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Seminar N2
Targeted Therapies in Hospital Pharmacy – One Problem, Two Views

Conflicts of interest

Participation in Advisory Boards

- Amgen GmbH, MSD Sharp & Dome GmbH, Roche AG

Speakers´ honorarium

- Amgen GmbH, Berner International GmbH, Celgene GmbH, MSD Sharp & Dome GmbH

No other conflicts of interest to declare

Agenda

- Targeted therapies in oncology: examples and limitations
- Difference to stratified and personalized therapy
- Biomarkers: Definitions, examples and challenges
- The story of (k)-ras as a biomarker in colorectal cancer

Targeted therapies

Attempt to focus on a biochemical structure likely playing an important role in tumor pathology

Objective: Focus only on main pathological structure in and on tumor cells, less side effects

- Cell-surface-protein antibodies (i.e. CD- or growth-factor-antibodies)
- Tyrosine-kinase-inhibitors (i.e. bcr-abl, k-ras, b-raf)
- Anti-Cytokines (i.e. against TNF-α, IL-6)

„Targeted“ Therapies: examples

Drug	Indication	Molecular marker	Significant advantage
Arsenic trioxide (Trisenox®)	AML M3 (Promyelocyte leukemia)	t(15;17)-translocation a/o PML/RARα-Gen	24-month-OS-probability: 99% in combination with ATRA
Cetuximab (Erbitux®) **Panitumumab (Vectibix®)**	met. Colorectal-Ca locally advanced Head and Neck-Ca	RAS-wild type	Cetuximab+FOLFOX: med OS 2,9 months (not signif.) Panitumumab+FOLOX : med OS 5,8 months
Dasatinib (Sprycel®) **Imatinib (Glivec®)** **Nilotinib (Tasigna®)**	CML	Fusioned protein BCR-ABL (Philadelphia-Chromosome)	Imatinib: signifikantly less patients with progression to accelerated phase oder blast crisis (92 vs 85%) after 84 months
Gefitinib (Iressa®)	NSCLC	EGFR-mutation	vs Carboplatin/Paclitaxel: med PFS 3,2 months QoL: +25,7%
Lapatinib (Tyverb®) **Trastuzumab (Herceptin®)**	progressive met. Breast-Ca adjuvant Breast-Cancer-Therapy	HER2 (EGFR)-Overexpression (3+)	+ Capecitabin: TTP 5,6 months + Chemotherapie (AC → P): recurrent disease: -52%, death: -37%
Maraviroc (Celsentri®)	HIV, AIDS	HIV-Affinity to CCR5-receptor	+OBT : Significant Reduktion of HIV-1-RNA-Count after 48 weeks
Tamoxifen (Nolvadex®)	Adjuvant Mamma-Ca	Hormone receptor-expression	significantly reduced recurrence rates
Trastuzumab-Emtansin (Kadcyla®)	Locally advanced or metastatic Breast-Ca	HER2 (EGFR)-Overexpression (3+)	OS vs Lapatinib+Capecitabine 5,8 months

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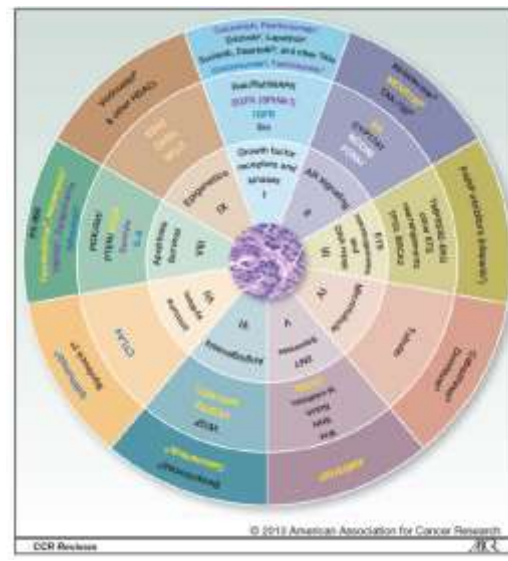
Clinical relevance?

