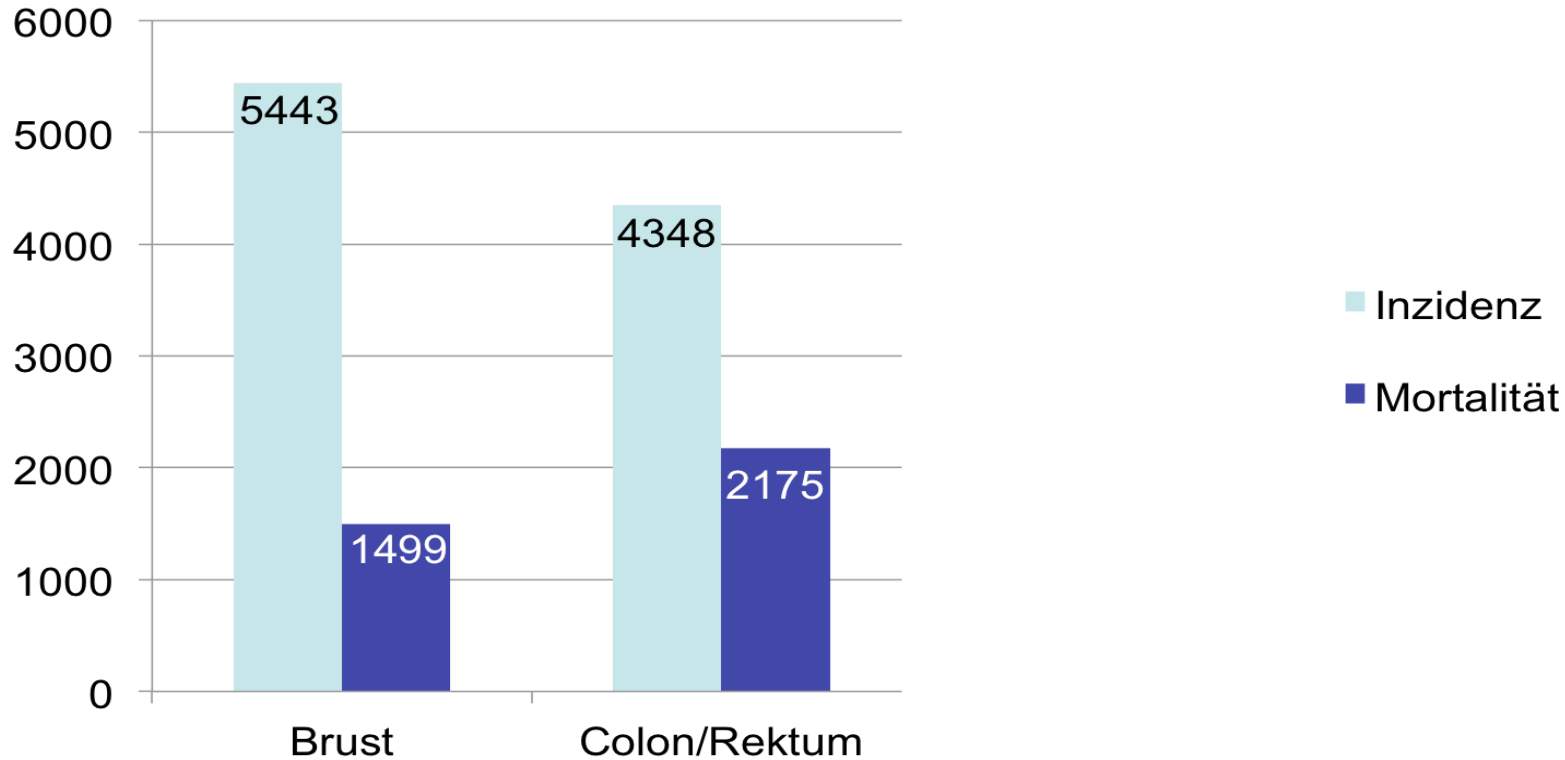


Die Rolle der Pathologie in der onkologischen Präzisionsmedizin

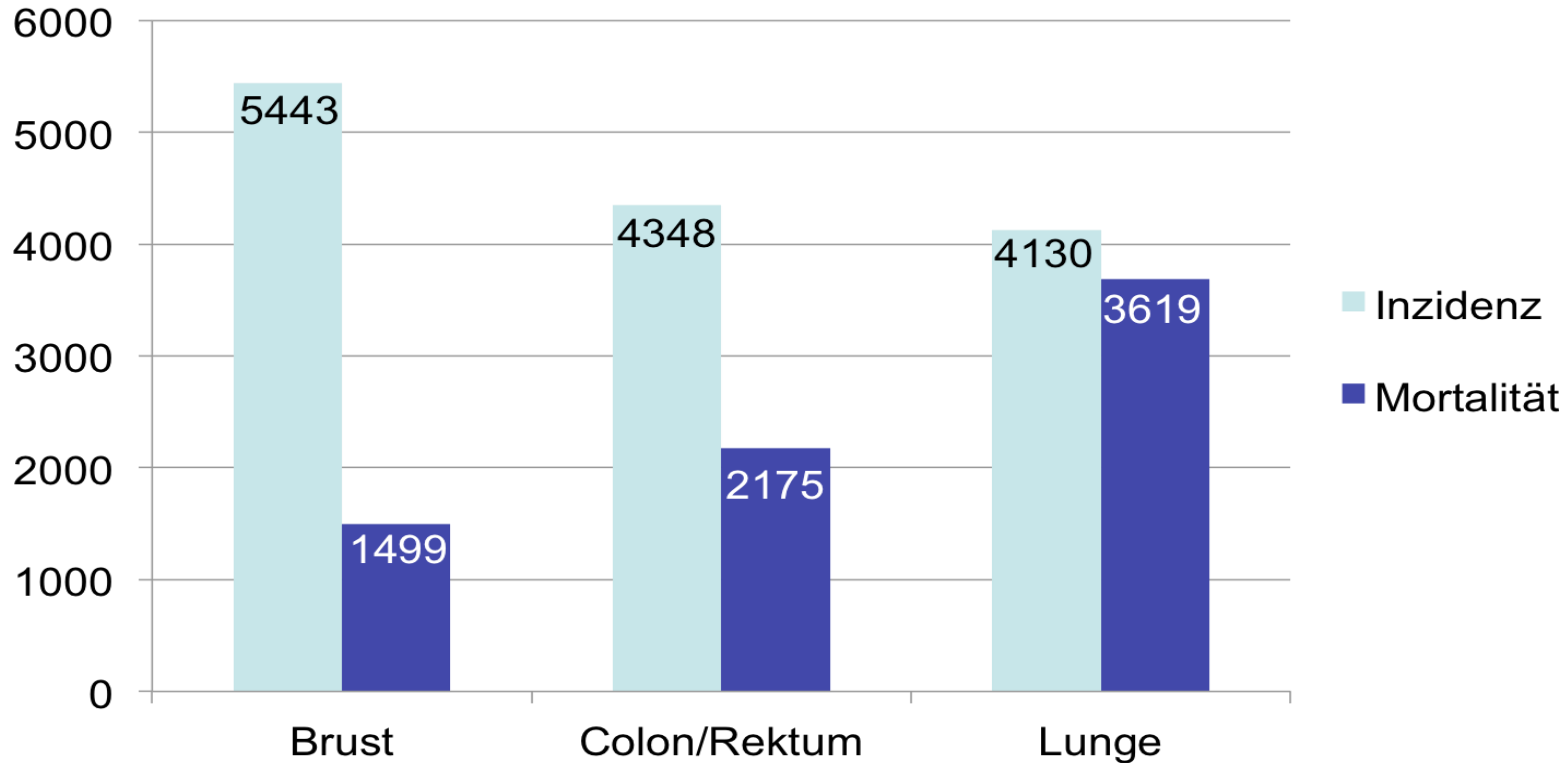
Andreas Chott

Institut für Pathologie und Mikrobiologie
Wilhelminenspital und Otto Wagner Spital

Krebs in Österreich



Krebs in Österreich



Die Rolle der Pathologie in der onkologischen Präzisionsmedizin

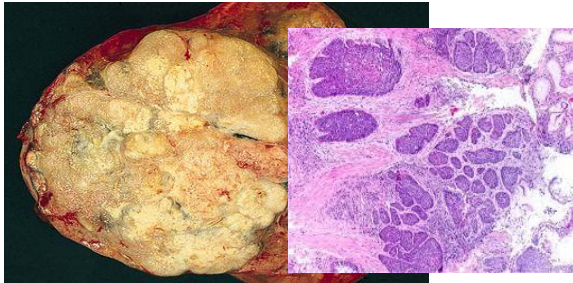


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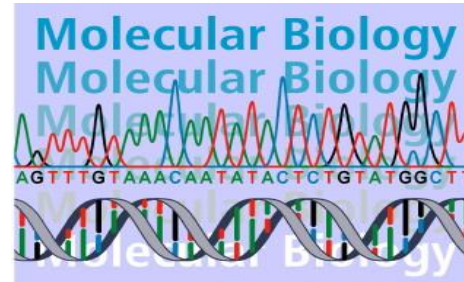
Klinische Pathologie und Molekularpathologie

