Lung cancer and Companion Diagnostics

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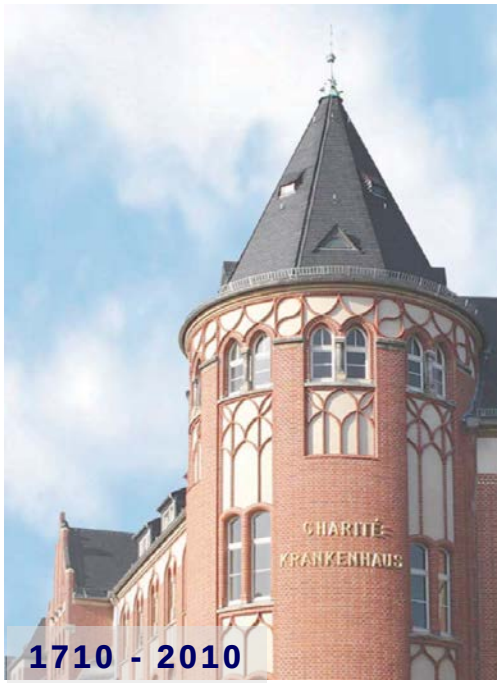

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Disclosures

- Participation in several industry-sponsored advisory boards for which honoraria were received.

- Travel costs have also been refunded

Structure of the talk on NSCLC Testing

- General introduction on molecular pathology
- What to test: sampling / tissue / cytology
- How to test
  - Methods / quality control
    - FISH
    - IHC
    - Sanger-, pyro- or NG Sequencing
- How to report
- Who to test
- When to test
- Future development

Today's Challenges in Anatomic and Molecular Pathology

The goal of diagnostic pathology was to provide a correct diagnosis, but today the task is greatly extended to

extract from the patient's tissue as many information as possible

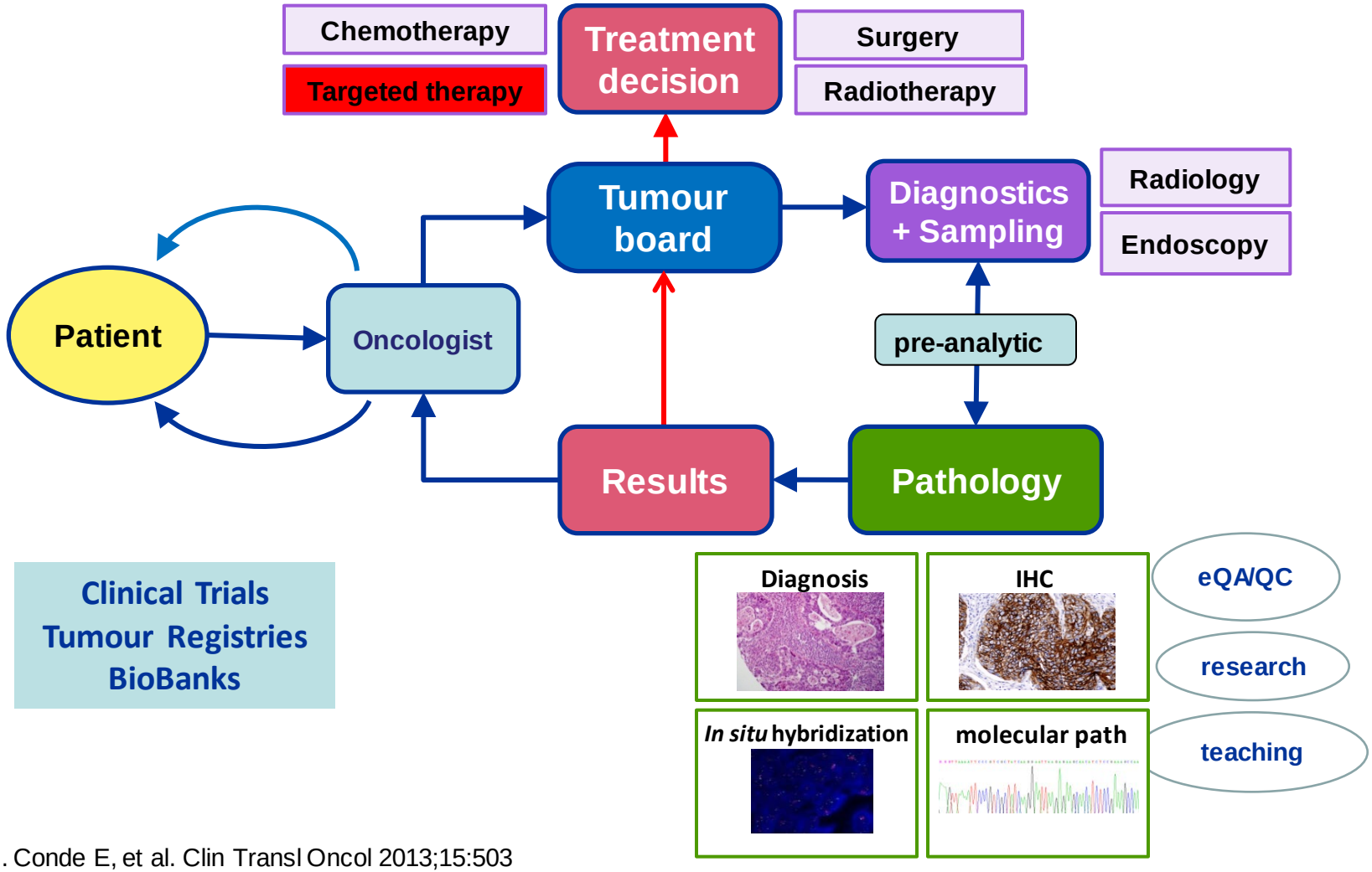
by applying classical, immunological (proteomic) and molecular techniques.

This is the prerequisite for personalized medicine.

The capability to predict pre-therapeutically the response of infections or individual tumors to certain (targeted) drug(s) is based on reliable and reproducible biomarker and predictive assays.

But it should not be forgotten that the methodological results have to be interpreted by an experienced tumor board including pathologists. Only then the numerous diagnostic, prognostic and predictive information can be interpreted adequately to assign the optimal treatment to individual patients.

Multidisciplinary cooperation enables personalised oncology



Mod. acc. Conde E, et al. Clin Transl Oncol 2013;15:503

Predictive tissue-based biomarkers for targeted therapies

FDA / EMA-approved drugs associated with eligibility tests* (selection)

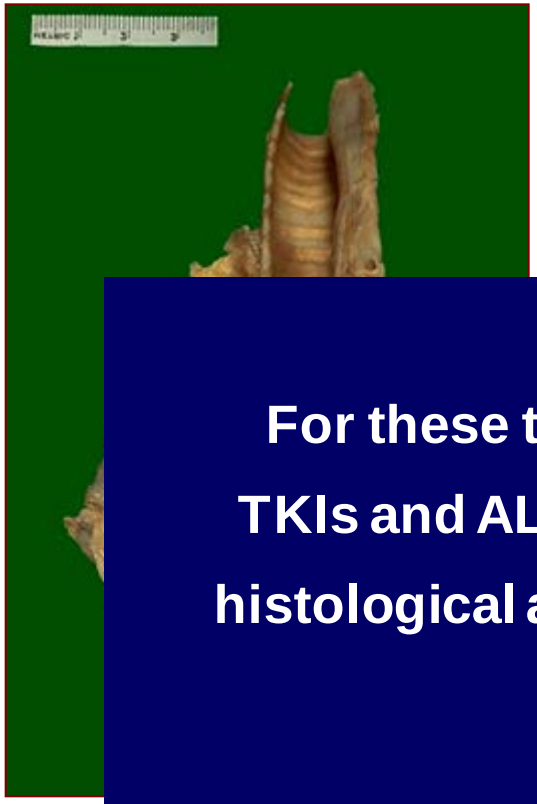
- Tra… *-2*
- Ta…
- Ce…
- Pa…
- Ge…
- Erl…
- Cr…
- Nir…
- La…
- Ve…
- Im…
- Im…
- Rit…
- Ola…

Already now, in 35% of all tumors a predictive molecular test is appropriate. Notably, prediction of tumour response is exclusively tissue-based.

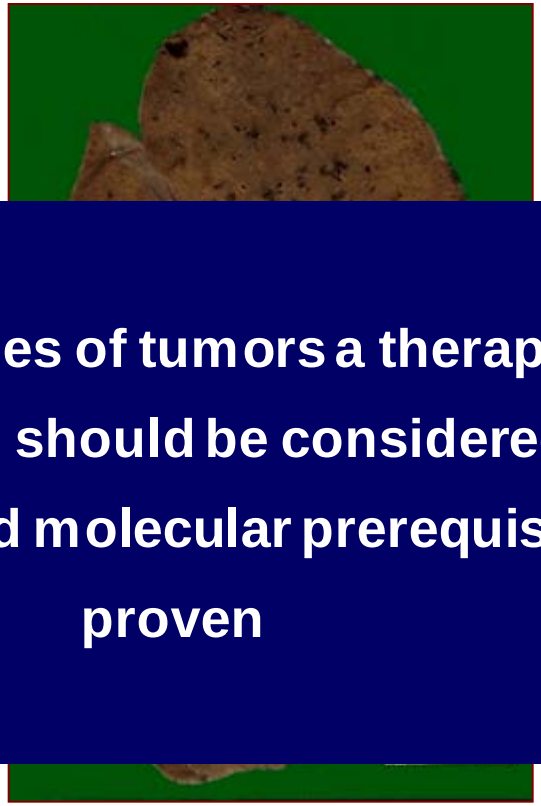
All these substances have been developed on the basis of histologically characterised human tissue. This underlines the importance of biobanks.

*Strongly suggested by FDA's Drug-Diagnostic Co-Development Initiative

NSCLC - Macroscopy

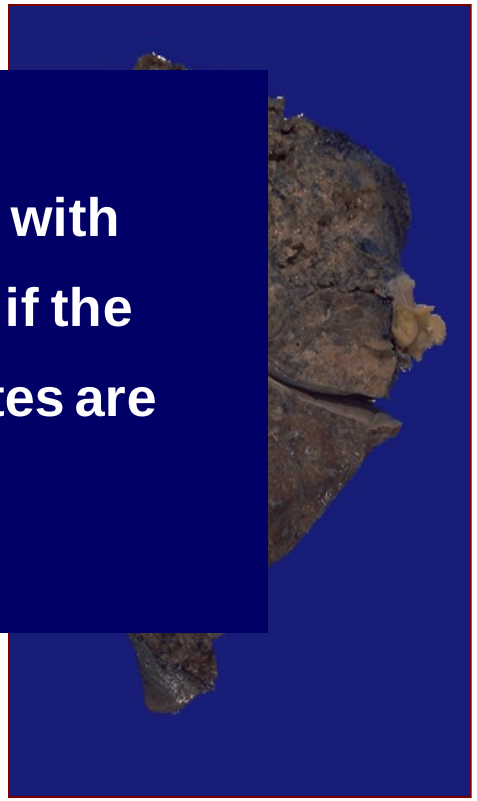


central
squamous cell carcinoma



peripheral
adenocarcinoma

adeno carcinoma
broncho-alveolar type



For these types of tumors a therapy with TKIs and ALKI should be considered if the histological and molecular prerequisites are proven

Currently, Two Approved Personalised Treatment Options: Substantial Benefit for ~15 – 20 % of Patients

Crizotinib in ALK-positive NSCLC (US, EU filed)[1]

RR 60%, PFS 8 months, OS 14 -16

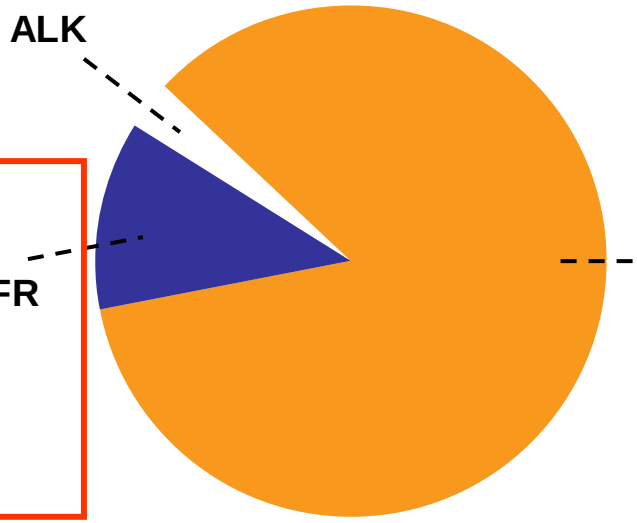
EGFR-TKIs in EGFR-mut NSCLC

Gefitinib, Erlotinib (US, EU)

(Afatinib filed in EU)[3–5]

RR 60–80%, PFS 10–13 months,

OS 19–30 months



Chemotherapy in unselected patients[2]

RR 20%, OS <12 mths

Dacomitinib (PF-00299804; Pfizer Inc.) is an investigational compound not currently licensed for use in any market; Crizotinib (PF-02341066; Pfizer Inc.) is not yet approved in member states of the European Union. Crizotinib is currently licensed for use in Argentina, Canada, Israel, India, Japan, South Korea, Macau, Mexico, Switzerland, and the USA.