Possible targets in prostate cancer, their physiologic function and targeting drugs



Source: Schoenborn JR et al. Clin Cancer Res 2013; 15: 4058-66

Dreams and reality

- Focus on one target leads to higher effectiveness
  - → Target might be one of several pathologic proteins
  - → Understanding of pathologic aberrations on a molecular basis can be much more difficult
  - → Salavage pathways in tumor biology
  - → Chronic treatment approach leads to more aggressive gene mutations with higher proliferation rates after progression
- Focus on one target leads to less side effects
  - → Target often plays an active role in „healthy“ physiology
  - → new, formerly unknown side effects

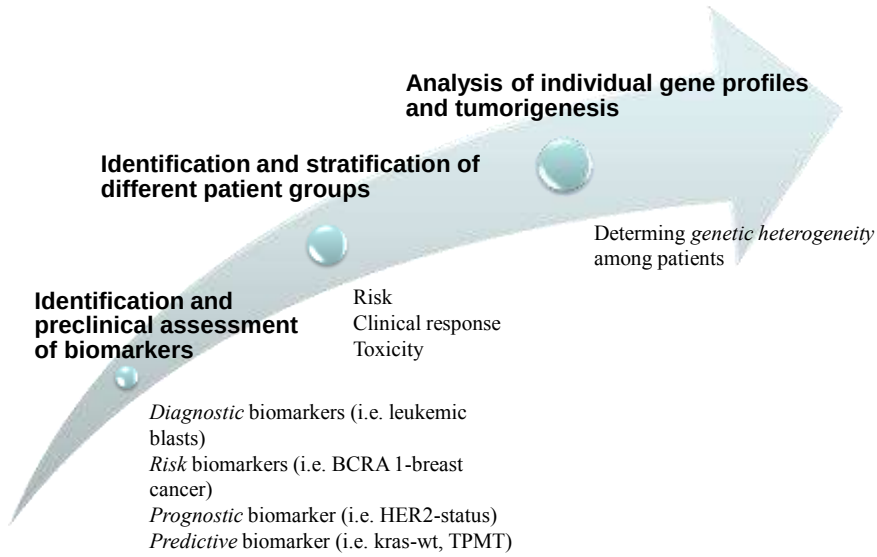
sm-TKI: toxicites

dermal:	heart:	liver:
all, different forms	Imatinib, Dasatinib, Nilotinib, Lapatinib, Sunitinib, Sorafenib	all
gastrointestinal:	thyroid gland:	blood pressure, wound healing:
all, different forms	Sunitinib, Pazopanib	VEGF-Hemmer, like Sunitinib, Sorafenib, Pazopanib

Definitions

- Stratified therapy
  → **Different groups** of treatment according to anticipated response to treatment or expected toxicities. Basis: prognostic or predictive biomarkers
- Personalised therapy
  → Analysis of genes and tumorigenesis **in the individual patient** to gain knowledge about risk for developing a certain tumor disease, response or resistance to therapies and risk for toxicites to find the best prophylaxis and treatment strategies

From „targeted“ to „stratified“ and „personalized“



Why do we need a *better* understanding of the tumors` genetic and molecular characteristics?

- Clinical outcomes of tumors with the same pathological patterns can vary substantially
- Genetic and molecular characteristics are the key to improve patient stratification
- Sufficient preclinical analysis if the discovered genome alterations might be of clinical relevance
- Identification of valid biomarkers which lead to information about treatment success and toxicity

What is needed for stratification?

- various technologies
- pre-clinical, epidemiological studies and clinical trials to assess possible biomarkers
- understanding of disease, especially tumorigenesis, on a molecular basis and the corresponding drug mechanisms
- development of reliable assays and tests
- consideration of ethical aspects

Prognostic biomarker
AML: cytogenetic risk

- Low-Risk:

t(8;21), inv(16), t(15;17)

- Intermediate Risk:

all aberrations, which are not categorised as low- or high-risik, normal karyotype

- High-Risk:

inv(3)/t(3;3), t(6;9), t(v;11q23)

