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A Paradigm Shift in Early Drug Development: Individualizing to More Patient Benefit

The Role of Tumor / Molecular Target Selection in the Success of a New Agent

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Conflict of Interest

I, Christian Dittrich, am consulting pharmaceutical companies on an irregular basis and receive financial compensation for this service.

The research institutes directed by me have received unrestricted research grants from various companies.

Shift of Breast Cancer Characterization over the Years

ER

PgR

[1]Luminal A

Luminal B

HER2+ / ER-

Basal-like

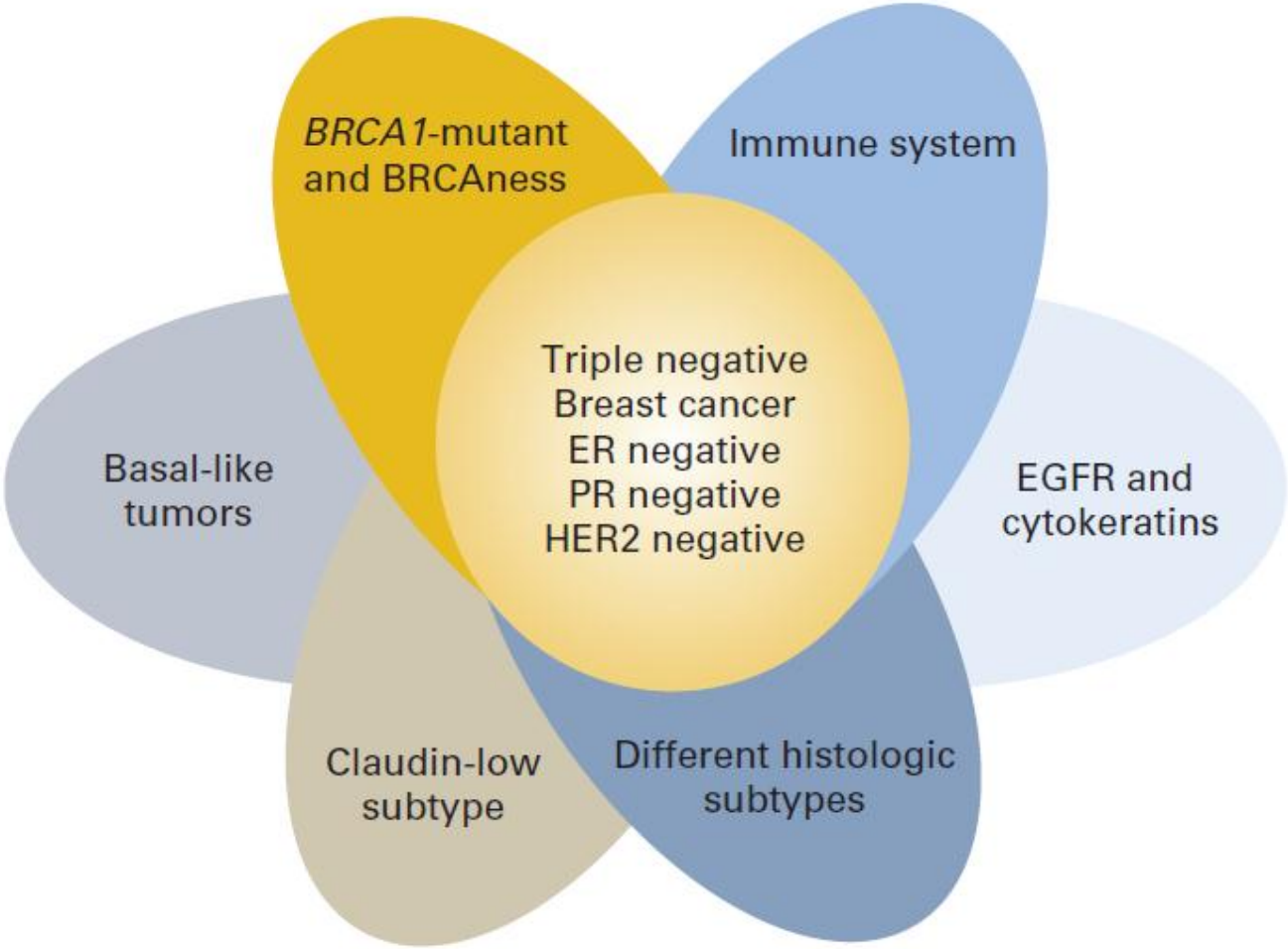
Normal breast-like

[2]Oncotype Dx
21 gene microarray

[3]Mammaprint
70 gene microarray

[1] Perou et al., Nature 406:747-752,2000
[2] Paik et al., NEJM 351:2817-2826,2004
[3] van de Vijver et al., NEJM 347:1999-2009,2002