1. Kim D-W, et al. Presented at ASCO 2012; Abstract 7533
2. Schiller JH, et al. N Engl J Med 2002; 346:92–8
3. Maemondo M, et al. N Engl Med 2010;362: 2380-8
4. Rosell R, et al. Lancet Oncol 2012;13: 239–46
5. Yang C-H, et al. Presented at ASCO 2012; Abstract LBA7500

Targeted Therapy in NSCLC

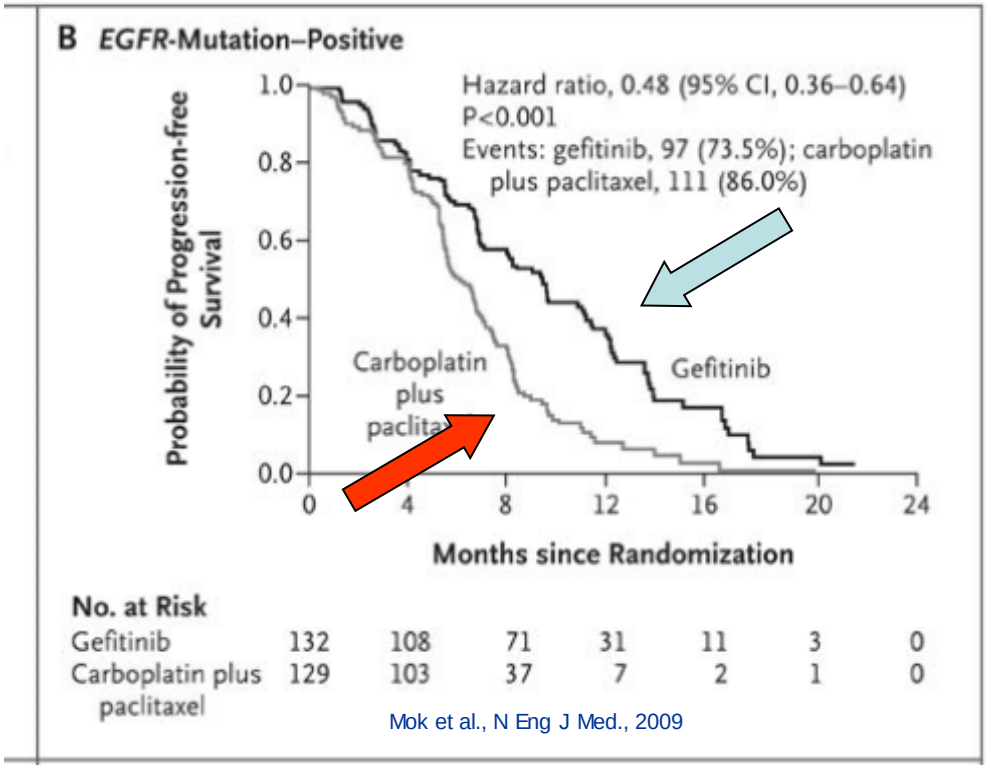
EMA/FDA: kinase inhibitors can be applied only in combination with a diagnostic eligibility test.

Example:

- therapeutic anti-EGFR
- kinase inhibitors

Gefitinib

(Iressa, Astra Zeneca)

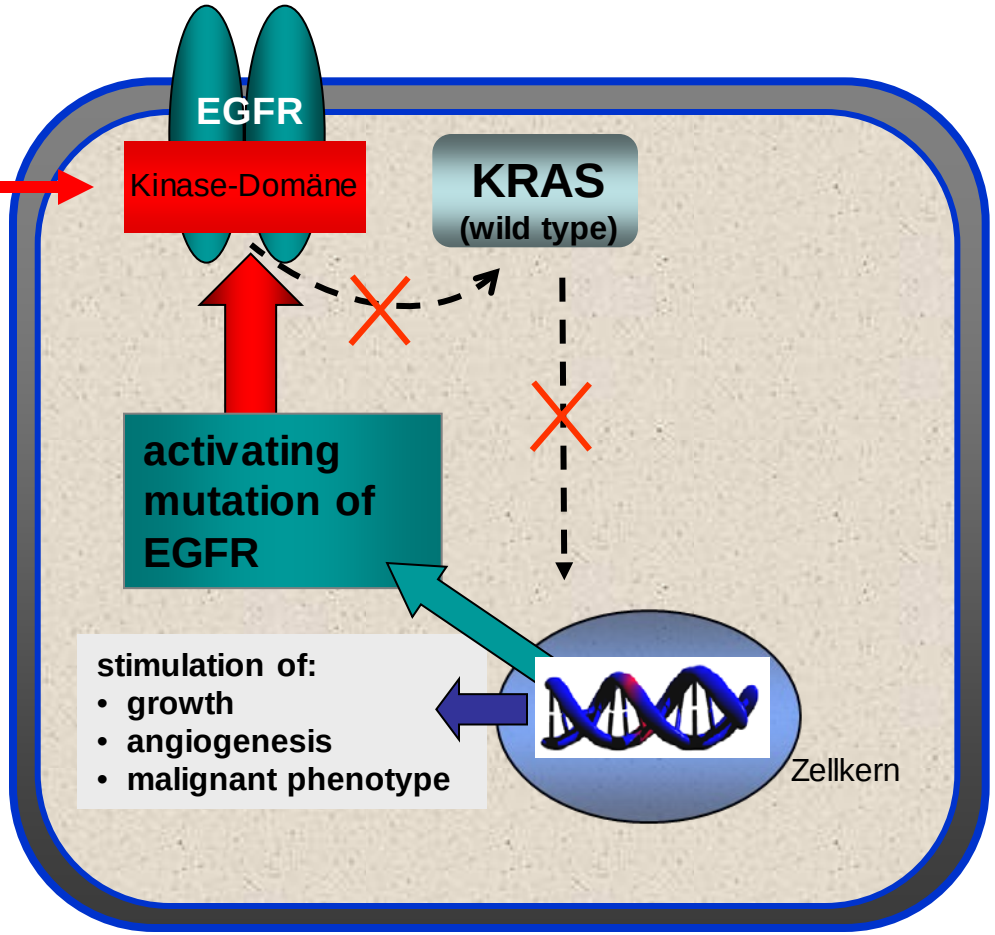


Mok et al., N Eng J Med., 2009

EGFR-mutations and EGFR tyrosine-kinase-inhibitors

EGFR-mutations of NSCLC (10-15%)

Tyrosine-kinase-inhibitors interfere with activated receptors and the corresponding pathway



Summary

577 cases* included,

174 cases no sufficient PCR product for exon 20

35 cases have less than 30% tumor.

=> 368 specimen sequenced.

Pro

Based on the experience of >3000 cases it is strongly recommended to test all 4 exons

56 M				
Exon 19	32 cases	8,7	**57,1**	45
Exon 21	14 cases	3,8	**25,0**	40-45
Exon 18	6 cases	1,6	**10,7**	5
Exon 20	4 cases	1,1	**7,2**	<1

The results correspond with those from the other institutes of the German panel institutes of the German Soc. of Path.

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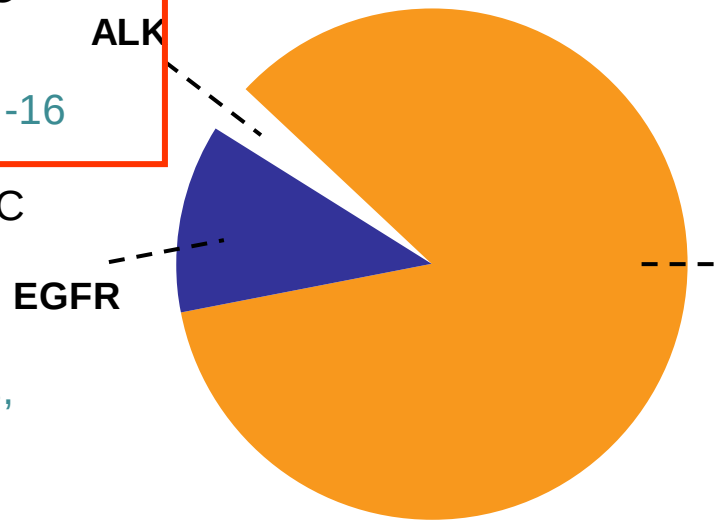

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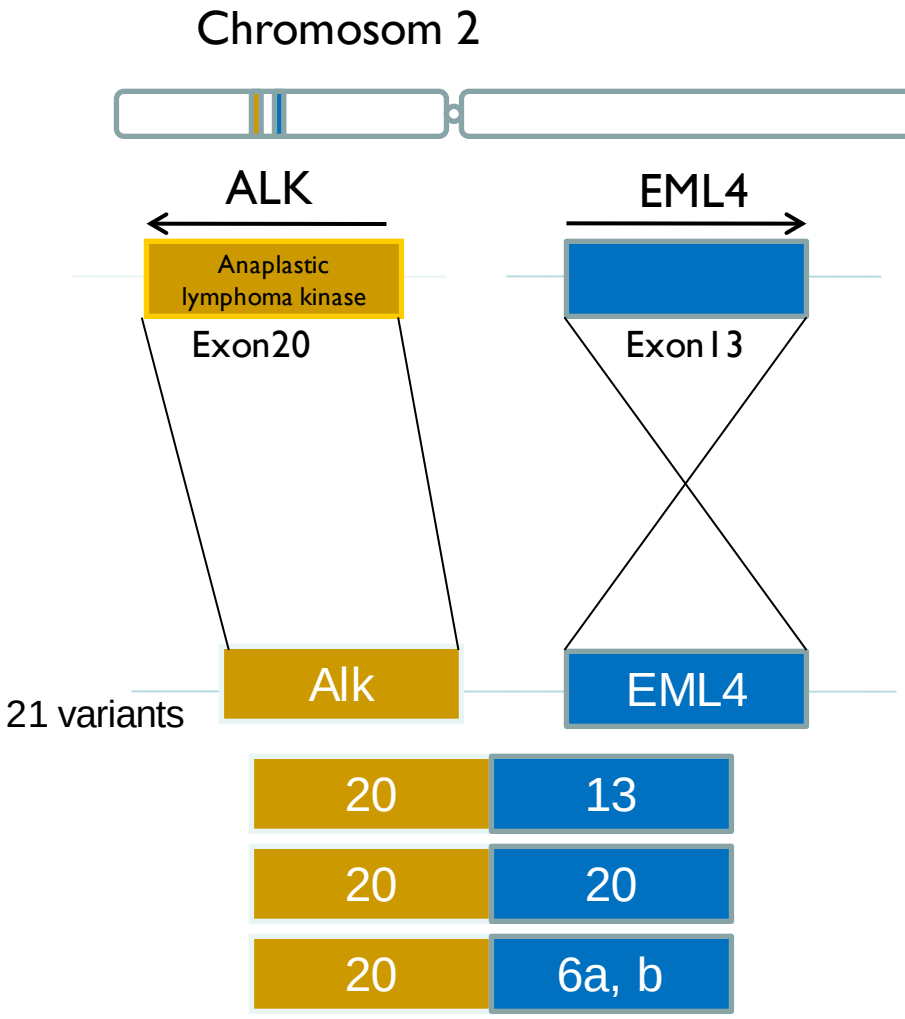
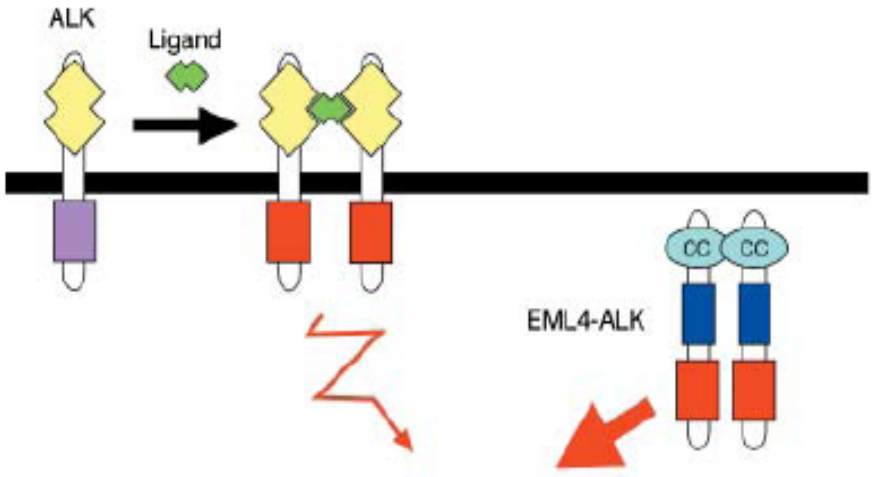
Oncogenic *EML4–ALK* gene product results from a genomic translocation