-5/5q-, -7, abn(17p), complex karyotype

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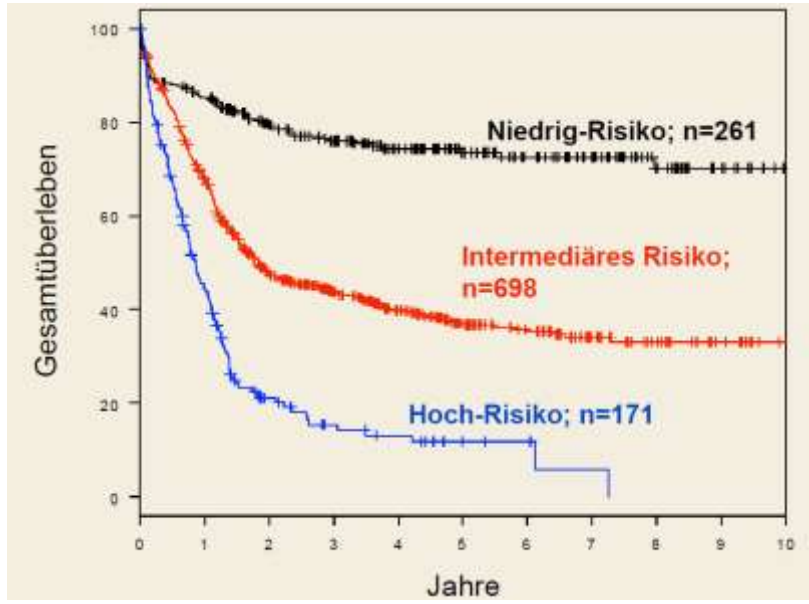
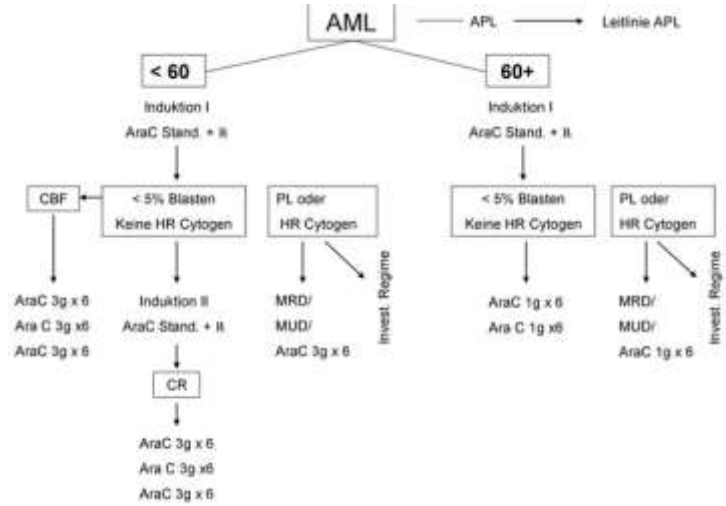


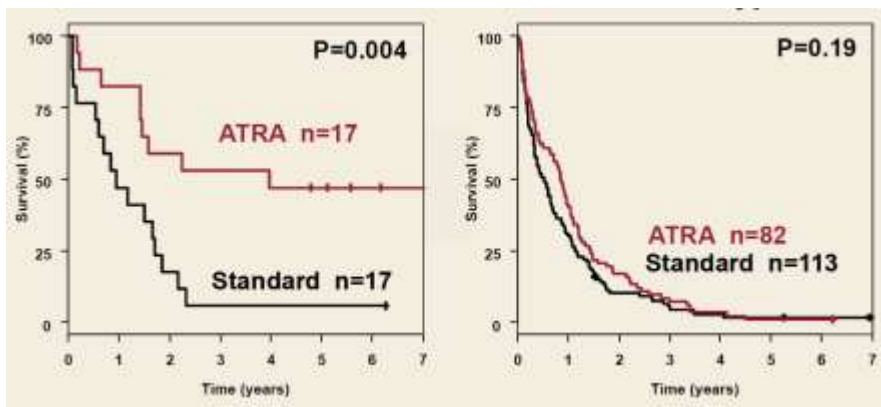
Source: AMLSG Therapiestudien 16-60 years

AML: therapy stratification (cytogenetic risk)



