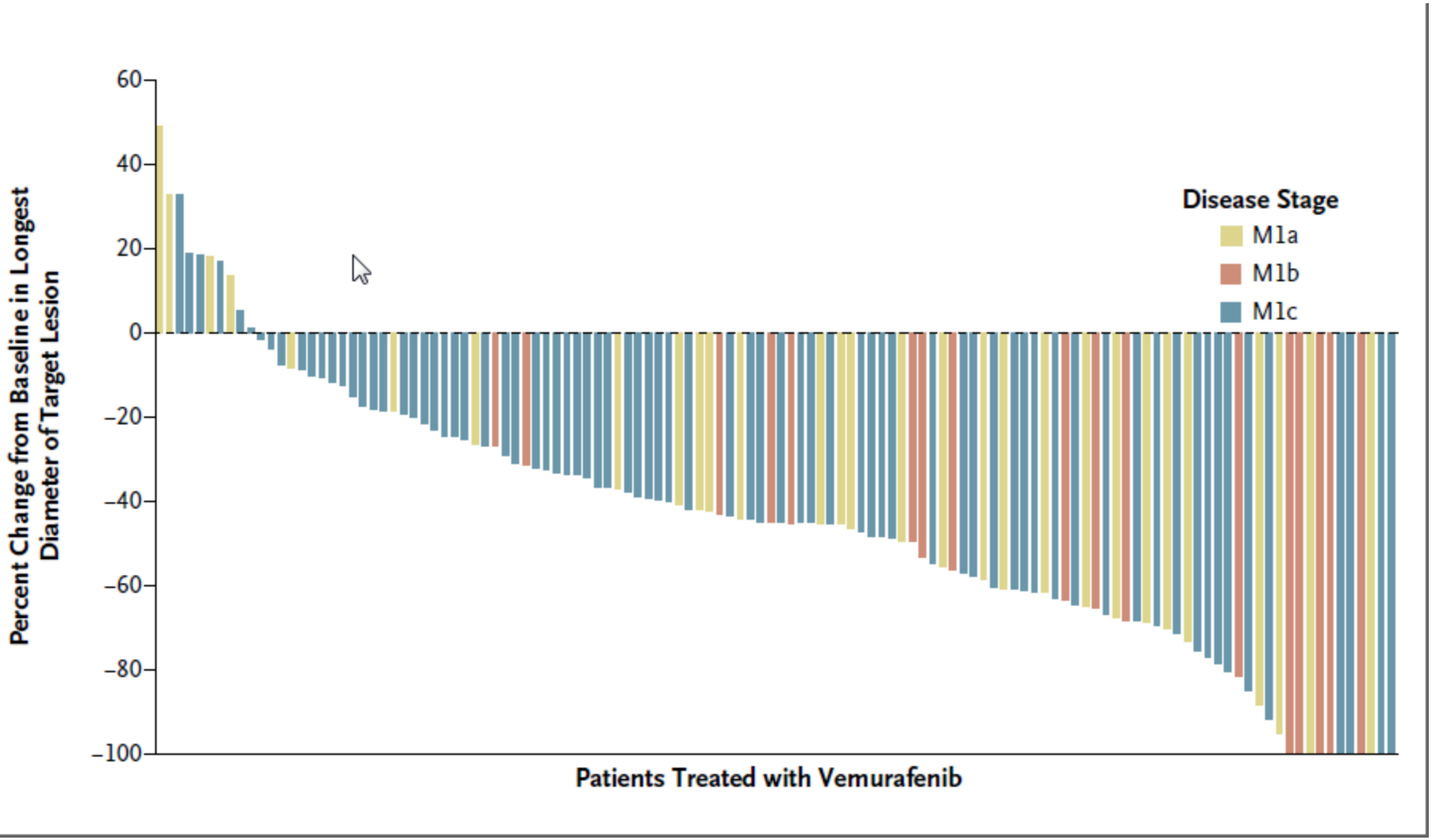
For anti-EGFR therapy only negative prediction for k-ras mutation

Graphic representation of a cohort of 100 patients with colorectal cancer treated with cetuximab or panitumumab