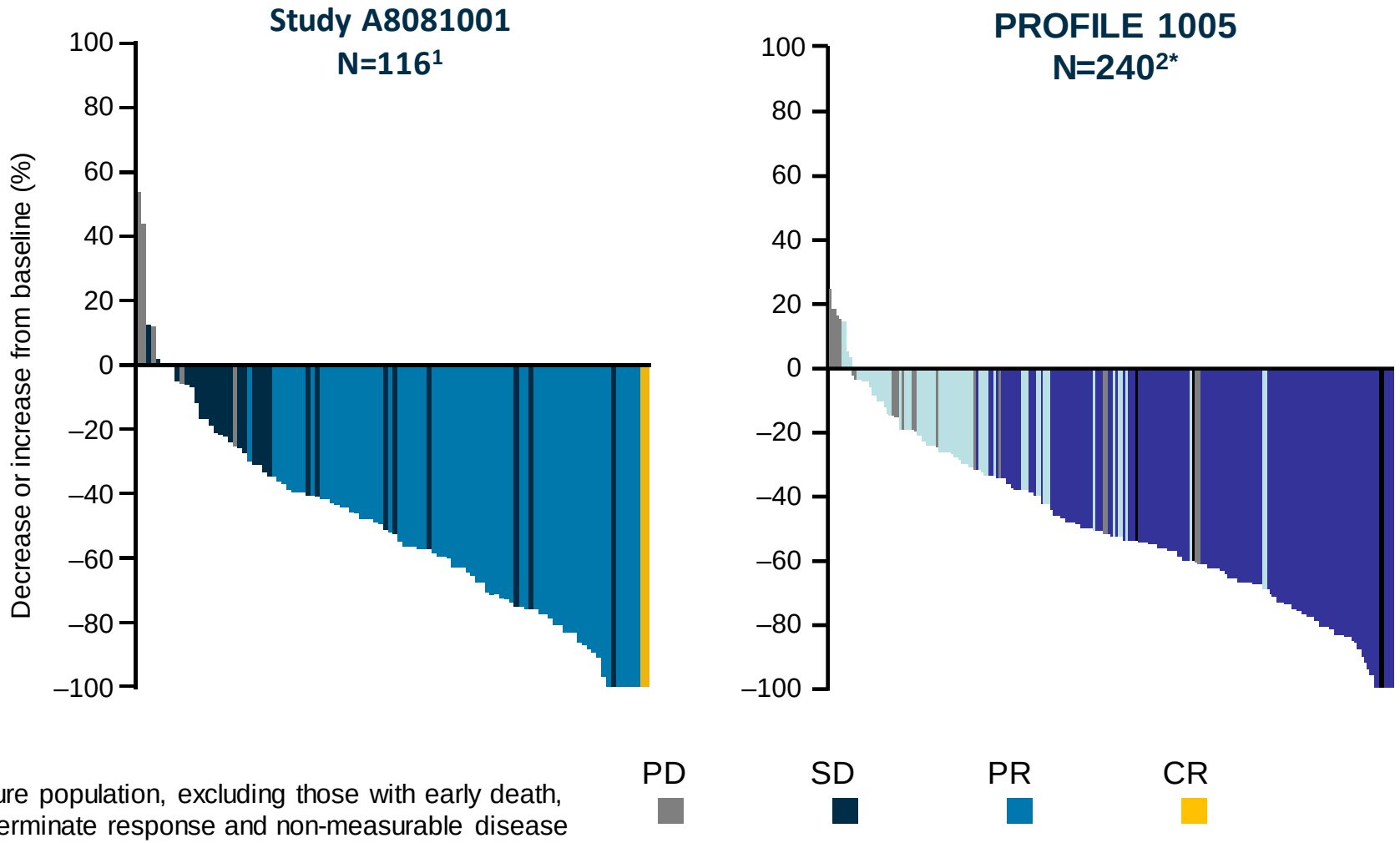


constitutive activation

cell growth

Modified according to
Soda et al. nature 448:561 (2007).

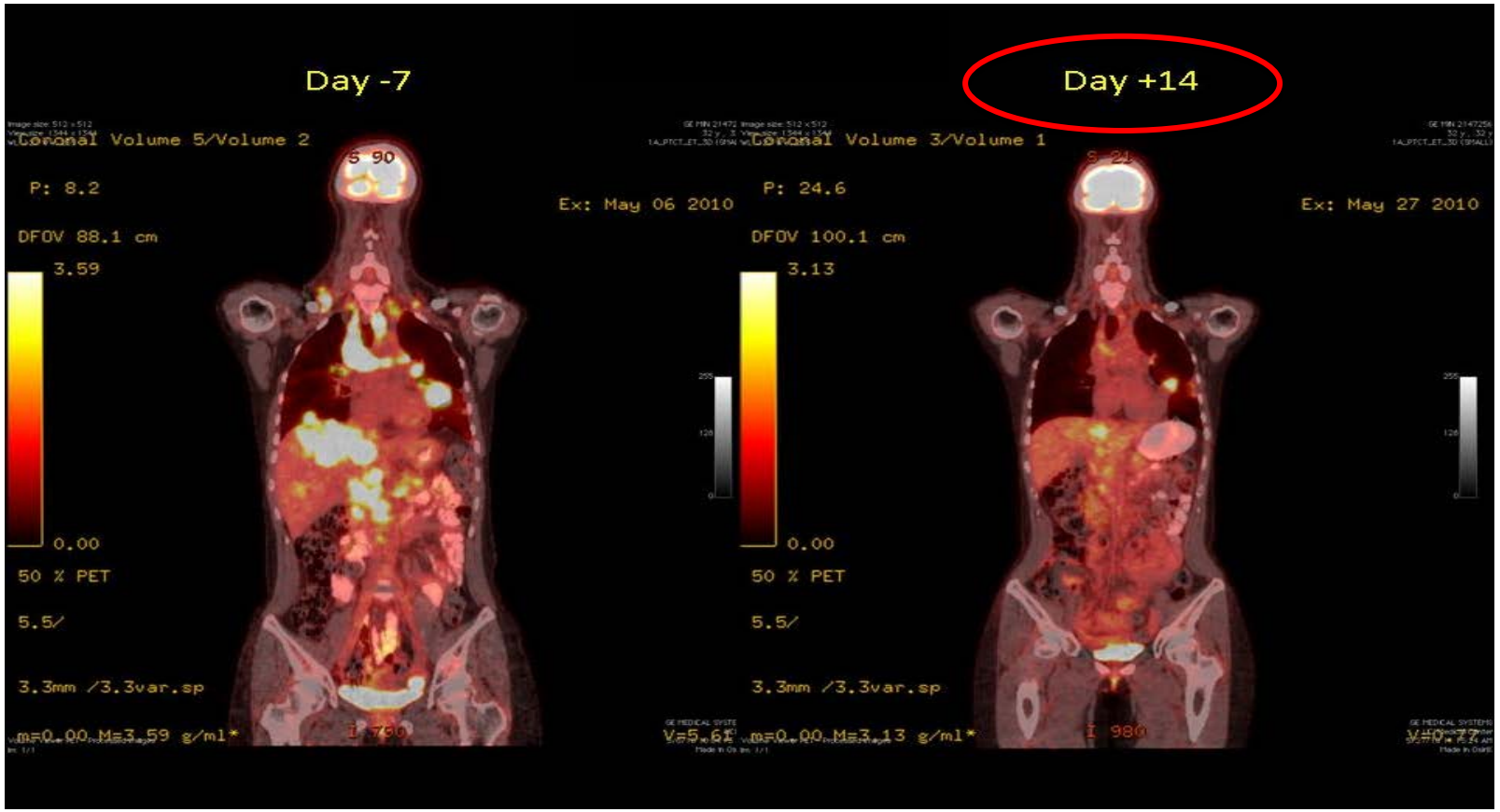
Tumour Responses to Crizotinib by Patient



*Mature population, excluding those with early death, indeterminate response and non-measurable disease

1. Camidge R, et al. Presented at ASCO 2011; Abstract 2501
2. Kim DW, et al. Presented at ASCO 2012; Abstract 7533

Rapid Responses Seen In Some Patients



Ou et al. J Thoracic Oncol 2010;5:2044–2046 Camidge RD et al.: ASCO 2011

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Acquisition of Tissue Samples

Comprehensive diagnosis of lung cancer requires:

- 1 or 2 4μm slides for H&E / PAS
- 4 to 6 4μm slides for IHC (syn, chrom A, CK5/6, CK7/8/18, p63, ERCC1, TTF1, ALK [IHC/FISH] ….controls)
- 2 to 3 10μm slides for EGFR-mut testing