Die Rolle der Pathologie in der onkologischen Präzisionsmedizin

Histologische Diagnostik



Molekulare Diagnostik



Obduktion



Mikrobiologische Diagnostik



Top ten words in Pathology 2016

-omic

Metagenomics

Epigenomics

Cardiometabolic

Actionable

Transcriptomic

Metabolomic

Personalized

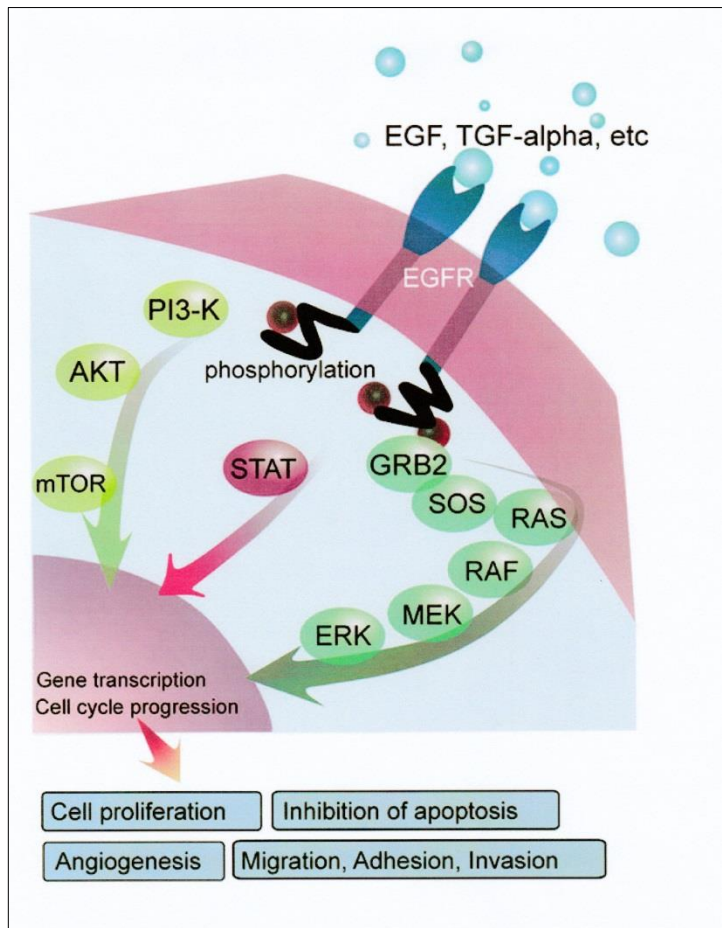
Metadata

Bioinformatic

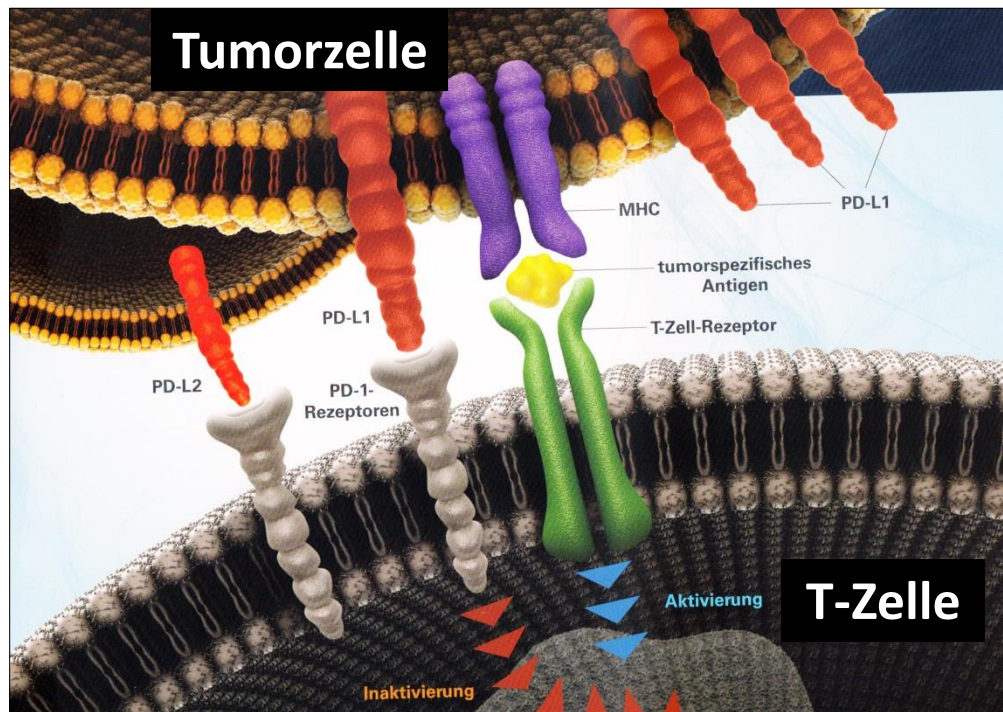
Unterschied Tumorzelle - Normalzelle

- Unabhängigkeit von Wachstumsfaktoren
- Unkontrolliertes Wachstum
- Ausschalten wachstumshemmender Faktoren
- Hemmung des programmierten Zelltodes (Apoptose)
- Täuschen des Immunsystems
- Neubildung von Gefäßen
- Verlust des Zellkontakts
- Einwachsen in Umgebung und Gefäße

Tyrosinkinaserzeptorhemmung



Immuntherapie

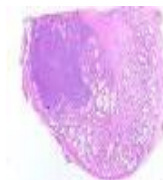
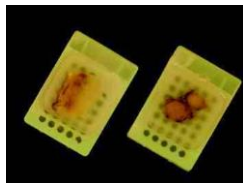


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Stomach and esophagus	99	Chondroepithelioma	122
Stomach and esophagus	100	Chondroepithelioma	122

Workflow : EGFR - Mutationsanalyse

NSCLC Patientengewebe



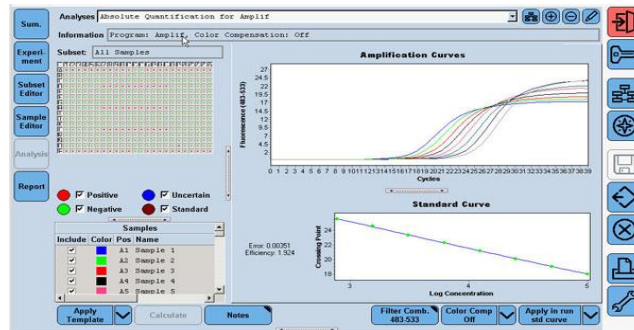
Pathologe kennzeichnet
relevantes Tumorareal