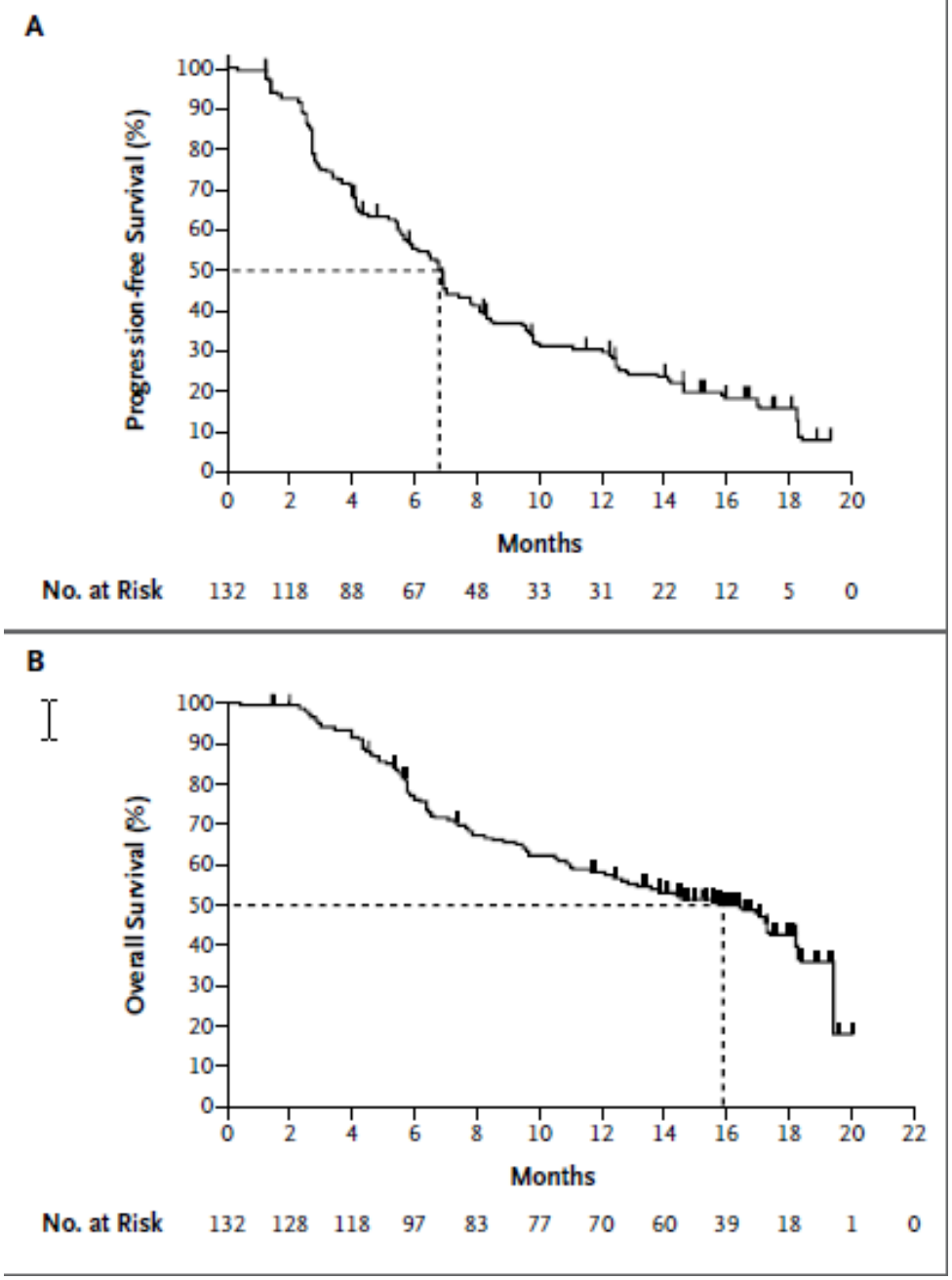


Bardelli, A. et al. J Clin Oncol; 28:1254-1261 2010

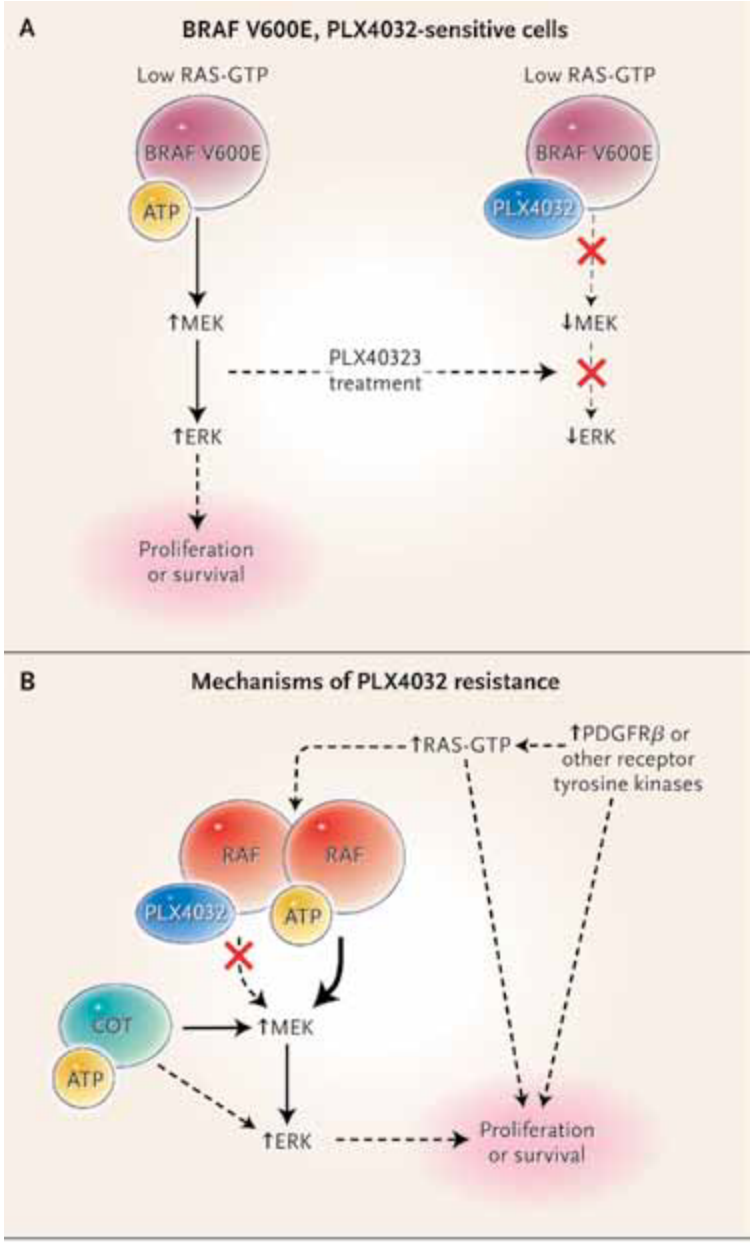
Targeted Therapy (Vemurafenib) in Malignant Melanoma (B-RAF Mutated)