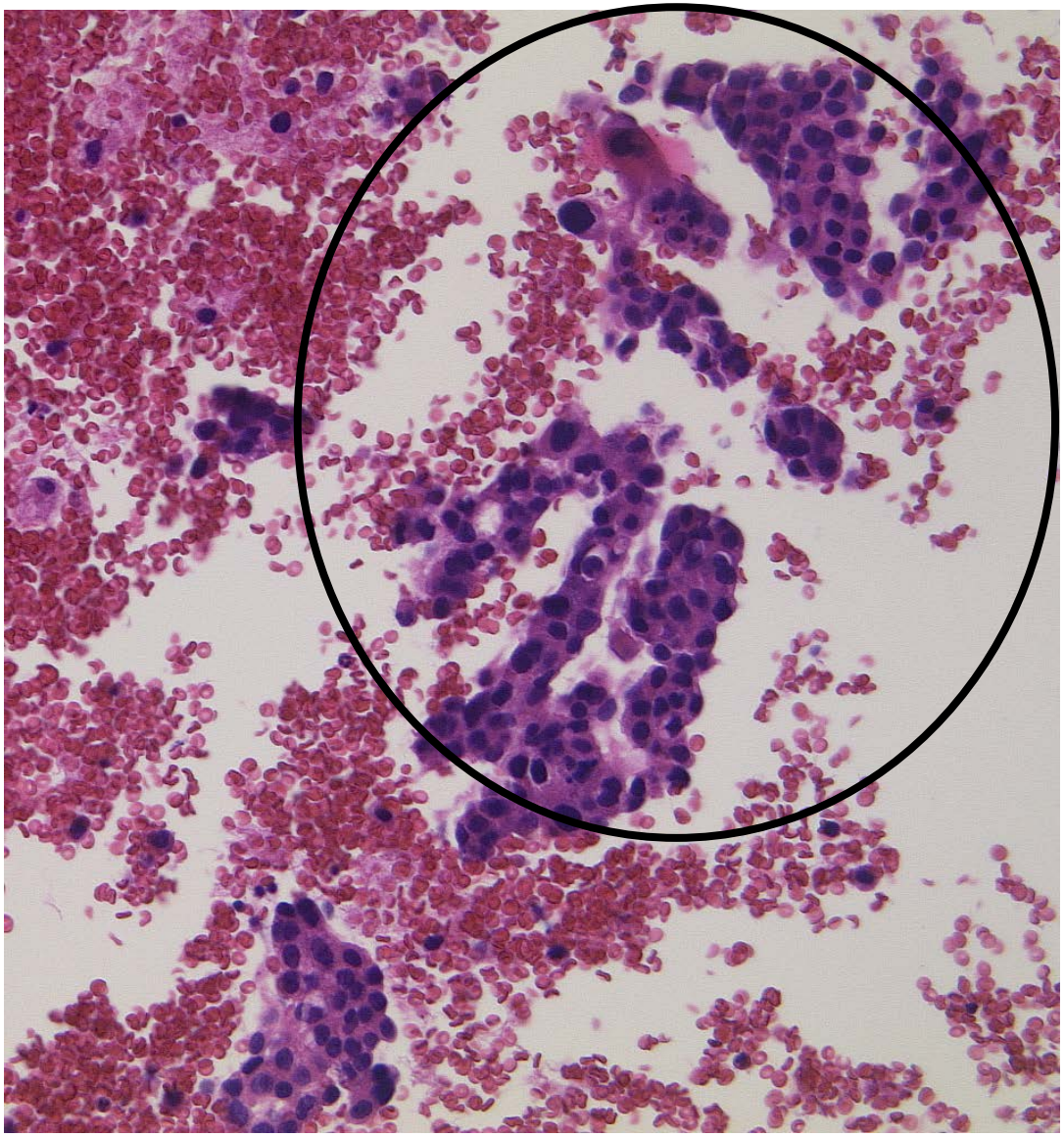
For biopsy material this means in general:

- The bigger the better
- The specimen in total should be 0.3 x 0.3 x 0.3 cm at a minimum
- Cytology, pleural effusion cell pellets or EBUS-FNA are sufficient for all tests, but the number of tumor cells have to be adequate

EBUS-FNA; endobronchial ultrasound fine-needle aspirate;
EGFR, epidermal growth factor receptor; ERCC1, excision repair cross-complementation group 1; EVG, Elastic Van Gieson;
H&E, hematoxylin and eosin; PAS, periodic acid shift;
syn, synaptophysin; TTF1, thyroid transcription factor

Thunnissen E, et al. Virchows Arch 2012;

EBUS-TBNA, EBB, TBB, cyto-block



1. **Histology/cytology**

2. **Immunohistochemistry**
   PEC: p63, CK5
   AdCA: TTF1, CK7, NapsinA
   SCLC: CD56, panCKAE1/3
   LCC
   other e.g. lymphoma metastases

3. **molecular diagnostic**

…and, and, and

slide given by R. Büttner, Köln

Cell Block

provided by Lukas Bubendorf – Universitätsspital Basel

Pellet & thrombin

FFPE Cell Block

- FFPE protocols for FISH and IHC
- Preservation of DNA and proteins

- DNA quality and morphology↓
- Often not available (tumor amount)

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Methods assessing *EGFR* mutations

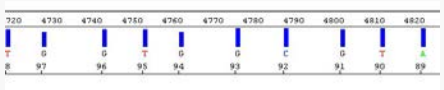
Techniques	Sensitivity (% of mutant DNA)	Mutations identified
Low sensitivity		
Direct sequencing	20	**Known and new**
TaqMan PCR	10	known only
Loop-hybrid mobility shift assay	10	Known only
Medium sensitivity		
Pyro-sequencing	5	**Known and new**
PCR-SSCP	5	**Known and new**
dHPLC	5	**Known and new**
Cycleave PCR	5	Known only
PCR-RFLP and length analysis	5	Known only
MALDI-TOF MS-based genotyping	5	Known only
Scorpions ARMS - Thera screen	1	Known only
PNA-LNA PCR clamp	1	Known only
High sensitivity		
Next generation sequencing	0.1	**Known (many)**

S. Benelloch, F. Blackhall, R. Butler, F. Ciardiello, Z. Deans, M. Dietel, M. Filipits, K. Kerr, F. Hirsch, S. Murray, N. Normano, S. Patton, S. Popat, R. Stahel, M. Taron, E. Thunnissen, A. Wallace

Molecular Methods used at Institute of Pathology, Charité Berlin

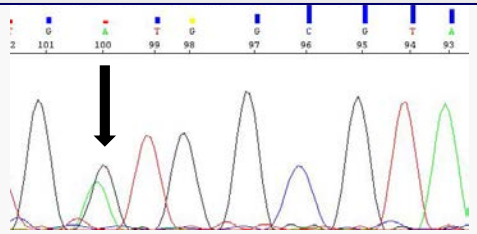
Sanger sequencing

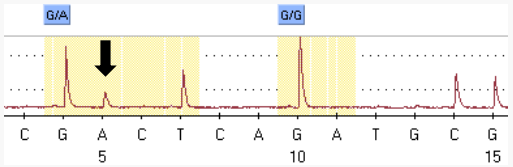
Pyro sequencing



I an own test series we found differences between Sanger- and pyro-sequencing only in 1 or 2 cases out of 200.

An explanation could be that tumor selection was done quite rigorously.

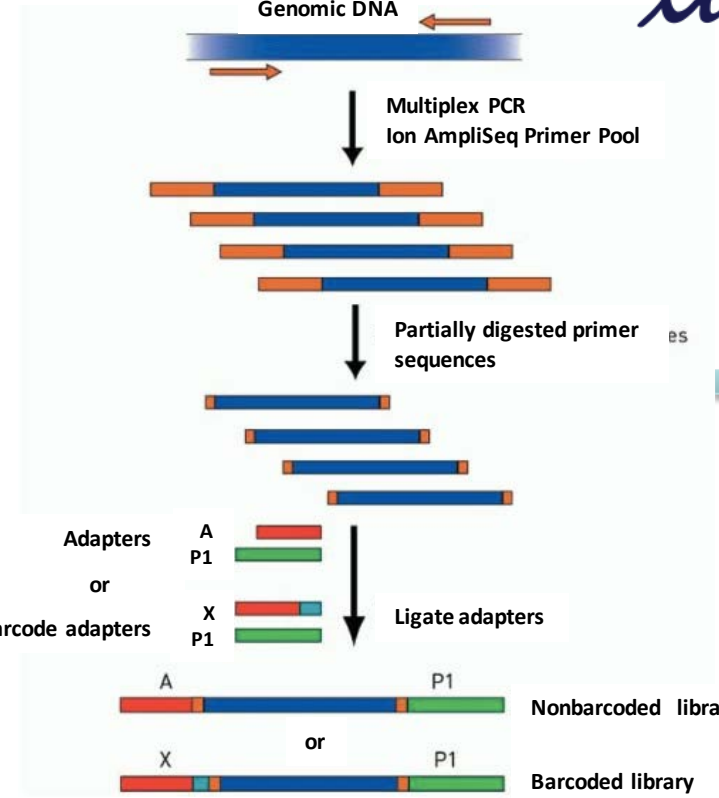




p.G12D

p.G12D

Integrating Next Generation Sequencing in Diagnostic Pathology



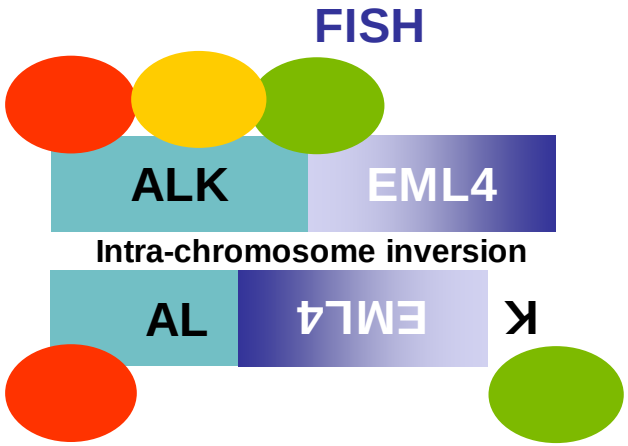
life technologies™

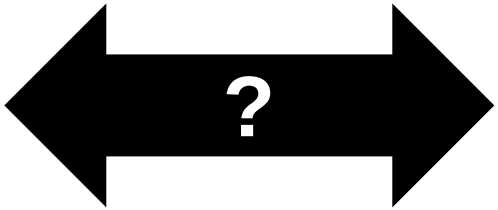
IonTorrent PGM

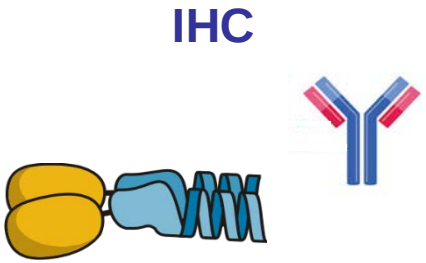
Ion AmpliSeq™ Cancer Panel targets 46 critical genes

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

Two CE-marked ALK testing kits are currently available and recommended by ESMO/CAP

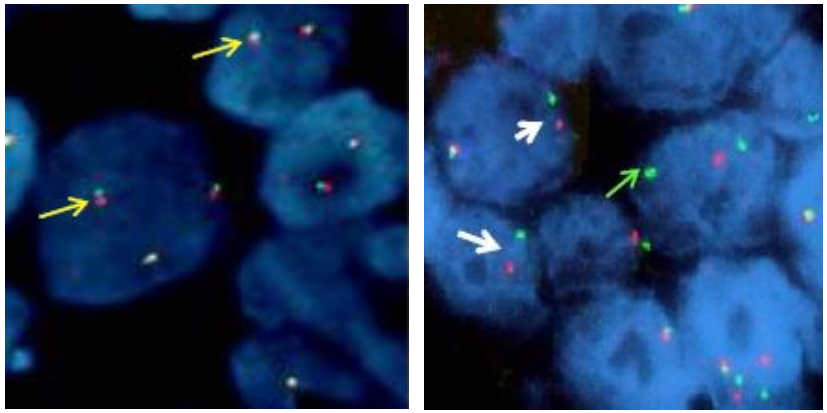






Vysis *ALK* break-apart FISH probe

VENTANA anti-ALK (D5F3) primary antibody



Wild type **ALK rearranged**

FISH, fluorescence, in-situ hybridisation

How should we test for ALK?: What the guidelines say

Second ESMO consensus conference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer

K. M. Kerr[1*], L. Bubendorf[2], M. J. Edelman[3], A. Marchetti[4], T. Mok[5], S. Novello[6], K. O'Byrne[7,8], R. Stahel[9], S. Peters[10], E. Felip[11] & Panel Members[*,†]

Level of evidence/grade of recommendation[1]

- Definitive assessment of ALK rearrangement is determined by **FISH**
- **IHC** methods **may be employed** for screening and may become validated for therapy
- Methodologies should be validated by an external **quality assurance** programme

Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology

Neal I. Lindeman, MD; Philip T. Cagle, MD; Mary Beth Beasley, MD; Dhananjay Arun Chitale, MD; Sanja Dacic, MD, PhD; Giuseppe Giaccone, MD, PhD; Robert Brian Jenkins, MD, PhD; David J. Kwiatkowski, MD, PhD; Juan-Sebastian Saldivar, MD; Jeremy Squire, PhD; Erik Thunnissen, MD, PhD; Marc Ladanyi, MD

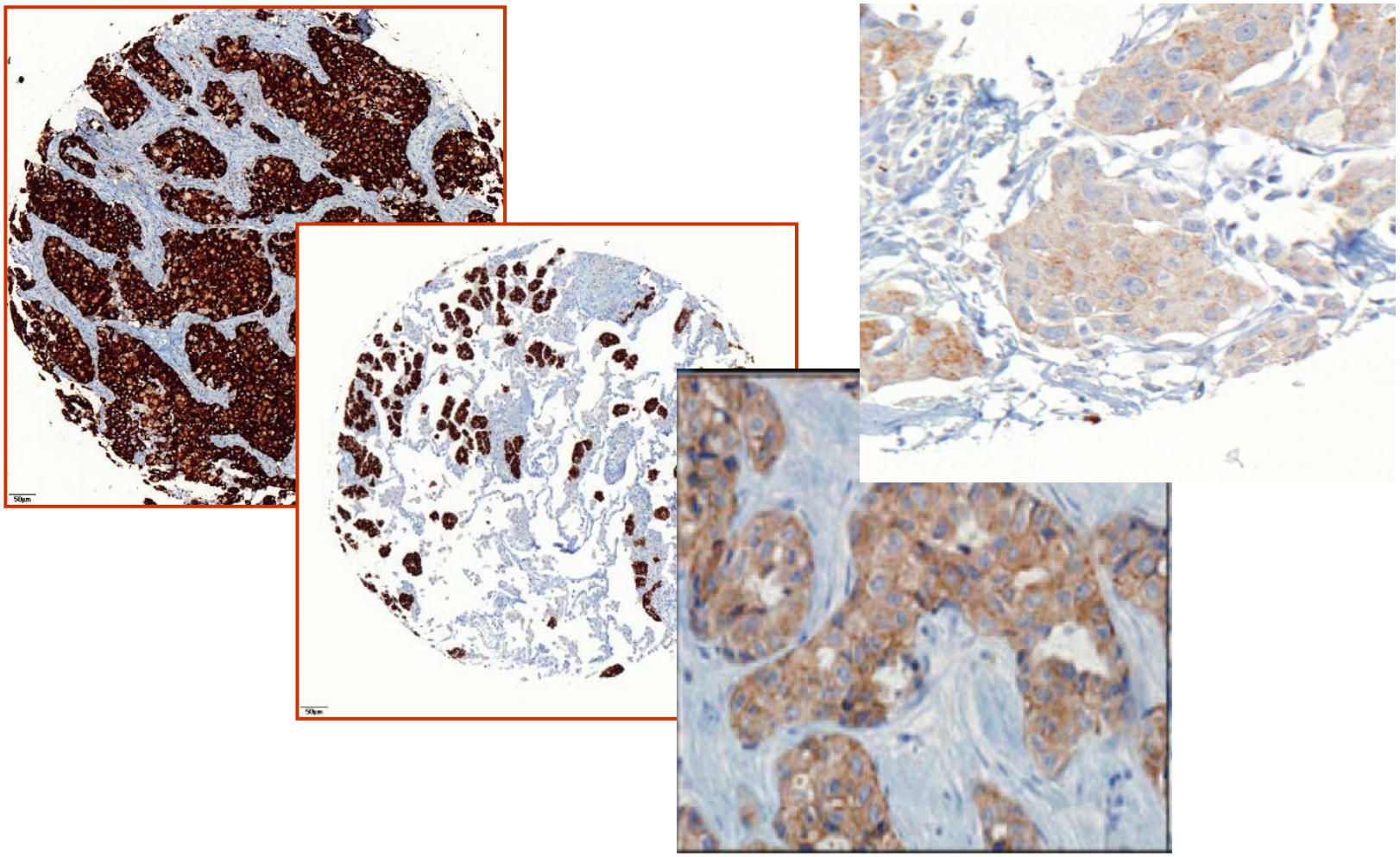
"Laboratories should use an *ALK* FISH assay using dual-labelled break-apart probes for selecting patients for ALK TKI therapy;
ALK IHC, if carefully validated**, may be considered** as a screening methodology"[2]

Consensus opinion: "A pathologist should be involved in the selection [and interpretation] of sections for *ALK* FISH…"[2]

TKI, tyrosine kinase inhibitor

1. Kerr KM, et al. Ann Oncol 2014;25:1681–90
2. Lindeman NI, et al. J Thorac Oncol 2013;8:823–59

ALK immunocytochemistry on tissue – (D5F3)



High concordance between IHC and FISH tests

100% concordance between FISH and IHC across most centres

Cleveland Clinic Foundation, USA[1]

- 318 samples from 296 patients, July 2010 to August 2012
- Ventana ALK D5F3 primary anitbody coupled with OptiView detection

Relative to FISH, IHC had 94% sensitivity and 100% specificity

National Cancer Center Hospital, Tokyo, Japan[2]

- 80 samples
- Ventana ALK D5F3 primary anitbody

98.8% concordance between IHC and FISH

Charité Berlin, Inst. of Pathology[3]

- 800 samples
- Ventana ALK D5F3 primary anitbody coupled with OptiView detection
- Web-based training for IHC interpretation (not jet published)

1. Minca EC, et al. J Mol Diagn 2013;5:341–6
2. Nitta H, et al. J Thorac Oncol 2013;8:1019–31
3. Dietel et al. in preparation

Parallel FISH and Immunohistochemical Studies of ALK Status in 3244 Non–Small-Cell Lung Cancers Reveal Major Discordances

Florian Cabillic, PharMD, PhD,†‡ Audrey Gros, PharMD, PhD,§ Frédéric Dugay, PharMD,*‡‖*
Hugues Begueret, MD, PhD,¶ Laura Mesturoux, MD,§ Dan Cristian Chiforeanu, MD,#
*Leila Dufrenot, MD,¶ Vincent Jauffret,‡ Dominique Dachary, MD,§ Romain Corre, MD,***
Alexandra Lespagnol, PhD,†† Gwendoline Soler, MD, PhD,§ Julien Dagher,‡‖*
Véronique Catros, PharMD, PhD,†‡ Michèle Le Calve, PharMD,*‡ Jean-Philippe Merlio, MD, PhD,§*
and Marc-Antoine Belaud-Rotureau, PharMD, PhD‡‖*

Results: … Thus, a single FISH or IHC analysis alone would have failed to detect approx. one-fourth of ALK-positive cases with similar findings in 2 centers.

Conclusions: …. Many pre-analytic factors may account for the apparent discrepancies ….
… The significant level of discrepancies supports the need of combined testing to optimize the detection of ALK-inhibitor-eligible patients …..

Journal of Thoracic Oncology® • Volume 9, Number 3, March 2014

Pfizer Oncology

November 14-16, Tucson

Following an expert meeting at Ventana-Roche together with Pfizer Oncology the

Harmonization-Study was initiated to test reproducibility of immunohistochemistry (IHC-D5F3/Roche-VENTANA detection system) in ALK-rearranged NSCLC in 16 labs around Europe

---

Manfred Dietel, Maximilian von Laffert, Michael Hummel

Institute of Pathology, Charité, Berlin, Germany

A cooperation between Inst. of Pathology (Charité, Berlin), Pfizer Oncology and Ventana/Roche Diagnostic.

Laffert M, et al. J Thorac Oncol; 2014

Framework Conditions

- Prior to the TMA-based case testing, each participating instrument was qualified using the VENTANA ALK 2 in 1 Control Slides.
- Qualification was done by Ventana staff.
- All participants used the same AB, dilution, detection system etc.
- A webinar-based training was given to all observers.
- This training included an overview of the ALK Interpretation Guide, a guided review of 50 patient cases using digital whole slide images, and a proficiency exam certifying each observer.

ALK-negative cases (n=7): binary evaluation ROCHE-VENTANA (pos. vs. neg.)

observer	case 2	case 4	case
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			

ALK-positive cases (n=8): binary evaluation ROCHE-VENTANA (poAs. vs. neg.)

observer	case 1	case 3	case (BL**)	case 8	case (BL**)	case 11	case 14	Case 15
1								
2				FISH		FISH		
3								
4								
5						FISH*		
6						FISH/ PCR		
7								
8				FISH*				
9						FISH*		
10								
11								
12						FISH*		
13								
14								
15						FISH*		
16						FISH		

negative
positive

von Laffert M, et al. Presented at WCLC 2013: P1.06–023, J Thorac Oncol 2014 published online

Consequence

Multicenter Immunohistochemical ALK-Testing of Non–Small-Cell Lung Cancer Shows High Concordance after Harmonization of Techniques and Interpretation Criteria

Maximilian von Laffert, MD, Arne Warth, MD, PhD,† Roland Penzel, MD,†*
Peter Schirmacher, MD, PhD,† Keith M. Kerr, MD, PhD,‡ Göran Elmberger, MD, PhD,§
Hans-Ulrich Schildhaus, MD, PhD,‖ Reinhard Büttner, MD, PhD,‖ Fernando Lopez-Rios, MD, PhD,¶
*Simone Reu, MD # Thomas Kirchner, MD, PhD # Patrick Pauwels, MD, PhD ** Katia Specht, MD, PhD ††*

ORIGINAL ARTICLE

An International Interpretation Study Using the ALK IHC Antibody D5F3 and a Sensitive Detection Kit Demonstrates High Concordance between ALK IHC and *ALK* FISH and between Evaluators

Murry W. Wynes, PhD, Lynette M. Sholl, MD,† Manfred Dietel, MD,‡ Ed Schuuring, PhD,§*
Ming S. Tsao, MD, FRCPC,‖ Yasushi Yatabe, ME, PhD,¶ Raymond R. Tubbs, DO,#
*and Fred R. Hirsch, MD, PhD***††*