Heterogeneity of Triple-Negative Breast Cancer



Metzger-Filho et al., JCO 30:1879-87,2012

TUMOR / MOLECULAR TARGET SELECTION

ER / PgR

HER2

EGFR

KRAS

BRAF

ALK

…..

EGFR-Based Predictive Marker Potential in NSCLC

EGFR Determination : EXPRESSION				TKI	MoAb Cetuximab
Authors	Acronym	retro / pro	Patient Pre-Selection		
Tsao 2005	BR.21	r	-	E: OS ns	
Gatzemeier 2007	TALENT	r	-	E: OS ns, ORR ns	
Capuzzo 2010	SATURN	r	-	E: PFS ns	
Khambata – Ford 2010	BMS 099	r	-		OS ns, PFS ns, ORR ns
O´Byrne 2011	FLEX	r	EGFR pos		OS ns, PFS ns, ORR ns
Pirker 2012	FLEX	r	EGFR pos		OS↑

EGFR-Based Predictive Marker Potential in NSCLC

EGFR Determination : GENE AMPLIFICATION / COPY NUMBER				**TKI**	**MoAb Cetuximab**
Authors	Acronym	retro / pro	Patient Pre-Selection		
Tsao 2005	BR.21	r	-	E: OS ns	
Gatzemeier 2007	TALENT	r	-	E: OS ns, ORR ns	
Capuzzo 2010	SATURN	r	-	E: PFS ns	
Khambata – Ford 2010	BMS 099	r	-		OS ns, PFS ns, ORR ns
O´Byrne 2011	FLEX	r	EGFR pos		OS ns, PFS ns, ORR ns

EGFR-Based Predictive Marker Potential in NSCLC

EGFR Determination : MUTATION				TKI	MoAb Cetuximab
Authors	Acronym	retro / pro	Patient Pre Selection		
Lynch 2004	-	r	-	G: mut ORR↑ (8/9) wt (0/7)	
Tsao 2005	BR.21	r	-	E: OS ns	
Mok 2009	IPASS	r	-	G: PFS↑, ORR↑	
Capuzzo 2010	SATURN	r	-	E: PFS↑, (EGFRmut > wt)	
Mitsudomi 2010	WJTOG	p	mut	G: PFS↑	
Zhou 2011	OPTIMAL	p	mut	E: ORR↑, PFS↑	
Rosell 2011	EURTAC	p	mut	E: PFS↑	
Khambata – Ford 2010	BMS 099	r	-		OS ns, PFS ns, ORR ns
O´Byrne 2011	FLEX	r	EGFR pos		OS ns, PFS ns, ORR ns

KRAS Mutational Status: Efficacy of Anti-EGFR Monoclonal Antibodies in mCRC

Author/Study/ Population/Phase	Treatment	Variable	KRAS wt		KRAS mut	
			+MoAb	Control	+MoAb	Control
Van Cutsem 2008 CRYSTAL, 1st line, Ph III	FOLFIRI ± Cetuximab	RR (p) PFS (p)	> (0.025) > (0.017)		(0.46) (0.47)	
Bokemeyer 2008 OPUS, 1st line, Ph II	FOLFOX ± Cetuximab	RR (p) PFS (p)	> (0.011) > (0.016)		(0.106) < (0.0192)	
Punt 2008 CAIRO, 1st line, Ph III	Capecitabine + Oxaliplatin + Bevacizumab ± Cetuximab	PFS (p) OS (p)	0.10 0.49		< (0.043) (0.35)	
Karapetis 2008 >2nd line	Cetuximab vs BSC	PFS (p) OS at 1 yr (p)	> 0.001 > 0.001		(0.96) (0.89)	
Amado 2008 CTX refractory	Panitumumab vs BSC	PFS (HR)	> (0.45)		(0.99)	