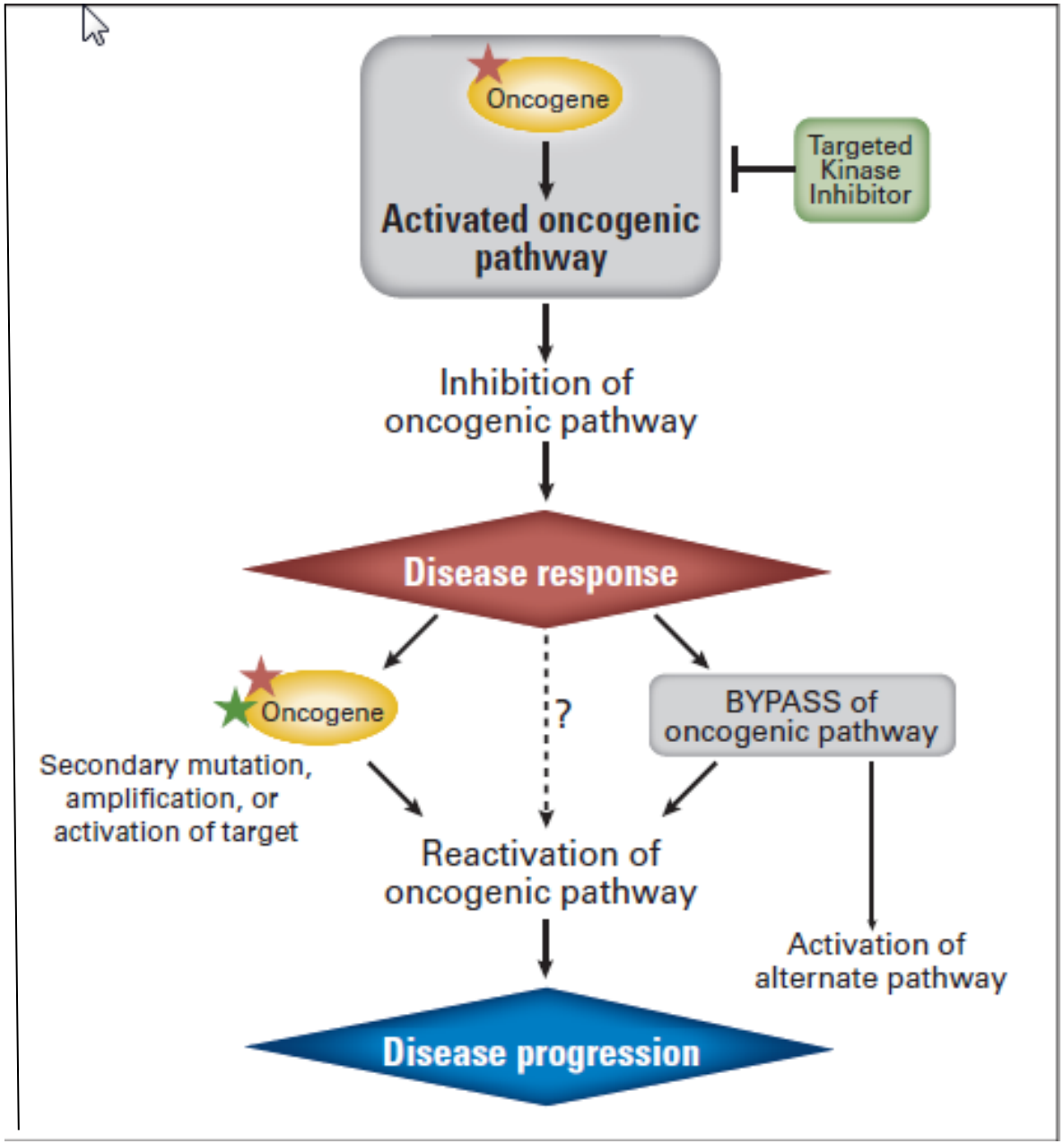
Sosman et al N Engl J Med 2012;366:707-14.



Sosman et al N Engl J Med 2012;366:707-14.



Novel Mechanism of Resistance against Vemurafenib in b-raf mutated malignant melanoma



Wagle et al, JCO 2011

Cancer Genomics – Promises and Limitations Technology

- **Whole Genome Sequencing**
  - **First generation (Sanger) sequencing**
    - **Read lengths of up to 1,000 base pairs**
    - **Resulted in completion of the Human Genome Project ($ 2billion, took a decade to complete)**
    - **Limitations: High cost and low throughput**
  - **Next generation sequencing**
    - **Improved cost and throughput**
    - **Short read length**
    - **Significant data storage and interpretation requirements**
  - **Third generation sequencing technologies**
    - **High accuracy, run time is short, potentially allowing for real time clinical application**
    - **$1000 genome sequencing within reach**

Tran et al, JCO 1012

Cancer Genomics – Promises and Limitations Technology

- **Targeted genome sequencing**
  - **Whole exome sequencing**
  - **Cancer genome (genes potentially involved in tumor biology)**
  - **Increased coverage of areas of interest**
- **Cancer genotyping**
  - **Mutation genotyping (recurrent mutations involved in certain cancer types)**
  - **SNP genotyping**
  - **High-throughput genotyping platforms, consisting of mulitplexed assays and microarrays**
  - **Limited to known genetic alterations**
- **Bioinformatics**