Schnittanfertigung und
DNA Extraktion

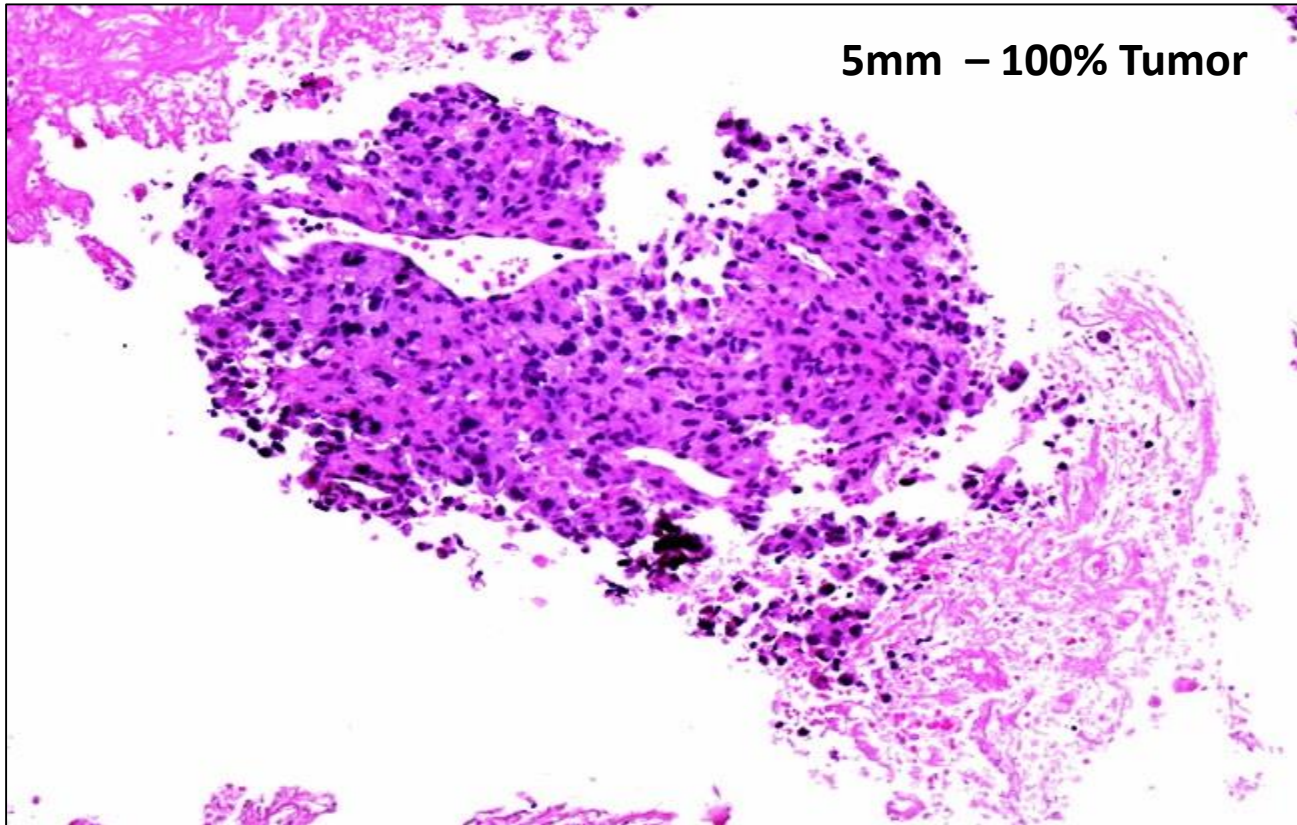


PCR Ansatz und
Real time PCR
Lauf

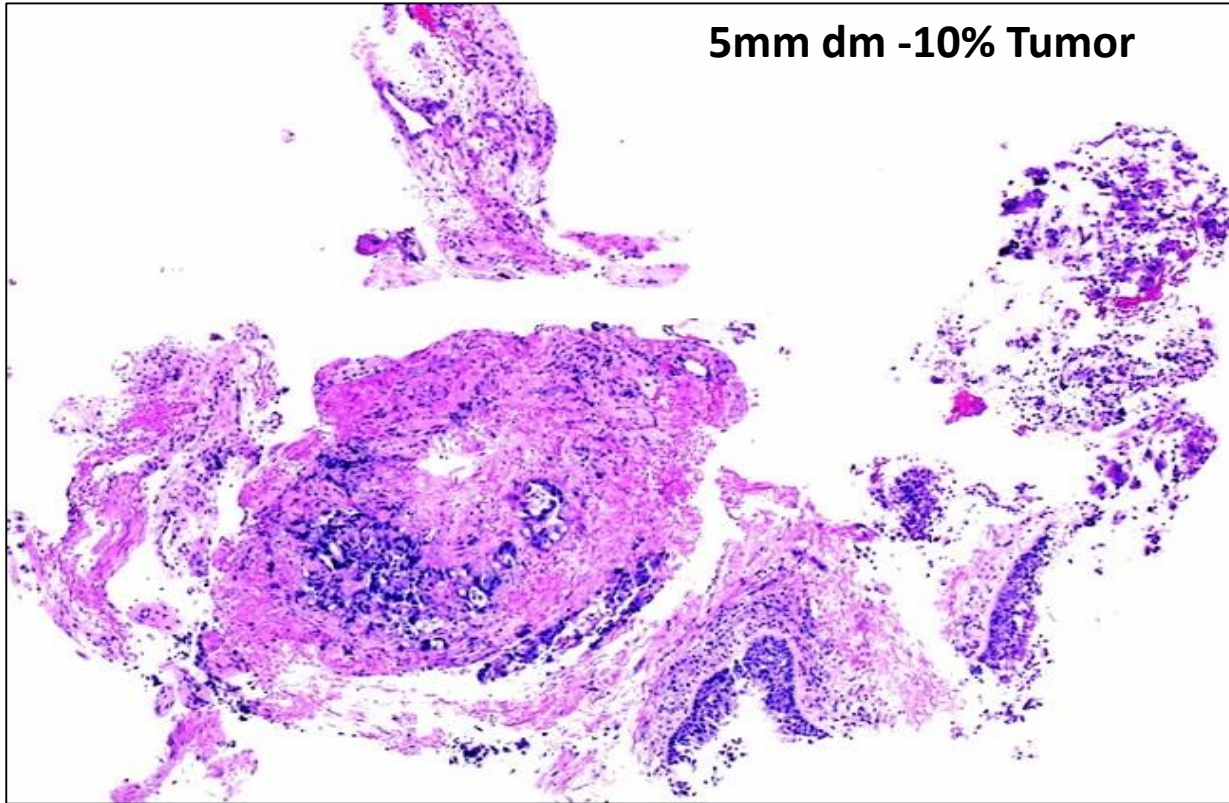


Kurvenauswertung

Materialanforderungen



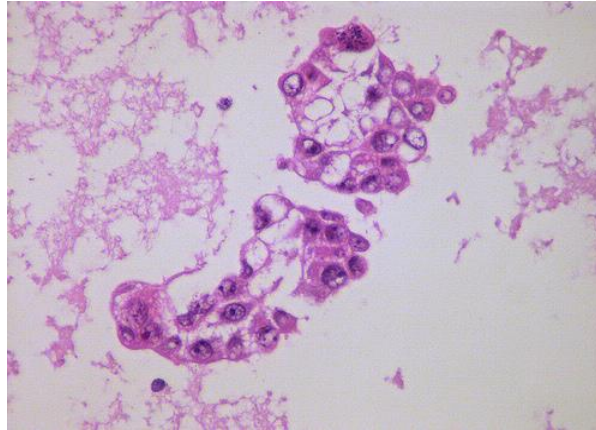
Materialanforderungen



Materialanforderungen

- ***Kann cytologisches Material verwendet werden ?***

Bürstenabstriche, EBUS-EUS Material - Zellblockverarbeitung

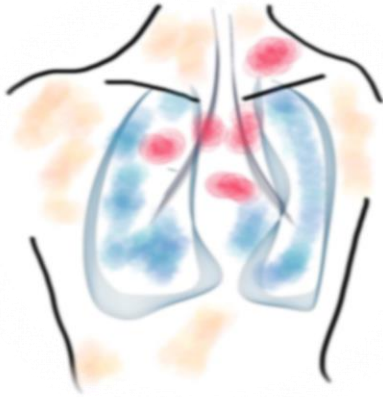


Zytoausstriche - **tumorzellreiche Präparate** : manuelles
Abkratzen ausreichend

- **tumorzellarme Präparate** :

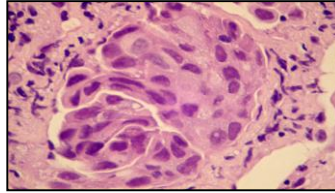
Laser – Mikrodissektionstechnologie empfohlen

Undifferenziertes Karzinom



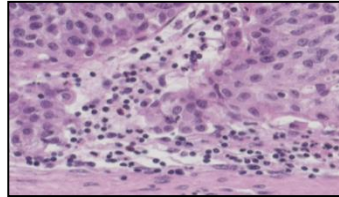
Lungen RH
Mediastinale und