Allegra et al., JCO 27:2091-2096,2009

Genetic Aberrations with Predictive Therapeutic Impact in CRC

Genetic Aberration	Impact	Class of Drugs Impacted	Author / Reference
EGFR amplified	-	MoAb	Lenz et al., JCO 24:4914-21,2006
EGFR mut	-	MoAb	Lenz et al., JCO 24:4914-21,2006
KRAS mut	+	MoAbs↓	Allegra et al., JCO 27:2091-96,2009
BRAF mut	+	TKIs↓	Di Nicolantonio, JCO 26:5705-12,2008
	-	MoAbs	Dasari and Messersmith, CCR 16: 3811-8,2010
BRAF mut-like	+	TKIs↓	Popovic et al., JCO 30:1288-95,2012
PTEN loss (*KRAS* wt)	+	MoAbs↓	Wang et al., CCP 69:1647-1655,2012
PIK3CA mut (*KRAS* wt)	+	MoAbs↓	Mao et al., Ann Oncol 23: 1518-25,2012

RAS Driven CRC´s Responsiveness

KRAS mut

- **Decreased (oxali-)platinum sensitivity**
  (Ratner et al., Oncogene 10.1038 / onc 2011,539)

- **Responsiveness to chemotherapy (CTX) alone > MoAb + CTX**
  (OPUS: Bokemeyer et al., JCO 27: 663-671,2009
  PRIME: Douillard et al., JCO 28: 4697-4705,2010
  PICCOLO: Seymour et al., EJC 47(51): S393,2011)

RAF Driven CRC´s Responsiveness

BRAF mut

- **No responsiveness to CTX**
- **Limited responsiveness to PLX 4032[1] and GSK 211 84 36[2]**

([1] Kopetz et al., JCO 28 (15 suppl) 2010: 3534)
([2] Kefford et al., JCO 28 (15 suppl) 2010: 8503)

Tissue specificity of gene mutation

EGFR-mediated MAPK pathway reactivation

(Corcoran et al., Cancer Discovery 2012; DOI: 10.1158 / 2159-8290)

BRAF mut in Metastatic Melanoma

Prevalence of *BRAF* mut in metastatic melanoma: 30-70%

Selectivity of PLX4032 (Vemurafenib) for ^{V600E}*BRAF* mut compared to *BRAF* wt

BRIM-1 : **Phase I: Vemurafenib in 49/55 metastatic melanoma pts in ^{V600E}*BRAF* mut pts**
Flathery, NEJM 2010
ORR 69% (11/16) : dose escalation cohort
81% (26/32) : expansion cohort

BRIM-2 : **Phase II: Vemurafenib in metastatic melanoma pts 184/344 (56%) mut positive**
Ribas, JCO 2011
ORR / SD : 53% / 29%

BRIM-3 : **Phase III: Vemurafenib (vs Dacarbacin) in ^{V600E}*BRAF* mut metastatic melanoma pts**
Chapman, NEJM 2011
ORR 48% (out of 219 pts)
PFS HR: 0.26, p<0.001
OS HR: 0.37, p<0.001

BRAF mut in Colorectal Cancer

Prevalence of *BRAF* mut in metastatic colorectal cancer: 8-10%

PLX 4032 (Phase I)
19/21 evaluable for response
1/19 (5%) PR
4/19 minor responses (≤ 10% shrinkage)
5/19 mixed responses

- **PK-PD: PK values ~ 20% lower than in melanoma?**
- **Redundant mechanism of MAPK activation in CRC?**

Kopetz et al., JCO 28 (15 suppl) 2010: abstract 3534

Anaplastic Lymphoma Kinase (ALK) Inhibition

- **Preclinical data (>600 cell lines):**
  a selective ALK inhibitor reduced proliferation of cells carrying genetic alterations in *ALK*