Source: www.dgho-onkopedia.de

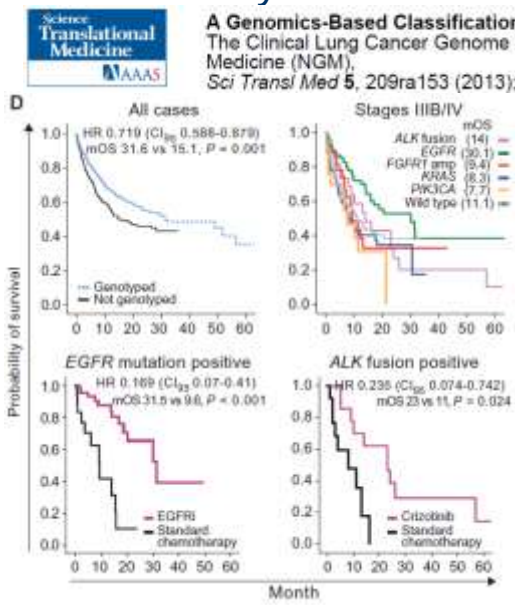
Predictive Biomarker for ATRA in AML: $NPM1_{mut}/FLT3\text{-}ITD_{neg}$



$NPM1_{mut}/FLT3\text{-}ITD_{neg}$

Haematologica 2009; 94:54-60

Prognostic Biomarkers
Is every biomarker of clinical relevance?



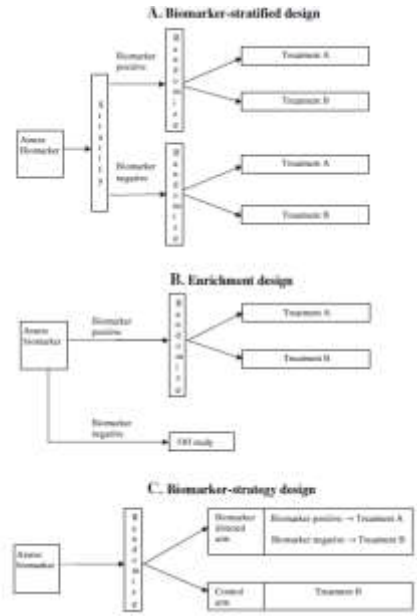
Stage IIIB/IV lung cancer

Biomarkers: challenges

- Sensivity and specifity
  - Knowledge about tumorigenesis and pathways
  - how reliable are biomarker assays in practical use
- Validation and qualification
  - standardisation of methods, procedures and results
- Cost of kits and efforts
- Prospective studies
  - selection of the optimal study design

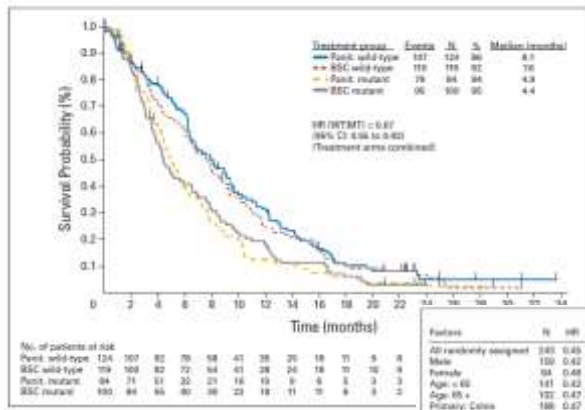
Biomarkers: trials

- Relationship between biomarker and treatment effect
- Classification of patients into distinct subgroups
- Alternative designs to evaluate biomarker-guided therapy



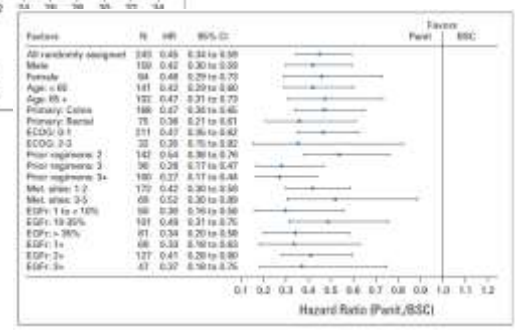
From: Freidlin B et al. J Natl Cancer Inst 2010;102: 152-160