supraclaviculäre LN

Blasenkrebs bekannt



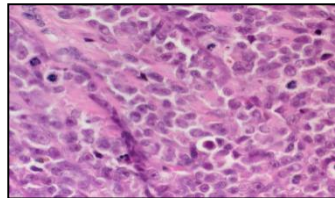
TTF1 +; CK 7 +,
CK 20-, P40 -, GATA3 -

**NSCLC,
eher
AdenoCA**



TTF1 -, CK 7 +, CK 20+
P40 +, GATA3 +

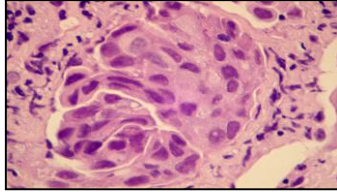
**Metastase
Blasen
Karzinom**



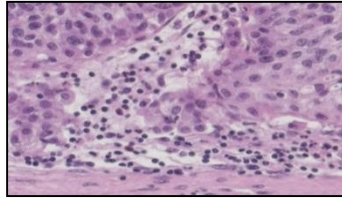
TTF1 -, P40 -, Pan CK -
S 100 +, MelanA +

**Malignes
Melanom**

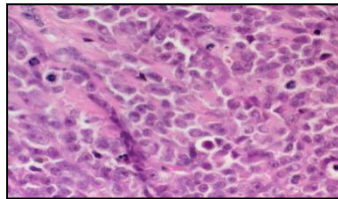
Undifferenziertes Karzinom



TTF1 +; CK 7 +,
CK 20-, P40 -, GATA3 -



TTF1 -, CK 7 +, CK 20+
P40 +, GATA3 +



TTF1 -, P40 -, Pan CK -
S 100 +, MelanA +

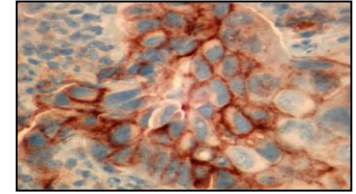
**NSCLC,
eher
AdenoCA**

**Metastase
Blasen
Karzinom**

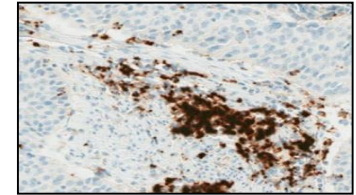
**Malignes
Melanom**

Target-/Immuntherapie?