Cancer Genomics – Promises and Limitations Discovery

- Sequenced cancer genomes
  - Discovery of new, clinically relevant mutations
- Epigenetic aberration in cancer
- Gene expression signatures, microRNA profiling
- Only minority of point mutations in exomes (0.6 %)
- Driver versus passenger mutations
- Identification of rare mutations requires hundreds of samples to be sequenced
- Functional validation in tissue cultures or model organisms

Cancer Genomics – Promises and Limitations Translation/ Molecular Profiling

- Ultimate goal of personalized cancer medicine: Real-time MP of individual tumor samples enables matching of the identified mutational profile with targeted therapy
- Von Hoff et al: modest increase of PFS (1.3 times greater)
- Validation of potential predictors of efficacy
- Focus on oncogenes, tumor suppressor genes and genomic stability genes
- Should include drug metabolism (pharmacogenomics)
- Profiling archival versus current tumor samples (longitudinal changes of MP)
- Separation of tumor versus tumor stroma
- Heterogeneity of tumor genome in individual patients (primary tissue versus metastases, intratumor heterogeneity)

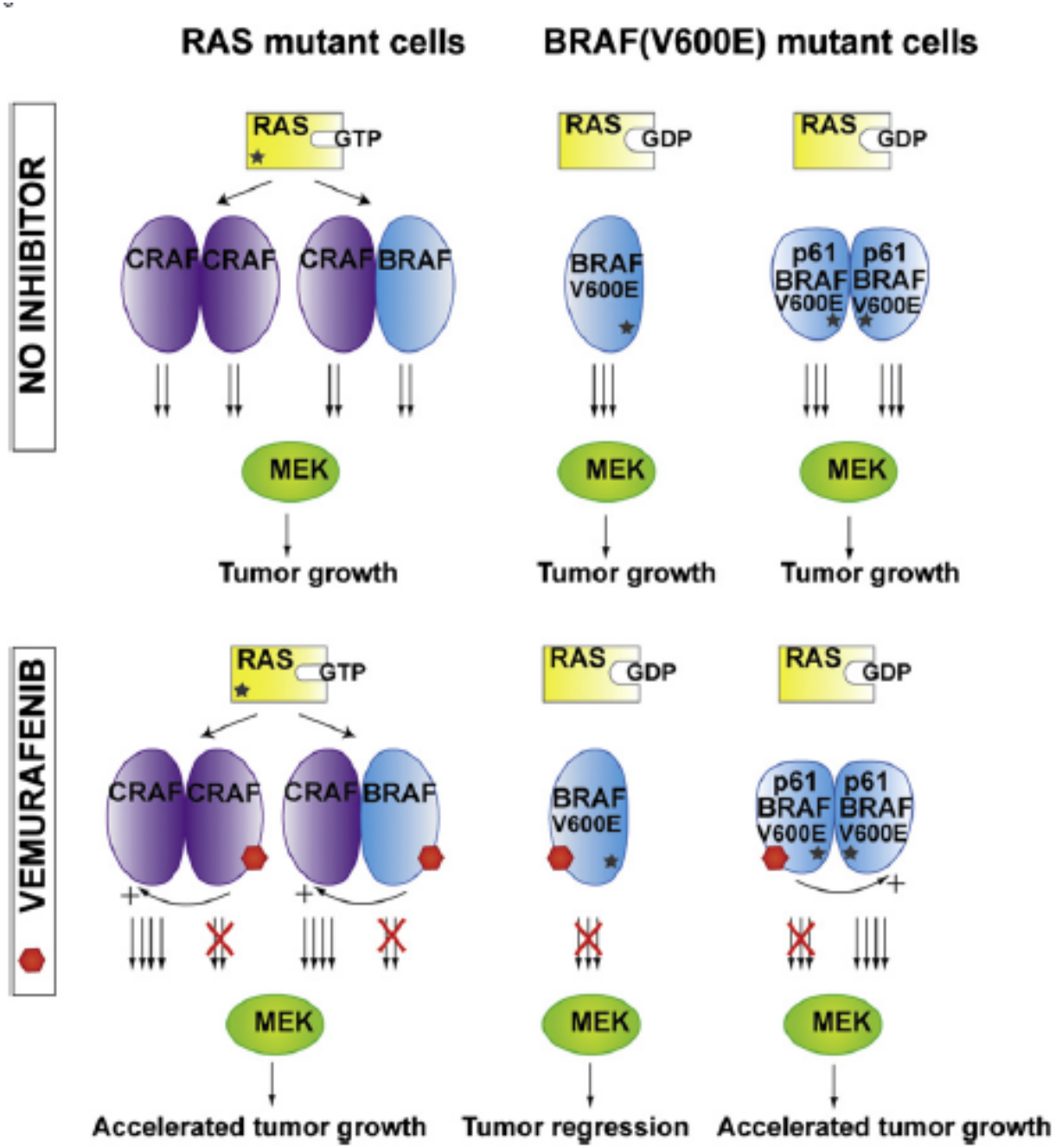
Conclusion

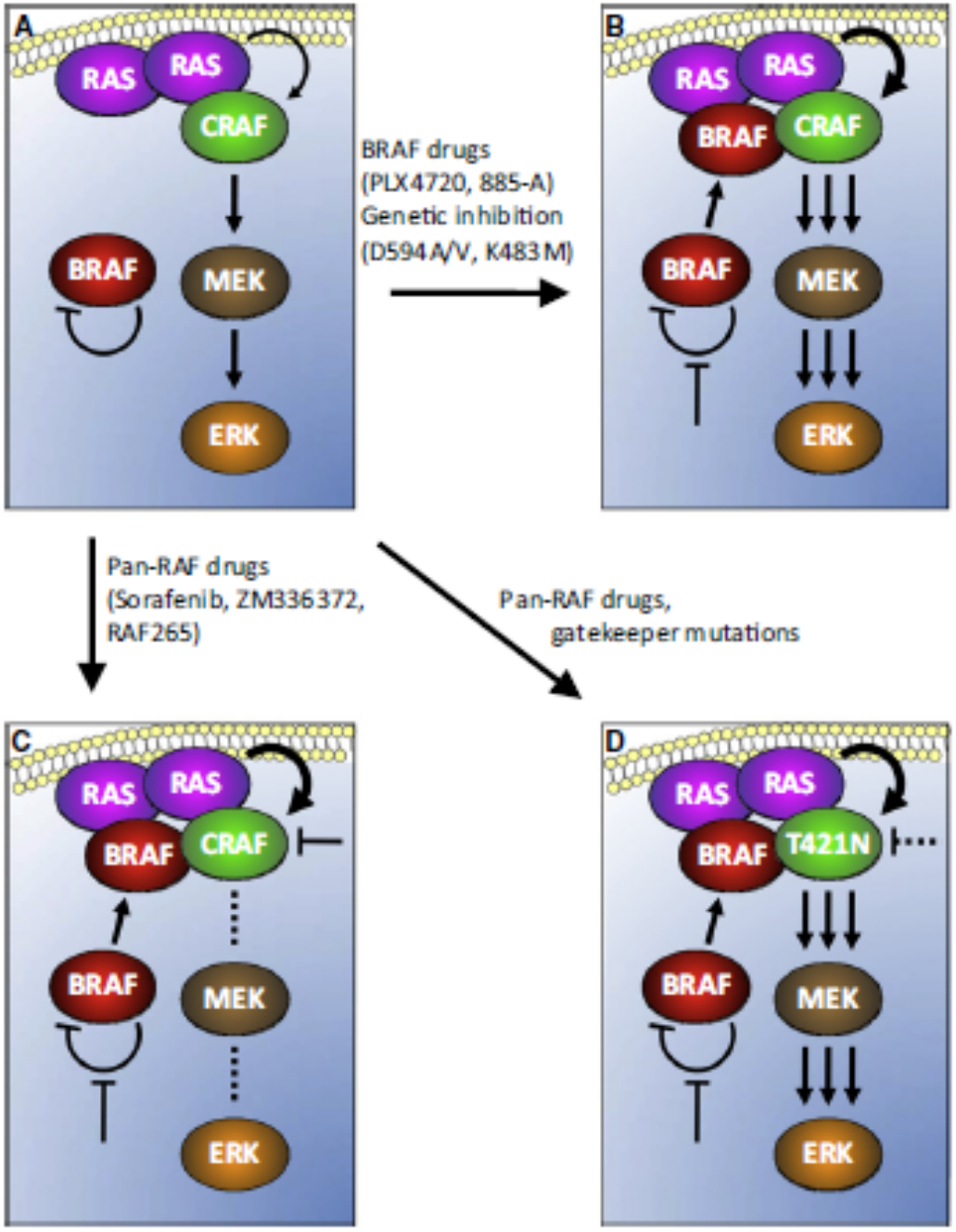
- **Potential impact of cancer genomics is enormous**
- **Technology advances and cost reduction make personalized cancer medicine potentially feasible**
- **Bioinformatics, data integration and quality control essential**
- **Challenges must be recognized and addressed**
- **Benefit of PCM versus current standard approach of cancer therapy must be validated in clinical trials**
- **Improvement of quality of life and cost effectiveness must be considered**

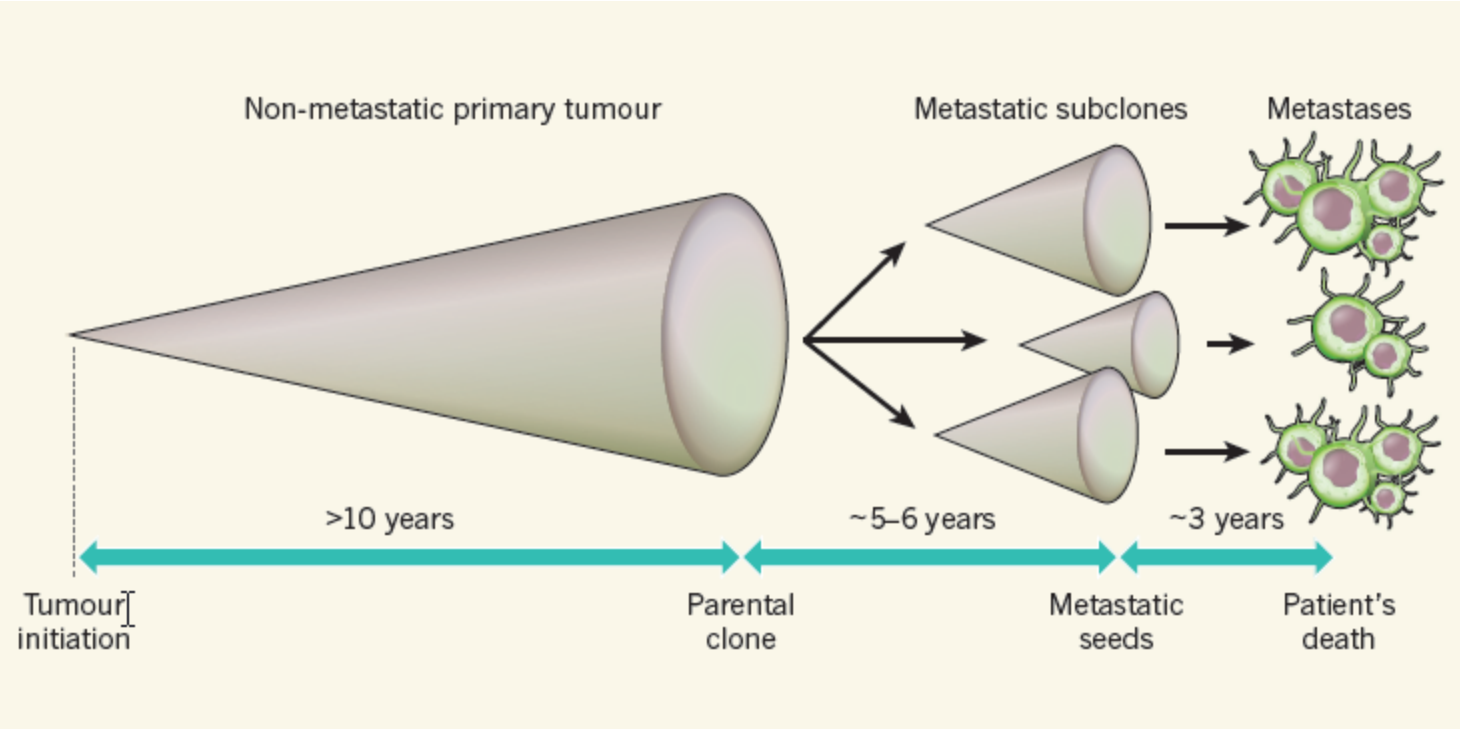
Thank you for your attention!