The story of ras in CRC



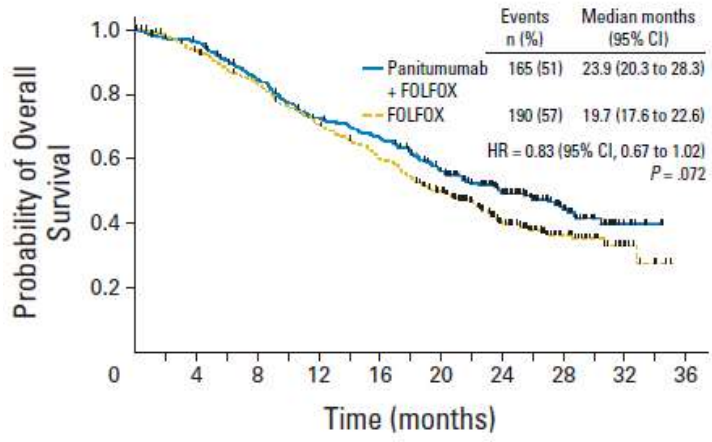
molecular alterations. The high positive predictive value (100% for lack of objective response rate) for mutant *KRAS* suggests that inhibition of the RAS/RAF/MAPK signaling pathway is primarily responsible for the clinical activity of panitumumab in metastatic CRC, and raises the possibility that mutant *KRAS* may be predictive in other tumor types. Indeed, EGFR inhibitors have shown modest or no activity in pancreatic cancer, a disease with a high prevalence of *KRAS* mutations,[9,27] and in patients with lung cancer

Amado et al., JCO 2010



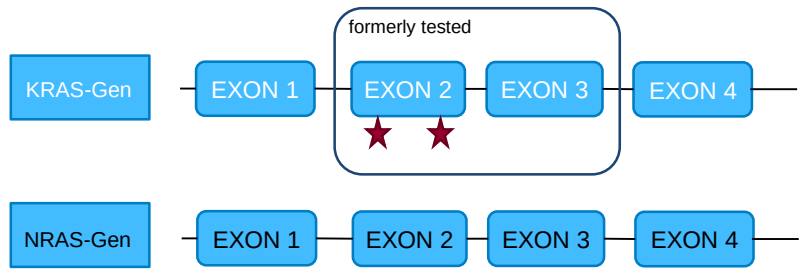
The story of ras in CRC

k-ras wildtype patients CRC St. IV



Douillard *et al*., JCO 2010

EGF-receptor – RAS-signalling

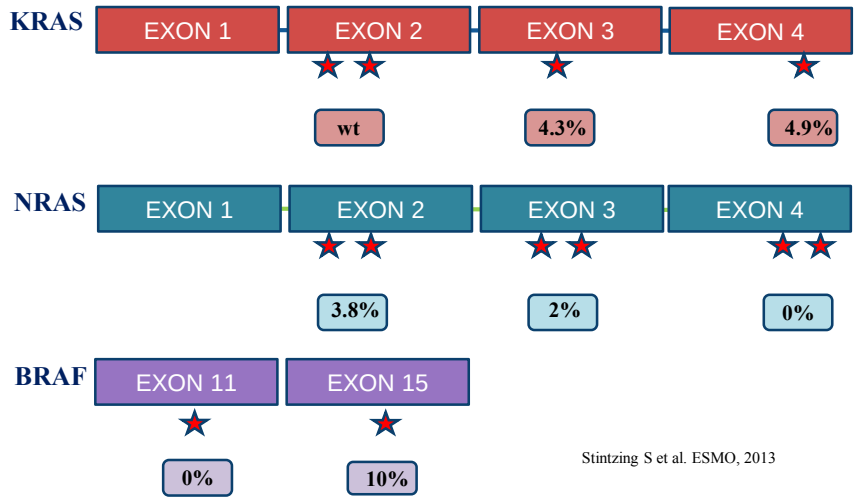


Recent studies with anti-EGFR-antibodies:

- negative outcome for subgroup with KRAS-Mutation in exon 2
- standard analysis since 2008

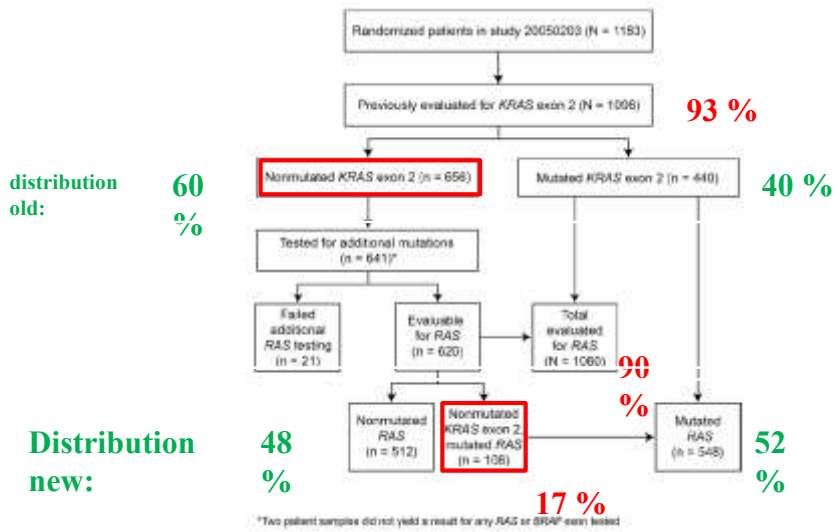
FIRE-3 - mutations

KRAS exon 2 wild-type subset



Stintzing S et al. ESMO, 2013

New all-ras-pathway



Douillard et al., NEJM 2013

Efficacy – old definition (kras)

Variable	Panitumumab–FOLFOX4	FOLFOX4 Alone	Hazard Ratio (95% CI)	P Value	P Value for Interaction Test*
No *KRAS* mutation in exon 2					
No. of patients	325	331			
Months of progression-free survival in primary analysis — median (95% CI)	9.6 (9.2–11.1)	8.0 (7.5–9.3)	0.80 (0.66–0.97)	0.02	
Months of overall survival — median (95% CI)					
Primary analysis	23.9 (20.3–28.3)	19.7 (17.6–22.6)	0.83 (0.67–1.02)	0.07	
Updated analysis	23.8 (20.0–27.7)	19.4 (17.4–22.6)	0.83 (0.70–0.98)	0.03	
***KRAS* mutation in exon 2**					
No. of patients	221	219			
Months of progression-free survival in primary analysis — median (95% CI)	7.3 (6.3–8.0)	8.8 (7.7–9.4)	1.29 (1.04–1.62)	0.02	
Months of overall survival — median (95% CI)					
Primary analysis	15.5 (13.1–17.6)	19.3 (16.5–21.8)	1.24 (0.98–1.57)	0.07	
Updated analysis	15.5 (13.1–17.6)	19.2 (16.2–21.5)	1.16 (0.94–1.41)	0.16	

Δ 4.4 months

Douillard et al., NEJM 2013

Efficacy – new definition (all-ras)

Variable	Panitumumab–FOLFOX4	FOLFOX4 Alone	Hazard Ratio (95% CI)	P Value	P Value for Interaction Test*
No *RAS* mutation					
No. of patients	259	253			
Months of progression-free survival in primary analysis — median (95% CI)	10.1 (9.3–12.0)	7.9 (7.2–9.3)	0.72 (0.58–0.90)	0.004	
Months of overall survival — median (95% CI)					
Primary analysis	26.0 (21.7–30.4)	20.2 (17.7–23.1)	0.78 (0.62–0.99)	0.04	
Updated analysis	25.8 (21.7–29.7)	20.2 (17.6–23.6)	0.77 (0.64–0.94)	0.009	
No *KRAS* mutation in exon 2, other *RAS* mutation	51	57			
No. of patients					
Months of progression-free survival in primary analysis — median (95% CI)	7.3 (5.3–9.2)	8.0 (6.4–11.3)	1.28 (0.79–2.07)	0.33	0.04
Months of overall survival — median (95% CI)					
Primary analysis	17.1 (10.8–19.4)	18.3 (13.0–23.2)	1.29 (0.79–2.10)	0.31	0.07
Updated analysis	17.1 (10.8–19.4)	17.8 (13.0–23.2)	1.39 (0.91–2.13)	0.12	0.01