→ EGFR -
ALK -
ROS -
PD-L1



PD-L1 TC 90%



PD-L1 IC > 10%TA

→ BRAF -

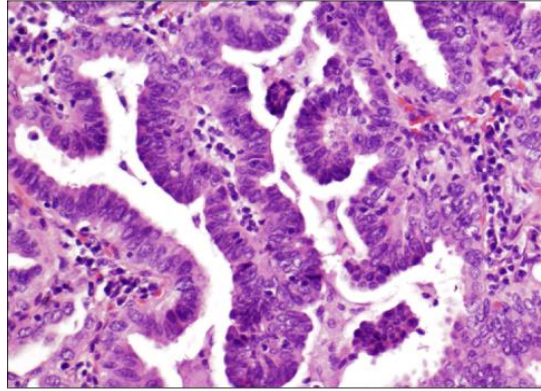
Kein PD-L1 Test



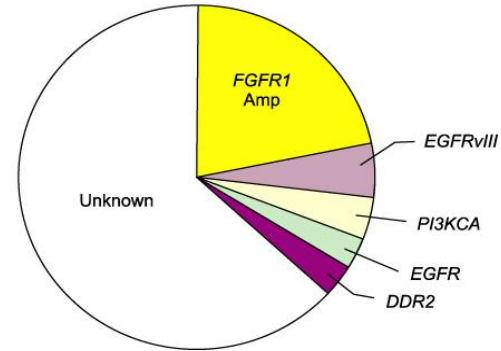
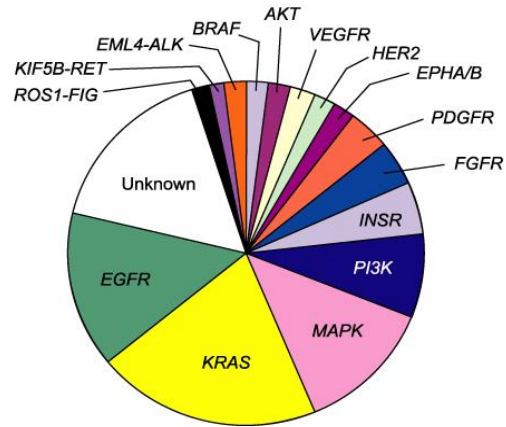
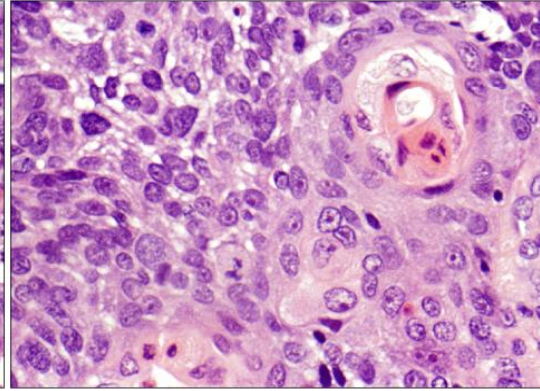
Lungen RH
Mediastinale und
supraclaviculäre LN