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logists

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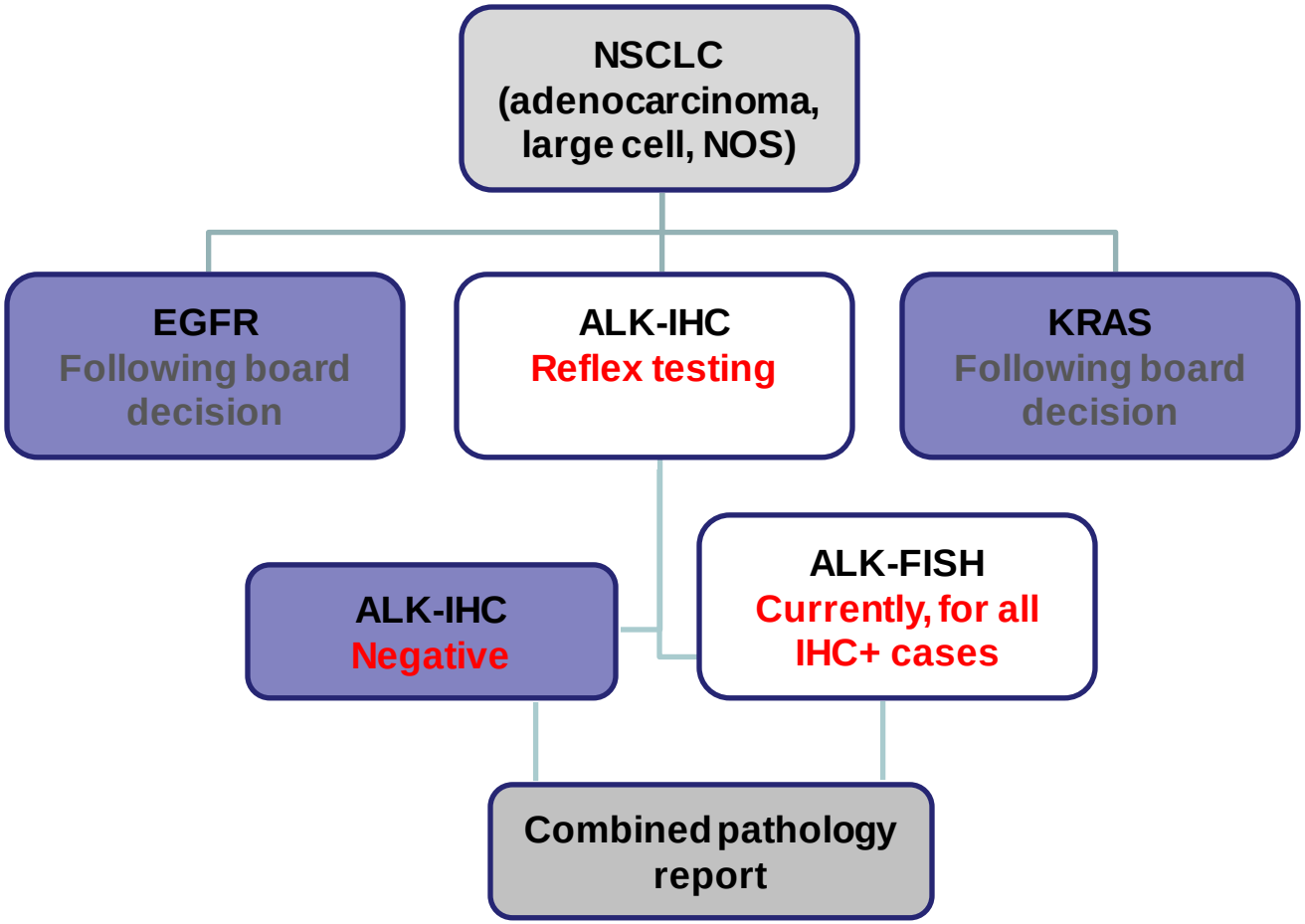
approach for predictive diagnoses.

Von Laffert et al. J Thorac Oncol 2014 published online

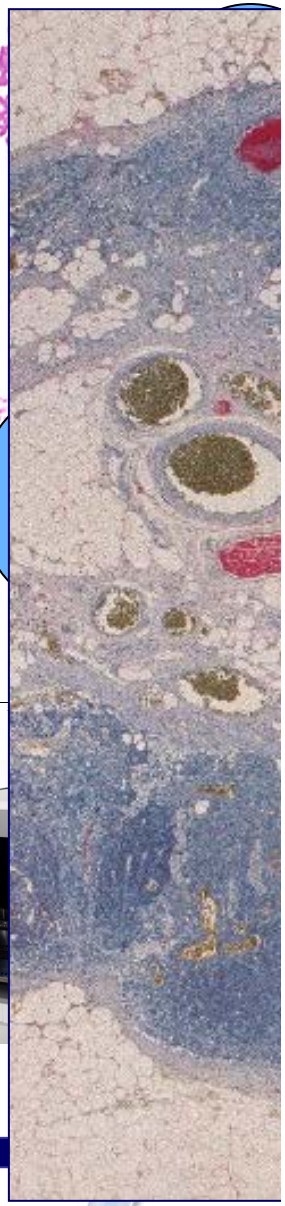
NSCLC molecular testing algorithm at University Hospital Charité



Quality Control

What is the irreplaceable role of anatomic pathology in the procedure of molecular biomarker analysis?

One key point is tissue selection!



Qualitätssicherungs-Initiative Pathologie

QuIP

Ringversuche Immunhistochemie
und Molekularpathologie

Teilnahmezertifikat

4. Ringversuch EGFR-Mutationsbestimmung beim NSCLC.

2013

Prof. Dr. med. Manfred Dietel
Charité - Universitätsmedizin Berlin
Institut für Pathologie
Charitéplatz 1
10117 Berlin

hat am Ringversuch ‚EGFR-Mutationstestung beim NSCLC' mit Erfolg teilgenommen.

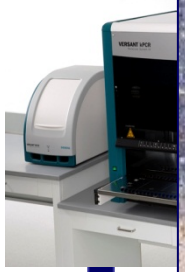
Leitung des Ringversuches:
Prof. Dr. med. P. Schirmacher, Prof. Dr. med. M. Dietel,
Dr. R. Penzel, Dr. Chr. Schewe

Prof. Dr. med. P. Schirmacher
Deutsche Gesellschaft für Pathologie e. V.

Prof. Dr. med. W. Schlake
Bundesverband Deutscher Pathologen e. V

Bestandteil dieser Teilnahmebescheinigung ist die getrennt gefasste, inhaltliche Beurteilung der Untersuchung.

Träger der Ringversuche Immunhistochemie und Molekularpathologie QuIP
Deutsche Gesellschaft für Pathologie e.V., Berlin, Tel: 030 / 25760727, Mail: geschaeftsstelle@dgp-berlin.de
Bundesverband Deutscher Pathologen e.V., Berlin, Tel: 030 / 3088197-0, Mail: bv@pathologie.de



té Berlin

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CHARITÉ

QC of EGFR Mutation Analyses

Quality in Pathology*
QuIP

Final recommendations based on > 5000 cases processed in routine diagnostic

- Primarily (2006) 15% of participants failed → QC is absolutely essential
- Today the failure rate is < 5%.
- Clinicians should cooperate only with institutes, which passed the quality control (although in Germany there is no respective law)
- Clinical studies should involve only certified institutes,
- Currently mutation analyses are mandatory for routine diagnostic only of exon 19 und 21, but 18 and 20 are also recommended,
- otherwise 5 - 10% of all mutated cases will not be detected.
- The certified institutes are published on the home pages of the DGP

* Quality in Pathology, an initiative of the German Soc. of Pathology (DGP) and the German Association of Pathologists (BDP)

Structure of the talk on NSCLC Testing

- General introduction on molecular pathology
- What to test: sampling / tissue / cytology
- How to test
  - Methods / quality control
    - FISH
    - IHC
    - Sanger-, pyro- or NG Sequencing
- How to report
- Who to test
- When to test
- Future development

Reporting of Mutation Analyses – EGFR, ALK

Main Issue: **The report should be readily understandable for clinicians. It should contain a clear statement to select appropriate therapy.**

Charité's pathology report* includes

- **standard patient identifier**
- **histological diagnosis, including all relevant morphological characteristics**
- **technical information on the assay performed, assay sensitivity**
- **percentage of tumor cells**
- **number of cell analyzed**
- **each exon sequenced**
- **each mutation detected**
- **clinically significant mutations, terminology adapted to local agreement**
- **clear statement on the likelihood of the tumor to respond.**

Modified from the Guidelines from the College of Am. Pathologists, Int. Ass.for the Study of Lung Cancer and Ass. for Mol. Path. --- Lindeman et al. Molecular Testing …. J Thoracix Oncol, 8: 823, 2013

Who to test for ALK? ESMO/CAP/IASLC/AMP 2013 guidelines

Major recommendations

ALK-testing should be performed in

- **all patients with advanced-stage adenocarcinoma,**
- **regardless of sex, race, smoking history, or other clinical risk factors,**
- **selected squamous tumours (from patients with minimal or remote smoking history) should be strongly considered for testing**

ESMO, Europ.Soc. For Medical Oncology

AMP, Association for Molecular Pathology; CAP, College of American Pathologists; EGFR, epidermal growth factor receptor; IASLC, International Association for the Study of Lung Cancer

Lindeman NI, et al. J Thorac Oncol 2013;8:823−59

Kerr KM, et al. Ann Oncol 2014;25:1681–90

Recommendations from the CAP/IASLC/AMP guidelines: How quickly should results be available? Who should be involved

"EGFR and ALK results should be available within 2 weeks (10 working days) of receiving the specimen in the laboratory"

Due to the clinician's demand and patient's wish in Germany we try to provide the results within 5 days

Consensus opinion: "A pathologist should (must be – by German law) be involved in the selection and interpretation of sections for ALK FISH……"

Lindeman T, et al. J Mol Diagn 2013;15:415–53

Structure of the talk on NSCLC Testing

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AZD9291 Clinical Development Programme in Advanced and Metastatic EGFR T790M+ NSCLC

Medical Affairs

AURA[1]

Ongoing, recruitment completed

Single-arm, Phase I dose escalation (N = 31) and Phase II extension (N=222) 2nd line (prior EGFR TKI only) and ≥3rd line[1–3]

Phase I: Safety, tolerability, PK and antitumour activity[1–3]	**Phase II:** Efficacy and tolerability 80 mg QD in T790M NSCLC[1–3]

AURA2[4]

Ongoing, recruitment completed

Single-arm, Phase II (N=210) 2nd line (prior EGFR TKI only) and ≥3rd line
Efficacy and tolerability
80 mg QD in T790M NSCLC

AURA3[5]

Recruitment completed

Randomised comparative Phase III (N=~410)
Efficacy and safety of AZD9291 80 mg QD vs platinum-based doublet CT in patients with T790M, advanced/metastatic NSCLC following prior EGFR TKI

Timelines

EMA Submission
June 2015

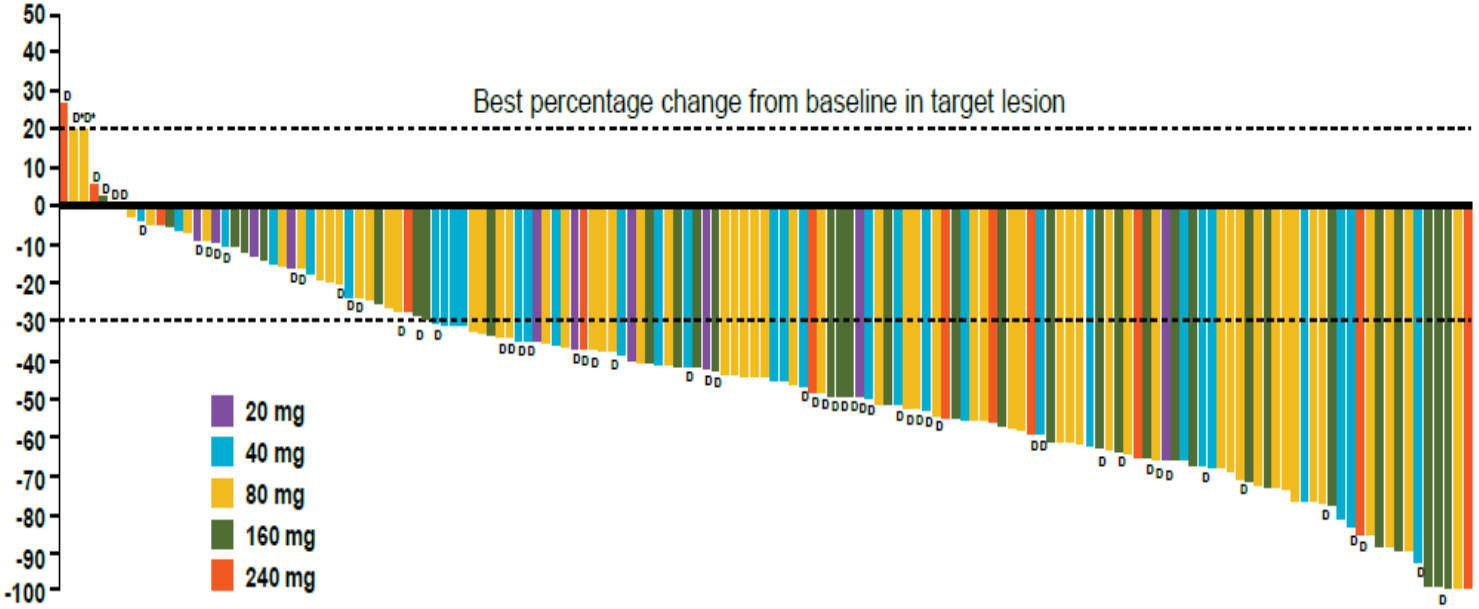
Potential label:
T790Mpos after treatment with TKI

1. NCT01802632. www.clinicaltrials.gov; 2. Jänne P, et al. ELCC 2015;Abstract #LBA3; 3. Jänne P, et al. NEJM 2015;372(18):1689-99; 4. NCT02094261. www.clinicaltrials.gov; 5. NCT02151981. www.clinicaltrials.gov.