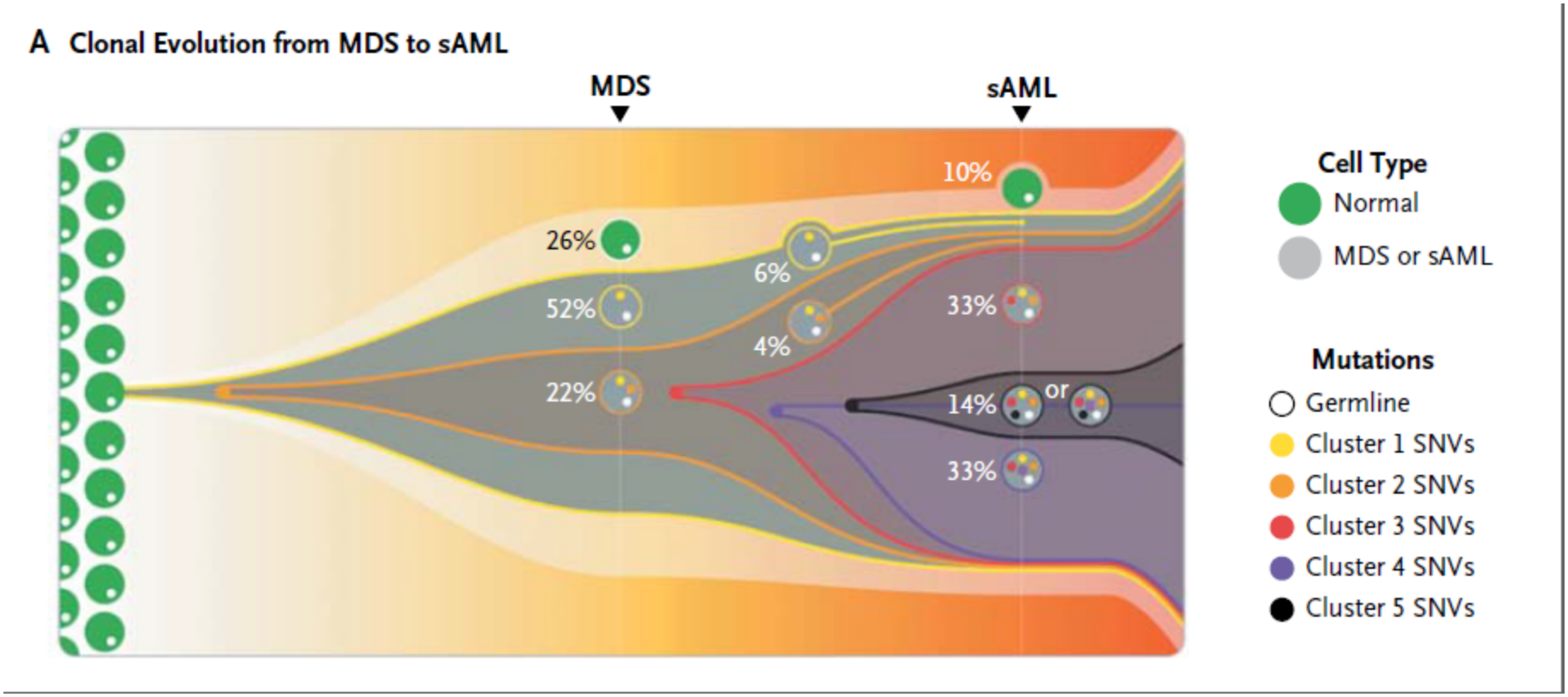
Table 2. Exemplary Mechanisms of Acquired Resistance to Kinase Inhibitors