St.p. Blasenkrebs

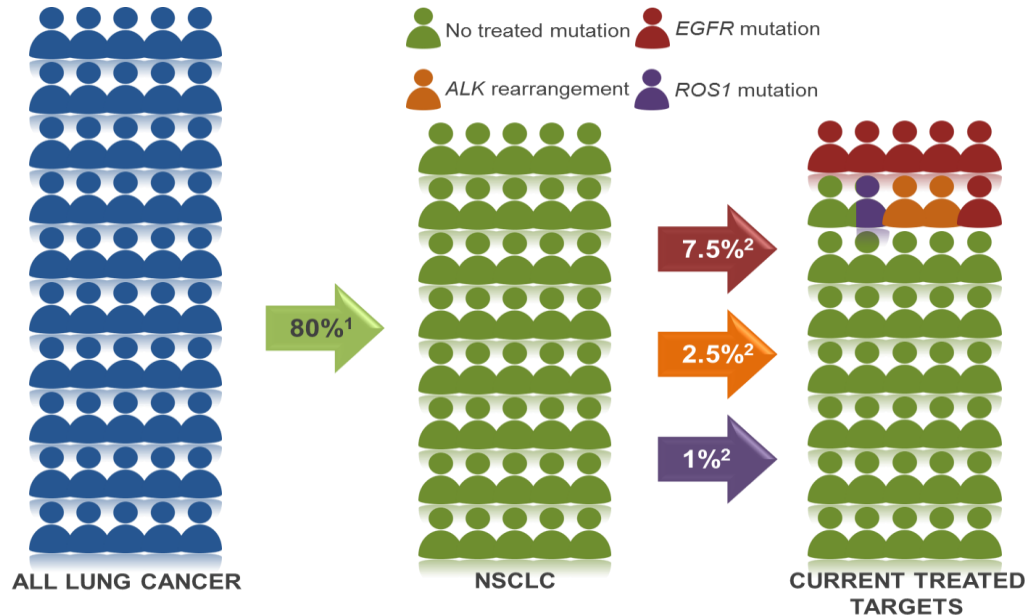
Adenokarzinom



Plattenepithelkarzinom



“Targetable” Lung Cancers

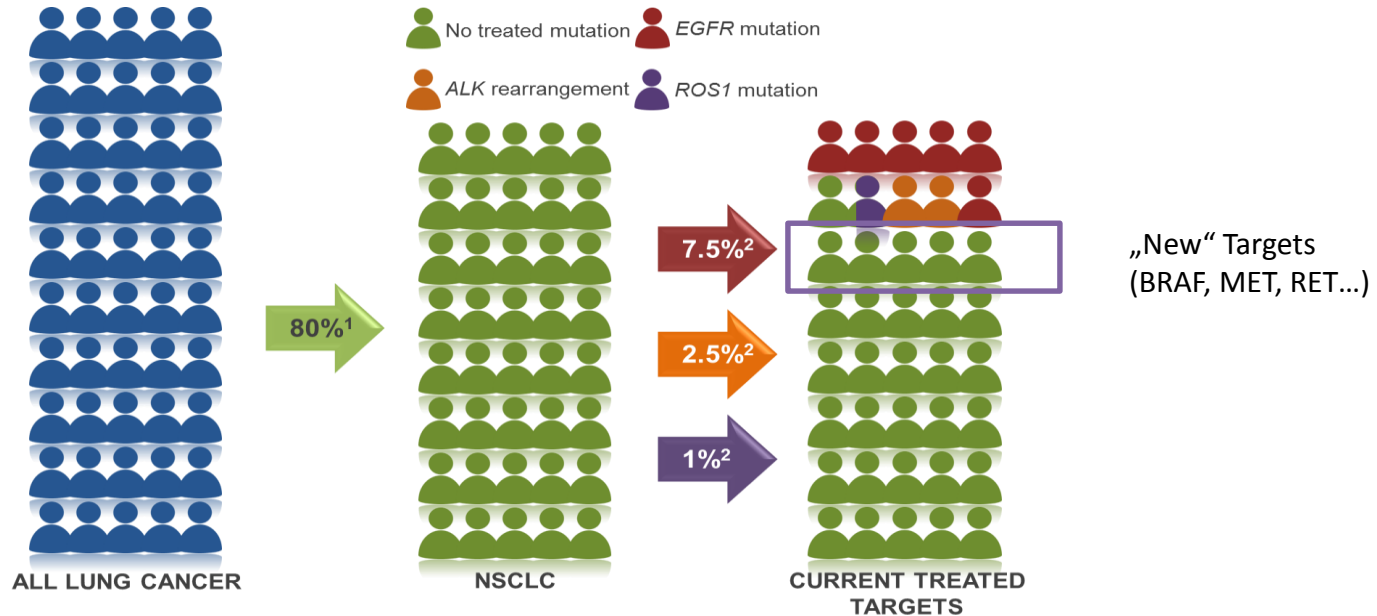


- Current first-line treatment options in advanced NSCLC without oncogenic drivers (*EGFR* mutation or *ALK* translocation) are limited to cytotoxic chemotherapy³
- Approximately 23–28% of patients with advanced NSCLC have high expression of PD-L1 ($\geq 50\%$)⁴

ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; PD-L1: programmed death ligand 1.

1. Devesa SS, et al. *Int J Cancer* 2005;117:294–299; 2. Chan BA and Hughes BG. *Transl Lung Cancer Res* 2015;4:36–54; 3. Novello S, et al. *Ann Oncol* 2016; 27 (Suppl. 5): v1–v27; 4. Reck M, et al. *N Engl J Med* 2016; DOI: 10.1056/NEJMoa1606774.

“Targetable” Lung Cancers

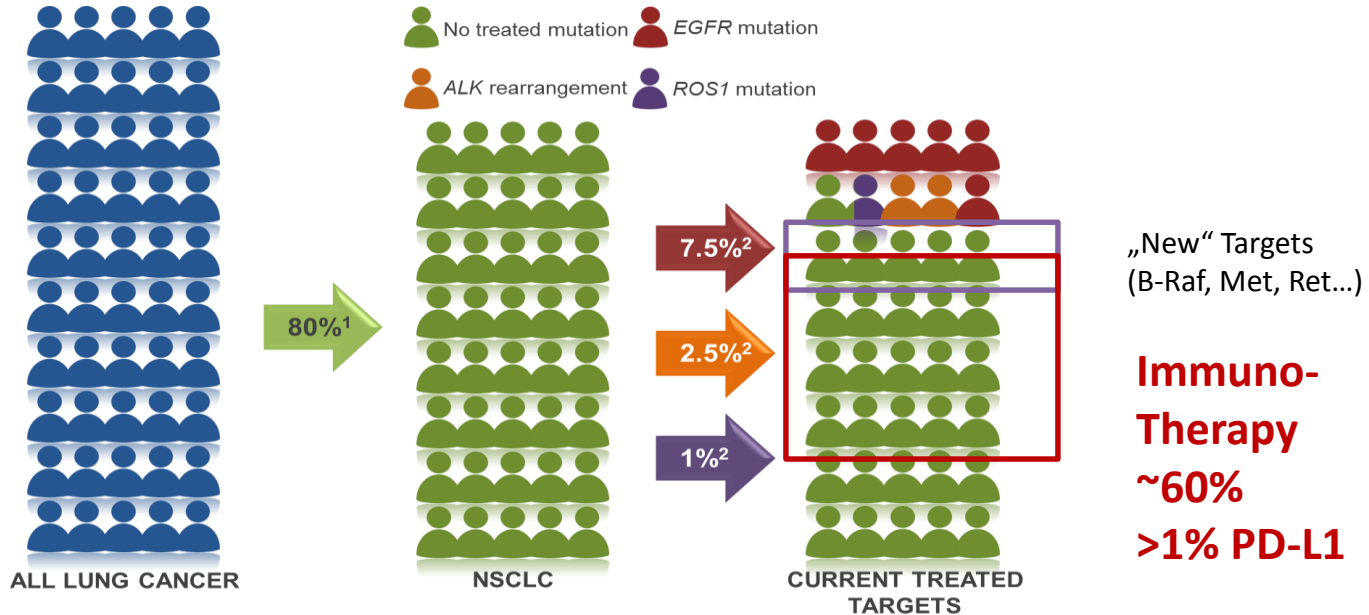


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“Targetable” Lung Cancers



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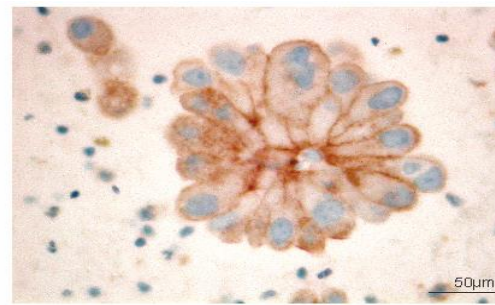
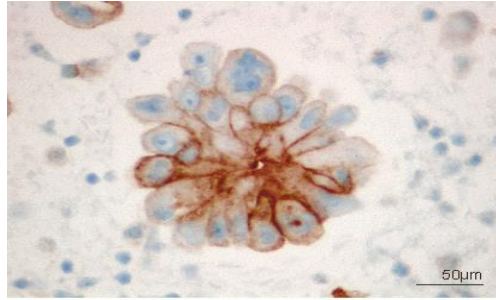
1. Devesa SS, et al. *Int J Cancer* 2005;117:294–299; 2. Chan BA and Hughes BG. *Transl Lung Cancer Res* 2015;4:36–54; 3. Novello S, et al. *Ann Oncol* 2016; 27 (Suppl. 5): v1–v27; 4. Reck M, et al. *N Engl J Med* 2016; DOI: 10.1056/NEJMoa1606774.