AZD9291 – 66% ORR in T790M positive patients*

Medical Affairs

*as assessed by central tumor tissue testing

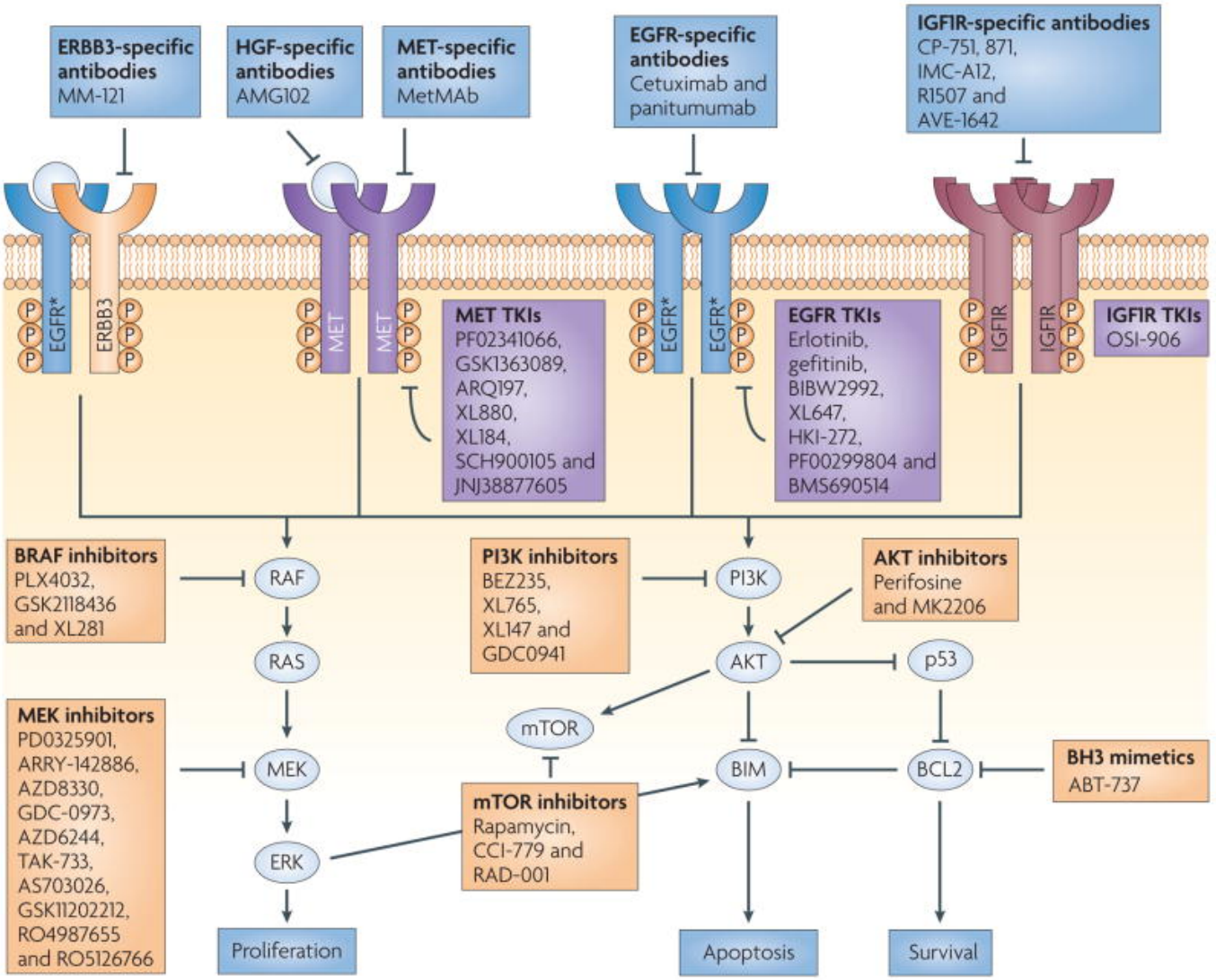


DCR (CR+PR+SD) in patients with centrally tested T790M positive tumours was 90% (141 / 157; 95% CI 84, 94)

	20 mg	40 mg	80 mg	160 mg	240 mg	Total
N (157)	10	32	61	41	13	157
ORR (95% CI)	50% (19, 81)	59% (41, 76)	66% (52, 77)	51% (35, 67)	54% (25, 81)	59% (51, 66)

Presented by Pasi A Jänne at the 2015 European Lung Cancer Conference. Ann Oncol 2015; 26(Suppl 1): i60, LBA3.

Multi-pathway Inhibition as Strategy to treat TKI-resistant NSCLC



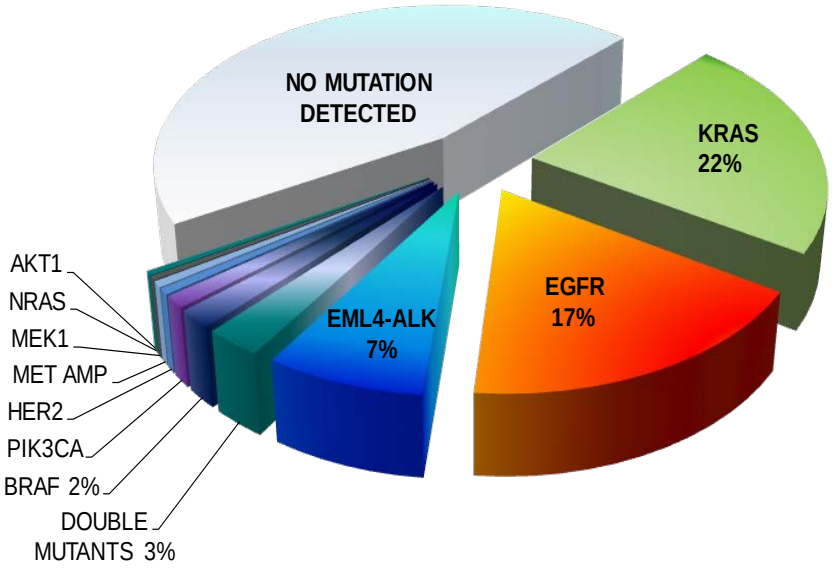
Pao et al., Nat Rev Cancer 2011

2nd Generation ALK-Inhibitors

Other ALK-inhibitors in development include:

ceritinib and alectinib

Irreversibly binding, pan-HER inhibitors in clinical development include:
dacomitinib (Phase 3) and HM781-36B (Phase 1; solid tumours)



Dacomitinib (PF-00299804; Pfizer Inc.) is an investigational compound not currently licensed for use in any market

1. Kim D-W, et al. Presented at ASCO 2012; Abstract 7533
2. Schiller JH, et al. N Engl J Med 2002; 346:92–8
3. Maemondo M, et al. N Engl Med 2010;362: 2380-8
4. Rosell R, et al. Lancet Oncol 2012;13: 239–46
5. Yang C-H, et al. Presented at ASCO 2012; Abstract LBA7500

Check-point Inhibitors: Up-coming Proteomic Diagnostics

The NEW ENGLAND JOURNAL of MEDICINE

Garon EB, ASCO 2015
Keynote-001 Phase Ib
NSCLC: 15% Adeno, 80% Platte
DAKO **22C3**

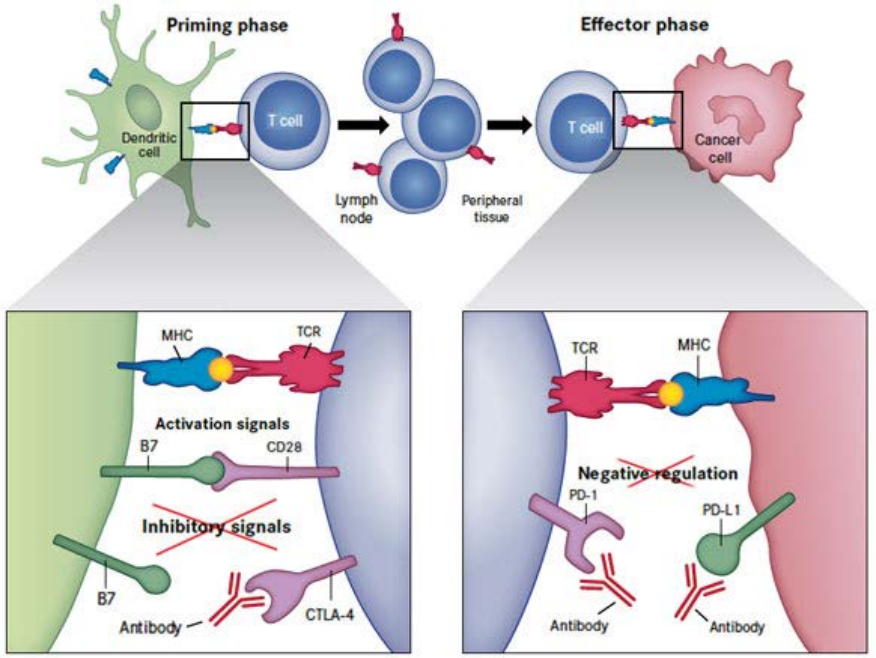
ORIGINAL ARTICLE

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

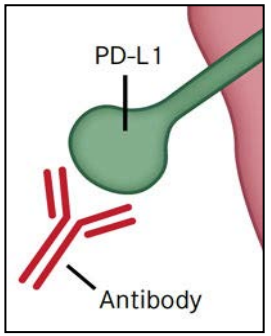
Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D., Enriqueta Felip, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.D., Omid Hamid, M.D., Jonathan W. Goldman, M.D., Jean-Charles Soria, M.D., Marisa Dolled-Filhart, Ph.D., Ruth Z. Rutledge, M.B.A., Jin Zhang, Ph.D., Jared K. Lunceford, Ph.D., Reshma Rangwala, M.D., Gregory M. Lubiniecki, M.D., Charlotte Roach, B.S., Kenneth Emancipator, M.D., and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators*

Immuntherapy of Cancer

Stimulation of the immunsystem by blocking immun-suppressive receptor protein interactions => PD-1/PD-L1