Δ 5.8 months

17 %

Douillard et al., NEJM 2013

Efficacy - Ras MT

Variable	Panitumumab–FOLFOX4	FOLFOX4 Alone	Hazard Ratio (95% CI)	P Value	P Value for Interaction Test*
***RAS* mutation**					
No. of patients	272	276			
Months of progression-free survival in primary analysis — median (95% CI)	7.3 (6.3–7.9)	8.7 (7.6–9.4)	1.31 (1.07–1.60)	0.008	<0.001
Months of overall survival — median (95% CI)					
Primary analysis	15.6 (13.4–17.9)	19.2 (16.7–21.8)	1.25 (1.02–1.55)	0.03	0.004
Updated analysis	15.5 (13.4–17.9)	18.7 (16.5–21.5)	1.21 (1.01–1.45)	0.04	0.001

negative predictive factor!

Douillard et al., NEJM 2013

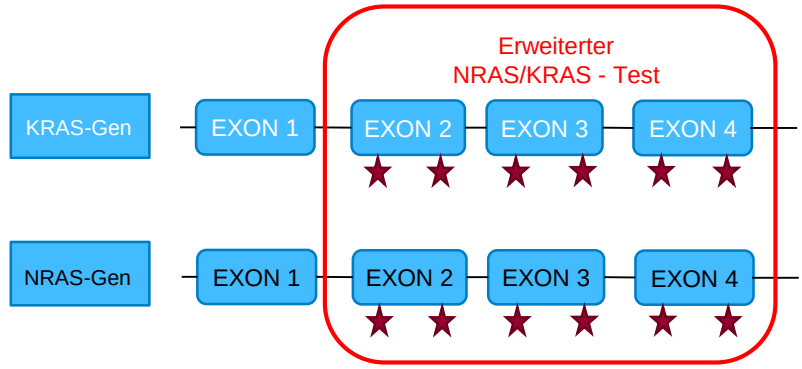
Efficacy - BRAF

Table 3. Efficacy Results According to *RAS* and *BRAF* Mutation Status in the Primary-Analysis Population.*

Variable	Panitumumab–FOLFOX4	FOLFOX4 Alone	Hazard Ratio (95% CI)	P Value
No *RAS* or *BRAF* mutations				
No. of patients	228	218		
Months of progression-free survival — median (95% CI)	10.8 (9.4–12.4)	9.2 (7.4–9.6)	0.68 (0.54–0.87)	0.002
Months of overall survival — median (95% CI)	28.3 (23.7–NE)	20.9 (18.4–23.8)	0.74 (0.57–0.96)	0.02
No *RAS* mutation, *BRAF* mutation				
No. of patients	24	29		
Months of progression-free survival — median (95% CI)	6.1 (3.7–10.7)	5.4 (3.3–6.2)	0.58 (0.29–1.15)	0.12
Months of overall survival — median (95% CI)	10.5 (6.4–18.9)	9.2 (8.0–15.7)	0.90 (0.46–1.76)	0.76

Negative prognostic factor!

Douillard et al., NEJM 2013



- RAS-analysis contains exons 2, 3, 4 of K- and N-RAS since 1.7.13 (solitary K-RAS analysis dismissed in HD)

Cost perspective

- Up to date there is no commercially available assay which covers all hotspots → only sequencing is a valid analysis
- Cost for ras-analysis has tripled in need to analyse 6 exons now instead of one

→ All-RAS € 377,- (formerly: € 156,- for K-RAS)

Conclusion

- We should avoid using the term „targeted“ too much as long we are not fully certain about the detailed biology of the tumor
- Knowledge about possible biomarkers has to be improved before introduction into clinical practice
- Retrospective analysis may be helpful to reassess the use of already approved drugs
- Reliable standardized and validated tests are necessary