SP 263

PD-L1

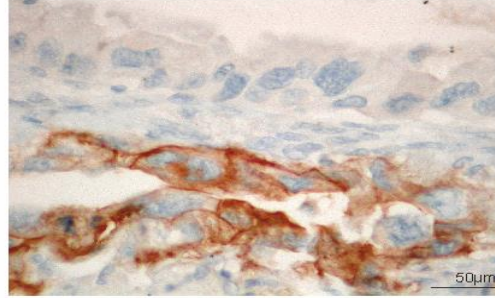
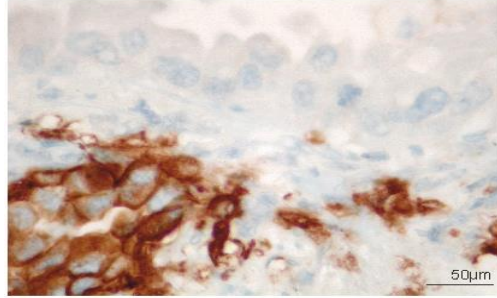
28.8

AdenoCA
Pleural Effusion



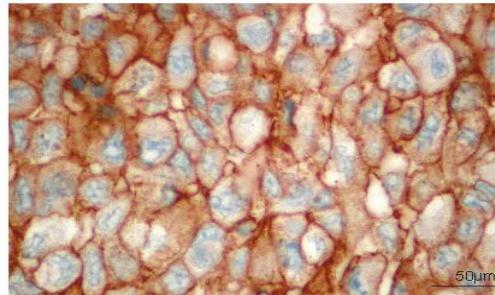
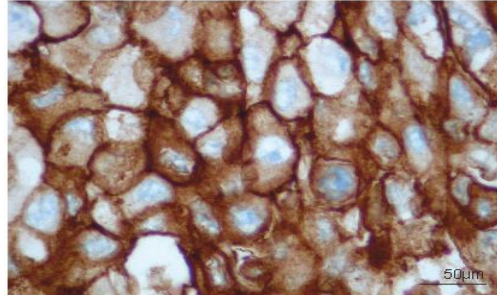
Cell block

AdenoCA



TBLB

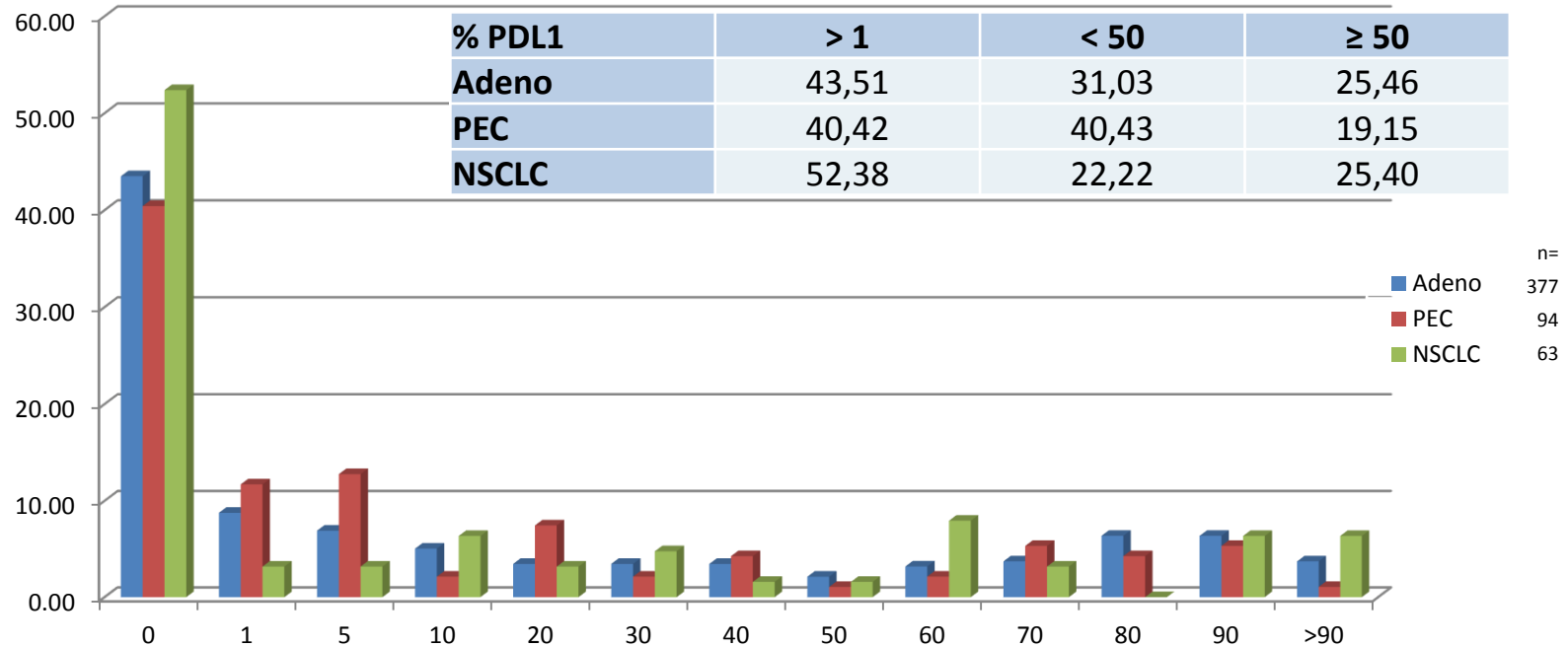
AdenoCA



Surgery

PD-L1 im OWS

NSCLC 11/15-08/16 n= 534



Richtlinien der Arbeitsgruppe Pulmopathologie

Reflextestung

- **AdenoCA, NSCLC NOS, NSCLC (AdenoKomponente)**
 - **EGFR-Mutationen**
 - Sequenzierung, RT-PCR
 - **ALK- Rearrangement**
 - Immunohistochemie (Klone D5F3 and 5A4)
 - Verifizierung mit FISH or RT-PCR (“second opinion”)
 - **ROS1 -Rearrangement**
 - Screening mit IHC
 - Positive IHC muss verifiziert werden (FISH or RT-PCR)
 - **PD-L1 expression**
 - Immunohistochemistry (28.8, SP263, 22C3, E1L3N)
 - Reflextestung **auch in Plattenepithelkarzinomen**

Biomarker -Test OWS

- Lungenkarzinom
- Reflex
 - **EGFR (Mutation)**
 - **ALK**
 - **ROS-1**
 - **PD-L1**
 - BRAF
- Auf Anfrage
 - KRAS
 - NRAS
 - EGFR (Expression)
 - ERBB2

Data Sheet: Cancer Genomics



TruSight® Tumor 15

Evidence-based gene content and an efficient workflow solution for evaluation of common somatic variants in FFPE solid tumor samples.