Targeted Agent	Target Gene	Acquired Resistance via Secondary Mutation, Amplification, or Activation of Target	Acquired Resistance via Bypass	Acquired Resistance via Downstream Mutation
Imatinib				
	ABL	T315I	*IGF1R* amplification	
		Y253F/H	AXL overexpression*†	
		E255K/V		
		ABL amplification		
		T670I		
		V654A		
		D816A/G/H/V		
		D820A/E/G/Y		
	KIT	Y823D		
		KIT amplification		
	PDGFRA	T674I		
Gefitinib or erlotinib	*EGFR*	T790M	*MET* amplification	
		D761Y	HGF overexpression*†	
		L747S	IGFBP3 loss*†	
		T854A		
		EGFR amplification*		
Trastuzumab	*HER2*			
Lapatinib	*HER2/EGFR*			
PKC412	*FLT3*	N676K		
	FGFR			
AZD6044	*MEK1*	MEK1 P124L		
		BRAF amplification*		
PLX4032	*BRAF*	NRAS Q61K	COT overexpression†	MEK1 C121S
			PDGFRβ overexpression†	
			CRAF overexpression*†	
			AXL overexpression*†	
			HER2 overexpression*†	
Crizotinib	*ALK/MET*	L1196M		
		C1156Y		
		F1174L		


RAS mutant cells
BRAF(V600E) mutant cells
NO INHIBITOR
VEMURAFENIB
RAS
GTP
GDP
CRAF
BRAF
V600E
p61
MEK
Tumor growth
Accelerated tumor growth
Tumor regression

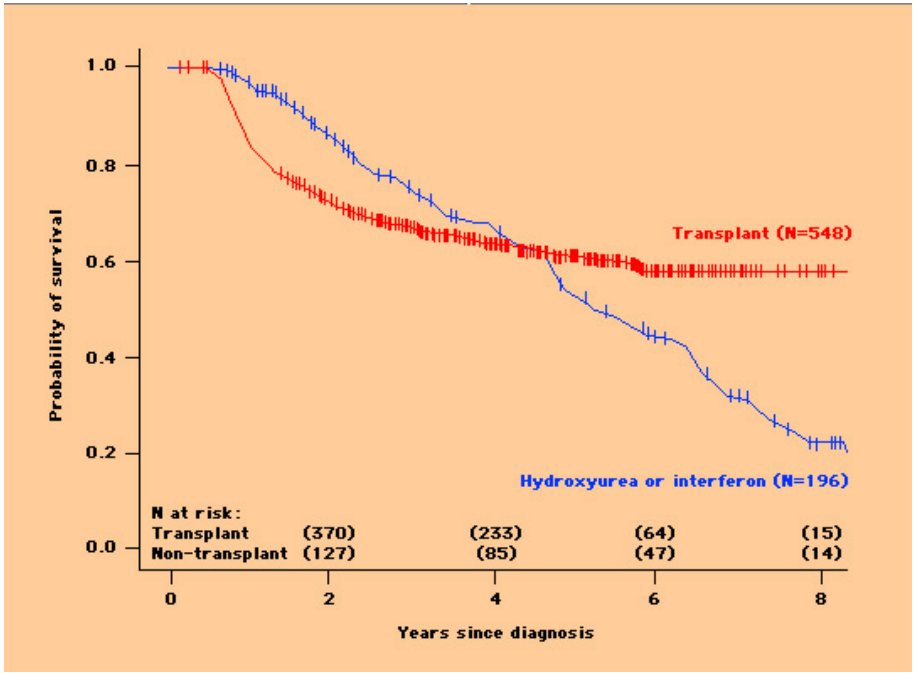

A
RAS
RAS
CRAF
BRAF
MEK
ERK
BRAF drugs
(PLX4720, 885-A)
Genetic inhibition
(D594A/V, K483M)
B
RAS
RAS
BRAF
CRAF
BRAF
MEK
ERK
Pan-RAF drugs
(Sorafenib, ZM336372,
RAF265)
Pan-RAF drugs,
gatekeeper mutations
C
RAS
RAS
BRAF
CRAF
BRAF
MEK
ERK
D
RAS
RAS
BRAF
T421N
BRAF
MEK
ERK


Non-metastatic primary tumour
Metastatic subclones
Metastases
>10 years
~5–6 years
~3 years
Tumour initiation
Parental clone
Metastatic seeds
Patient's death

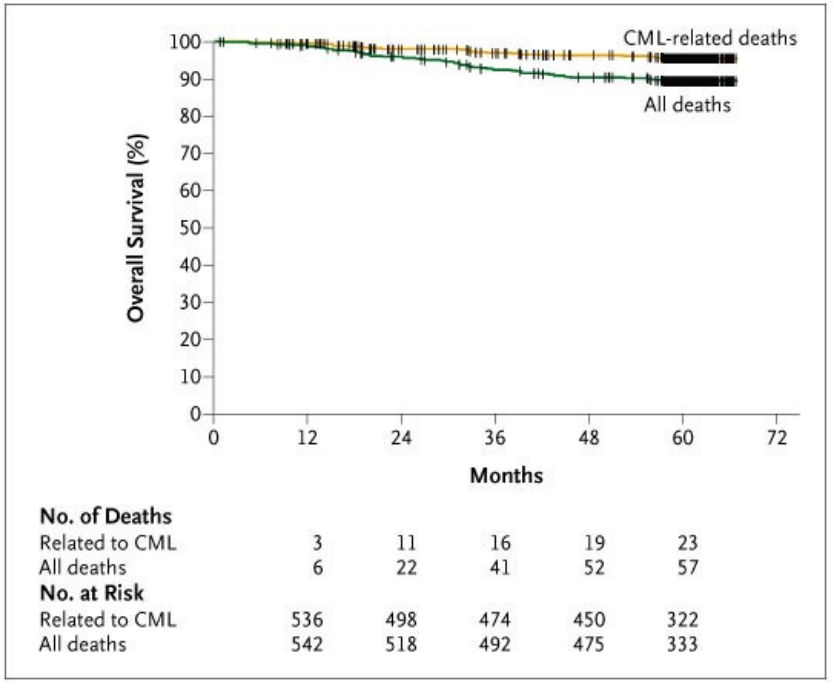

A Clonal Evolution from MDS to sAML
MDS
sAML
26%
52%
22%
6%
4%
10%
33%
14%
or
33%
Cell Type
Normal
MDS or sAML
Mutations
Germline
Cluster 1 SNVs
Cluster 2 SNVs
Cluster 3 SNVs
Cluster 4 SNVs
Cluster 5 SNVs