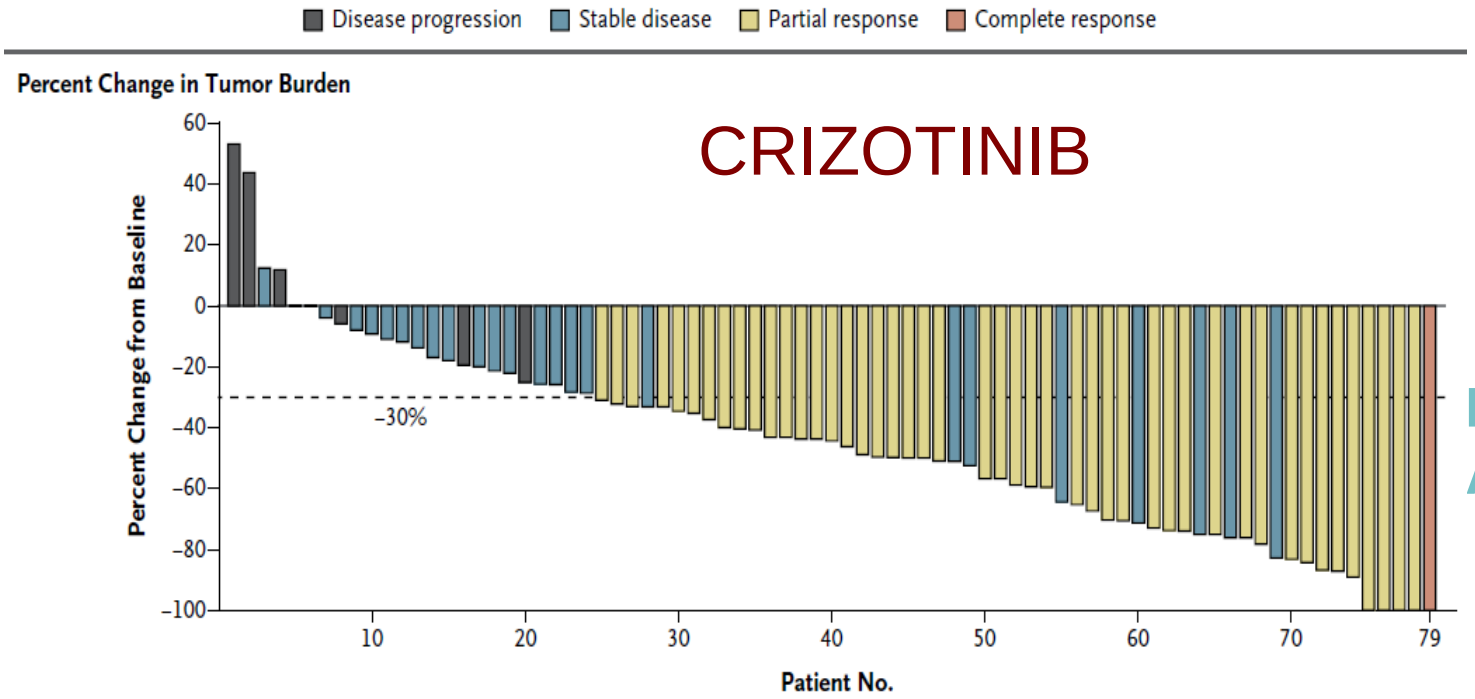
- **Crizotinib: oral ATP competitive selective inhibitor of the ALK and MET tyrosine kinases**

- **Phase I**
  Part 1: toxicity, MTD, PK in non-enriched patient cohort
  → 250mg crizotinib b.i.d., 28-day cycles
  Part 2: clinical activity at the MTD in several molecularly enriched cohorts (*ALK* rearranged)

Howells et al., Cancer Prev Res 4:1419-25,2011

ALK-Inhibition in NSCLC

***EML4-ALK*: aberrant fusion gene encoding for a chimeric protein with constitutive kinase activity (in 2-7% of NSCLC; non/never smokers, adeno-CAs)**