Table 1: Gene Content on TruSight Tumor 15

<i>AKT1</i>	<i>GNA11</i>	<i>NRAS</i>
<i>BRAF</i>	<i>GNAQ</i>	<i>PDGFRA</i>
<i>EGFR</i>	<i>KIT</i>	<i>PIK3CA</i>
<i>ERBB2</i>	<i>KRAS</i>	<i>RET</i>
<i>FOXL2</i>	<i>MET</i>	<i>TP53</i>

DNA Gene List: Entire Coding Sequence for the Detection of Base Substitutions, Insertion/Deletions, and Copy Number Alterations

ABL1	ABL2	ACVR1B	AKT1	AKT2	AKT3	ALK	AMER1 (FAM123B)	APC	AR
ARAF	ARFRP1	ARID1A	ARID1B	ARID2	ASK1	ATM	ATR	ATRAX	AURKA
AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6	BCOR
BCORL1	BLM	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTIK	C11orf30 (EMSY)
CARD11	CBFB	CBL	CCND1	CCND2	CCND3	CENPE	CD274	CD79A	CD79B
CDC73	CDH1	CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B
CDKN2C	CEBPA	CHD2	CHD4	CHEK1	CHEK2	CIC	CREBBP	CRKL	CRLF2
CSF1R	CTCF	CTNNA1	CTNNB1	CUL3	CYLD	DAXX	DDR2	DICER1	DNMT3A
DOT1L	EGFR	EP300	EPHA3	EPHA5	EPHA7	EPHB1	ERBB2	ERBB3	ERBB4
ERG	ERRF1	ESR1	EZH2	FAM46C	FANCA	FANCC	FANCD2	FANCE	FANCF
FANCG	FANCL	FAS	FAT1	FBXW7	FGF10	FGF14	FGF19	FGF23	FGF3
FGF4	FGF6	FGFR1	FGFR2	FGFR3	FGFR4	FH	FLCN	FLT1	FLT3
FLT4	FOXO2	FOXP1	FRS2	FUBP1	GABRA6	GATA1	GATA2	GATA3	GATA4
GATA6	GID4 (C17orf39)	GLI1	GNA11	GNA13	GNAQ	GNAS	GPR124	GRIN2A	GRM3
GSK3B	H3F3A	HGF	HNF1A	HRAS	HSD3B1	HSP90AA1	IDH1	IDH2	IGF1R
IGF2	IKBKE	IKZF1	IL7R	INHBA	INPP4B	IRF2	IRF4	IRS2	JAK1
JAK2	JAK3	JUN	KAT5A (MYST3)	KDMSA	KDMSB	KDR	KEAP1	KEL	
KIT	KLHL6	KMT2A (MLL)	KMT2C (MLL3)	KMT2D (MLL2)	KRAS	LMO1	LRP1B	LYN	LZTR1
MAGI2	MAP2K1	MAP2K2	MAP2K4	MAP3K1	MCL1	MDM2	MDM4	MED12	MEF2B
MEN1	MET	MITF	MLH1	MPL	MRE11A	MSH2	MTOR	MUTYH	
MYC	MYCL1 (MYCL1)	MYCN	MYD88	NF1	NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1
NOTCH2	NOTCH3	NPM1	NRAS	NSD1	NTRK1	NTRK2	NTRK3	NUP93	PAK3
PALB2	PARK2	PAX5	PBRM1	PDCD1LG2	PDGFRA	PDGFRB	PDK1	PIK3C2B	PIK3CA
PIK3CB	PIK3CG	PIK3R1	PIK3R2	PLCG2	PMS2	POLD1	POLE	PPP2R1A	PRDM1
PREX2	PRKARIA	PRKCI	PRKDC	PRSS8	PTCH1	PTEN	PTPN11	QKI	RAC1
RAD50	RAD51	RAF1	RANBP2	RARA	RB1	RBM10	RET	RICTOR	RNF43
ROS1	RPTOR	RUNX1	RUNX1T1	SDHA	SDHB	SDHC	SDHD	SETD2	SF3B1
SLIT2	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SNCAIP	SOC1	SOX10
SOX2	SOX9	SPEN	SPOP	SPTA1	SRC	STAG2	STAT3	STAT4	STK11
SUFU	SYK	TAF1	TBX3	TERC	TERT (promoter only)	TET2	TGFBP2	TNFAIP3	TNFRSF14
TOP1	TOP2A	TP53	TSC1	TSC2	TSHR	U2AF1	VEGFA	VHL	WISP3
WT1	XPO1	ZBTB2	ZNF217	ZNF703					

DNA Gene List: For the Detection of Select Rearrangements

ALK	BCL2	BCR	BRAF	BRCA1	BRCA2	BRD4	EGFR	ETV1	ETV4
ETV5	ETV6	FGFR1	FGFR2	FGFR3	KIT	MSH2	MYB	MYC	NOTCH2
NTRK1	NTRK2	PDGFR	RAF1	RARA	RET	ROS1	TMPRSS2		

Additional Assays: For the Detection of Select Cancer Biomarkers

Microsatellite status
Tumor Mutation Burden

Therapie Relevante Gene

EGFR

KRAS

ALK

BRAF

MET

RET

ERB2

ROS1

Biomarkertest - Befund - Dauer

- **Foundation One: 15 Tage**
 - Ab Einlangen der Schnitte im Labor (inkl. 2 Tage Logistik)
- **OWS: 7 Tage**
 - Ab Einlangen der unfixierten Probe im Labor (inkl. 2 Tage Befundung)

Liquid Biopsy
„Das Stethoskop der nächsten 200 Jahre“
Zitat *E.Topol*

Einsatz im klinischen Alltag

- ✓ Nachweis von Treibermutation bei fehlender Primärbiopsie
- ✓ Frühzeitige Identifizierung von Resistenzmutationen
- ✓ Bestimmung der „Tumorlast“ als Ergänzung zur Bildgebung
- ✓ Minimal residual disease im postoperativen Verlauf
- ✓ Blut enthält Pool aus ctDNA von Primärtumor und Metastasen



Zusammenfassung

- Präzisionsmedizin ist multidisziplinäre Aufgabe (R, P, NM, O)
- Pathologie spielt zentrale Rolle in Diagnostik und Zielidentifizierung
- Überwachung des Krankheitsverlaufs (liquid biopsy)
- Ablaufkonzentration in onkologischen Zentren