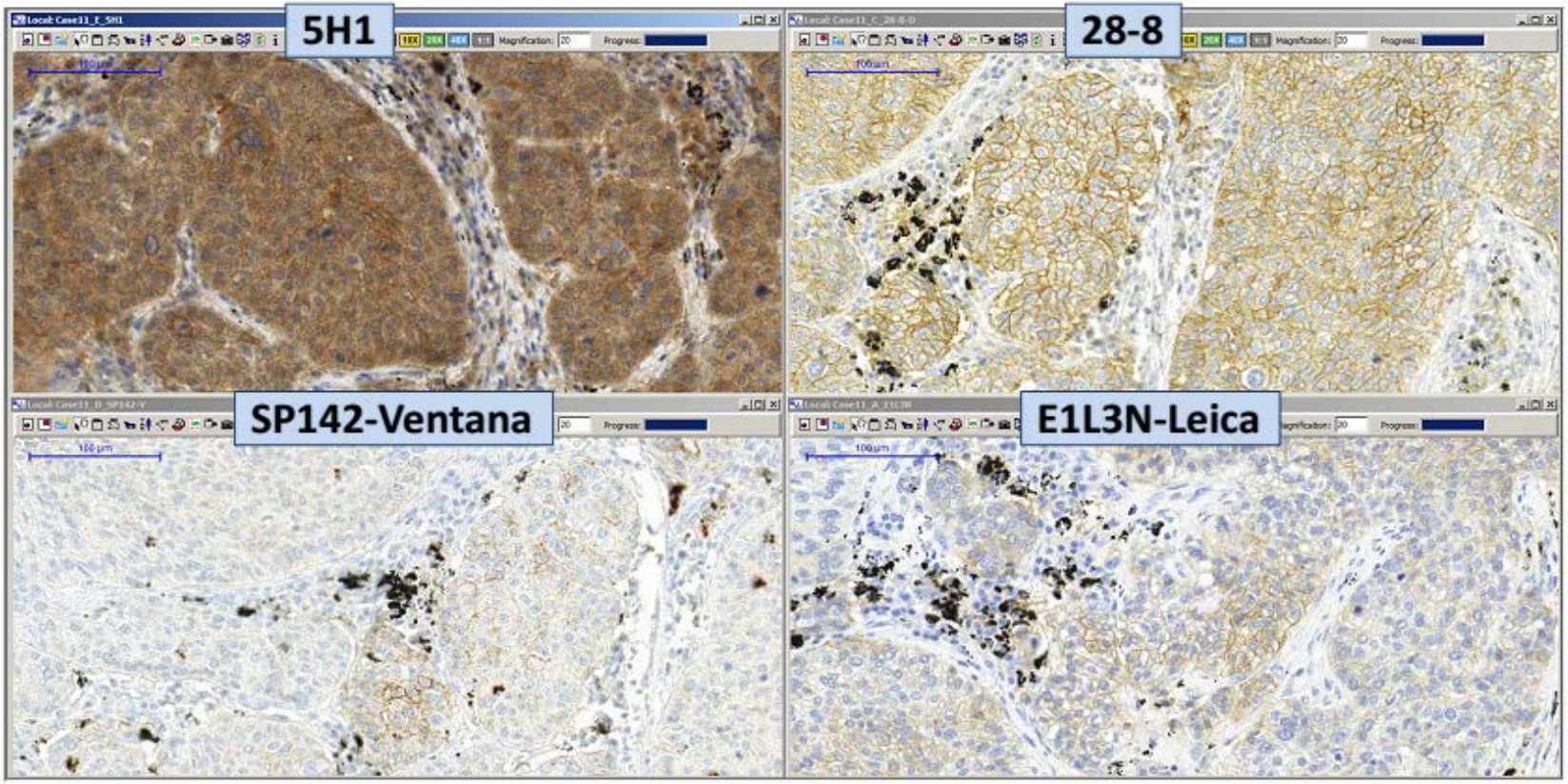


IHC of PD-L1



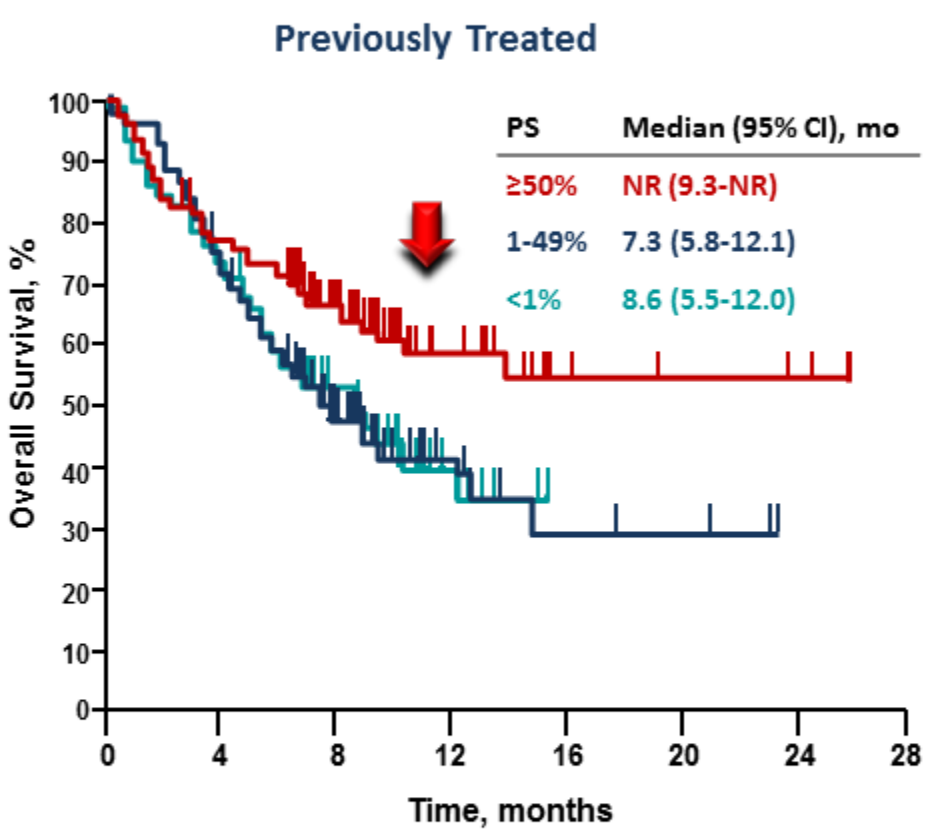
The Role of Anti-PD-L1 Immunotherapy in Cancer – OncLive - published online

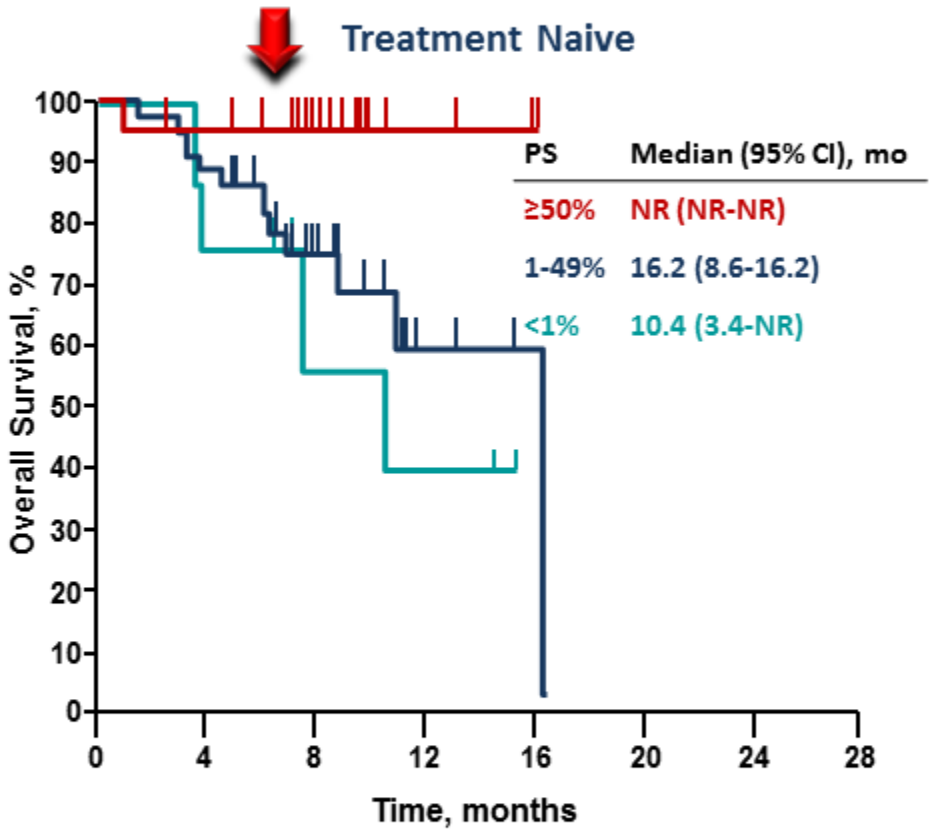
Check-point Inhibitors: IHC of PD-L1



Case 11	Pathologists									Modus	Agreement
	P1	P2	P3	P4	P5	P6	P7	P8	P9		
Tumor, E1L3N	4	2	3	4	4	5	4	4	6	4	56%
Tumor, SP142	5	4	3	4	5	5	5	4	5	5; 4	56%
ImmuneCells, E1L3N	1	0	0	1	1	1	0	0	0	0	56%
ImmuneCells, SP142	1	1	1	1	1	1	0	1	1	1	89%

OS by PD-L1 Expression, Evaluable Patients by Prior Treatment





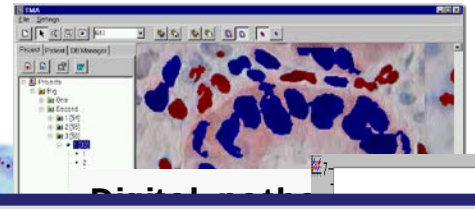
n at risk							
99	74	45	18	5	4	3	0
127	89	43	12	5	4	0	0
68	49	30	6	0	0	0	0

n at risk							
20	18	11	4	0	0	0	0
34	30	15	3	1	0	0	0
8	6	3	2	0	0	0	0

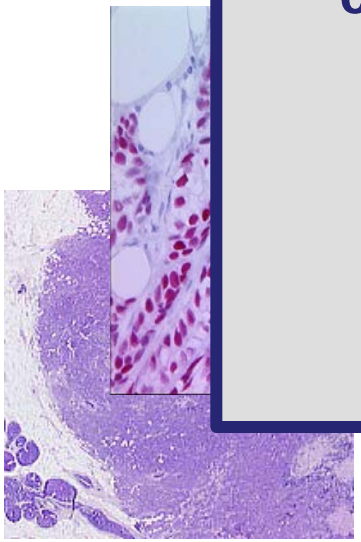
OS was assessed in all patients whose samples were stained within 6 months of cutting.
Analysis cut-off date: August 29, 2014.

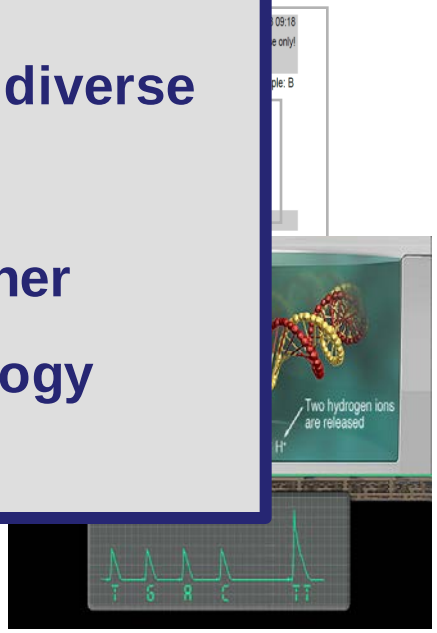
Clinical data tissue

All test are done on formalin fixed



Personalized medicine is based on a "combined morphological-molecular pathology report" including classical morphology (HE/IHC/FISH) and diverse molecular analyses – to do this in a fast and reliable manner will be the future challenge of pathology






Institut für Pathologie,
Rudolf-Virchow-Haus, Charité
Humboldt-Universität zu Berlin
Berliner
Medizin-historisches
Museum
Alexander Ufer

Conclusions

- Durable antitumor activity in a large, advanced NSCLC population
  - Median duration of response exceeds 1 year
- Manageable toxicity profile
  - Low incidence of possibly immune-mediated AEs
- PS ≥50% identifies those patients with the greatest likelihood of benefit
  - Represents 23.2% of the screened NSCLC population
  - ORR (validation set): 45.2%
    - Previously treated: 43.9%; treatment naive: 50.0%
  - Median PFS: 6.3 months
  - Median OS: not reached
- Benefit in the previously treated PS ≥50% subgroup substantially exceeds that expected from cytotoxic chemotherapy