Chronisch myeloische Leukämie
Modellerkrankung für„targeted therapy“

Gale et al, 1998



Druker et al, 2006



Molekulare Pathophysiologie:

Monogenetisch t(9;22)

BCR-ABL konstitutiv aktivierter Signalweg

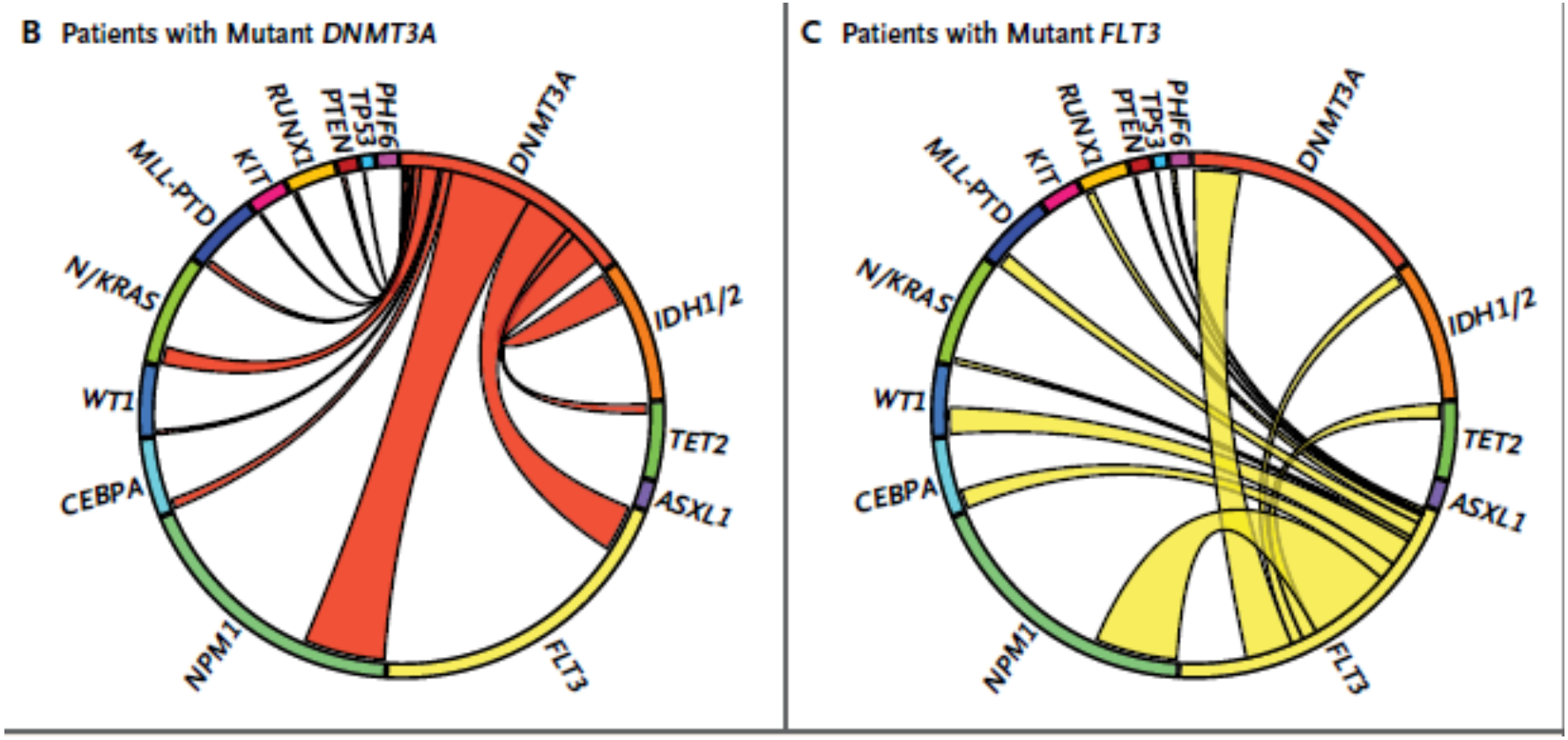
Ideales Mausmodell

Therapeutische Konsequenz:

TKI als Prototyp der targeted therapy

Biomarker (quant. bcr-abl)

Resistenzmutationen


B Patients with Mutant DNMT3A
DNMT3A
IDH1/2
TET2
ASXL1
FLT3
NPM1
CEBPA
WT1
N/KRAS
MLL-PTD
KIT
RUNX1
PTEN
TP53
PHF6
C Patients with Mutant FLT3
DNMT3A
IDH1/2
TET2
ASXL1
FLT3
NPM1
CEBPA
WT1
N/KRAS
MLL-PTD
KIT
RUNX1
PTEN
TP53
PHF6