CRIZOTINIB

Response to ALK Inhibition

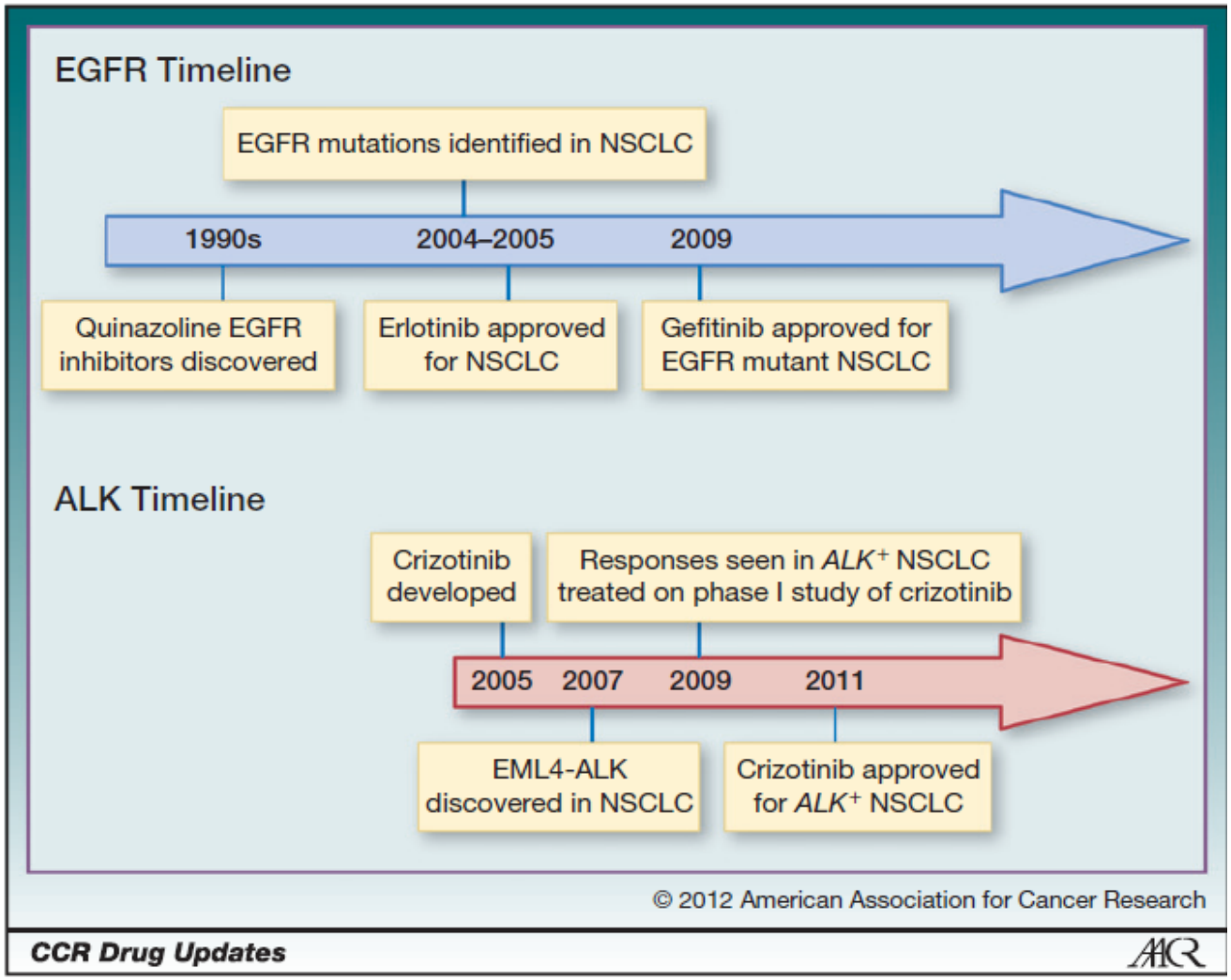
Kwak et al., N Engl J Med 363:1693-1703,2010

Crizotinib in *EML4-ALK* Positive NSCLC

No prior regimen	ORR % (N / N)
0	80 (4 / 5)
1	52 (14 / 27)
2	67 (10 / 15)
>3	56 (19 / 34)

Camidge et al., Ann Oncol 21 (Suppl 8),2010,Abstract #266 PD

Timeline for Approval of Kinase Inhibitors for Molecular Subsets of NSCLC



Gandhi and Jänne, CCR 18:3737-42,2012

ALK Gene Amplification

in 2% in overall breast cancer population

in 80% in inflammatory breast cancer

Phase I trial in *ALK* amplified inflammatory breast cancer with small molecule ALK/cMET inhibitors

Paradigm Shift

What cures / suppresses all types / stages of cancer ?

Success ?

What drives a patient's individual cancer ?

What drives us ?

- Scientific interest
- Economic restriction
- Patient benefit