Il ruolo delle biopsie in oncologia: cosa l'oncologo chiede al patologo

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Cosa l’oncologo chiede al patologo

1. Diagnosi di neoplasia primitiva e istotipo

2. Caratterizzazione biologica: ricerca di alterazioni molecolari «driver» di terapie personalizzate (*driver alterations*)

3. Partecipazione a Trials clinici

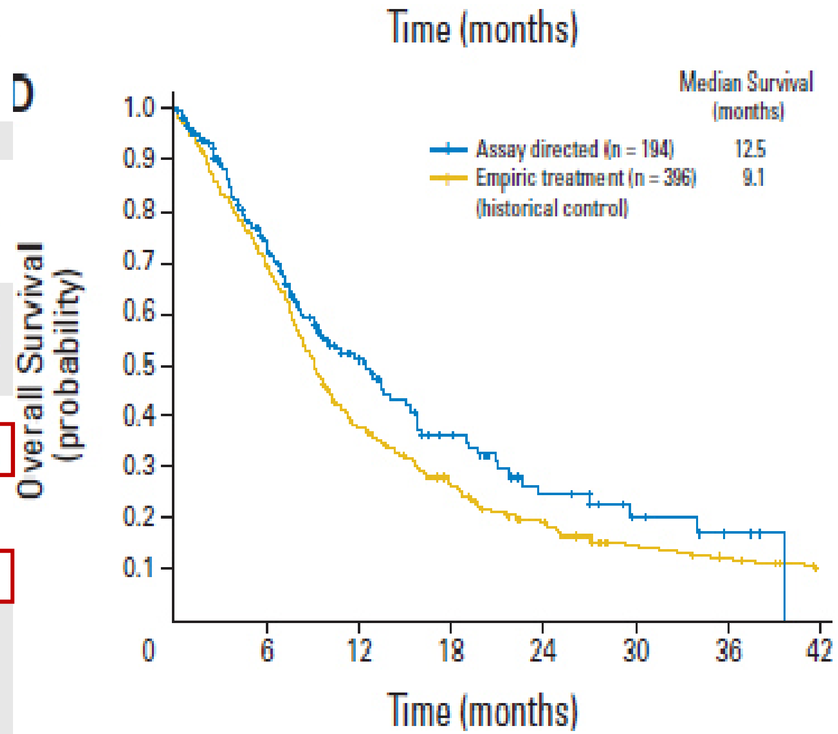
Molecular Gene Expression Profiling to Predict the Tissue of Origin and Direct Site-Specific Therapy in Patients With Carcinoma of Unknown Primary Site: A Prospective Trial of the Sarah Cannon Research Institute

John D. Hainsworth, Mark S. Rubin, David R. Spigel, Ralph V. Boccia, Samuel Raby, Raven Quinn, and F. Anthony Greco

Table 4. Survival in 194 Patients Who Received Assay-Directed Therapy and in Subsets

Patient Group	No. of Patients	Median Survival (months)	*P*
All patients	194	12.5	
Tumor type			
Treatment responsive	115	13.4	.04
Less treatment responsive	79	7.6	
Assay prediction probability			
≥ 80%	95	12.5	.03
< 80%	99	10.8	
Tumor type + prediction probability			
Treatment responsive, ≥ 80%	42	15.4	.03
Treatment responsive, < 80%	57	13.4	
Less treatment responsive, ≥ 80%	37	8.2	
Less treatment responsive, < 80%	58	7.0	
Individual tumor types			
Biliary tract	45	6.8	
Pancreas	12	8.2	
Colorectal	26	12.5	
NSCLC	23	15.9	
Ovary	10	29.6	
Breast	10	NYR (> 24)	

Abbreviations: NSCLC, non–small-cell lung cancer; NYR, not yet reached.



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ORIGINAL REPORT

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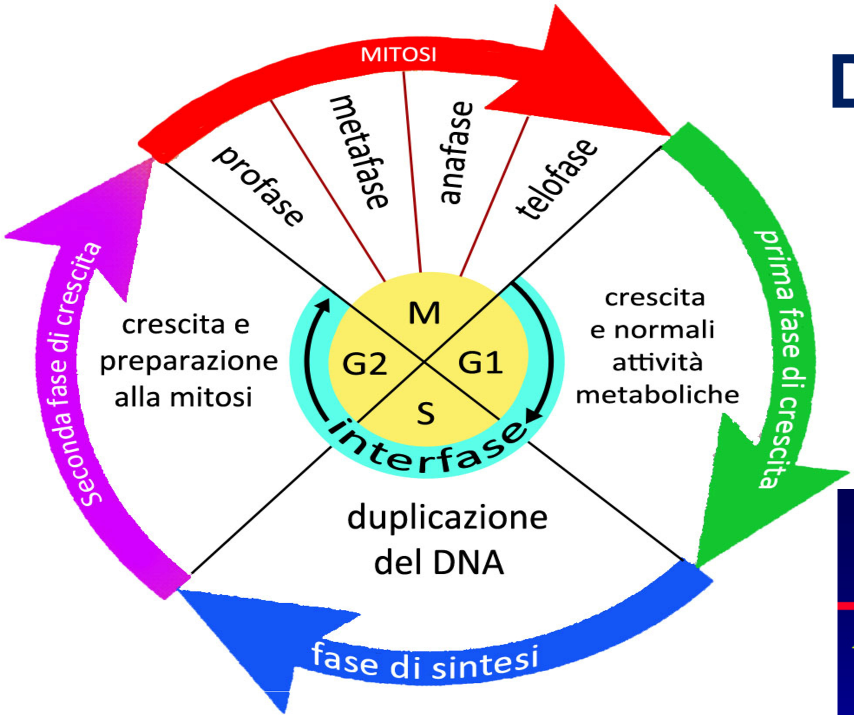
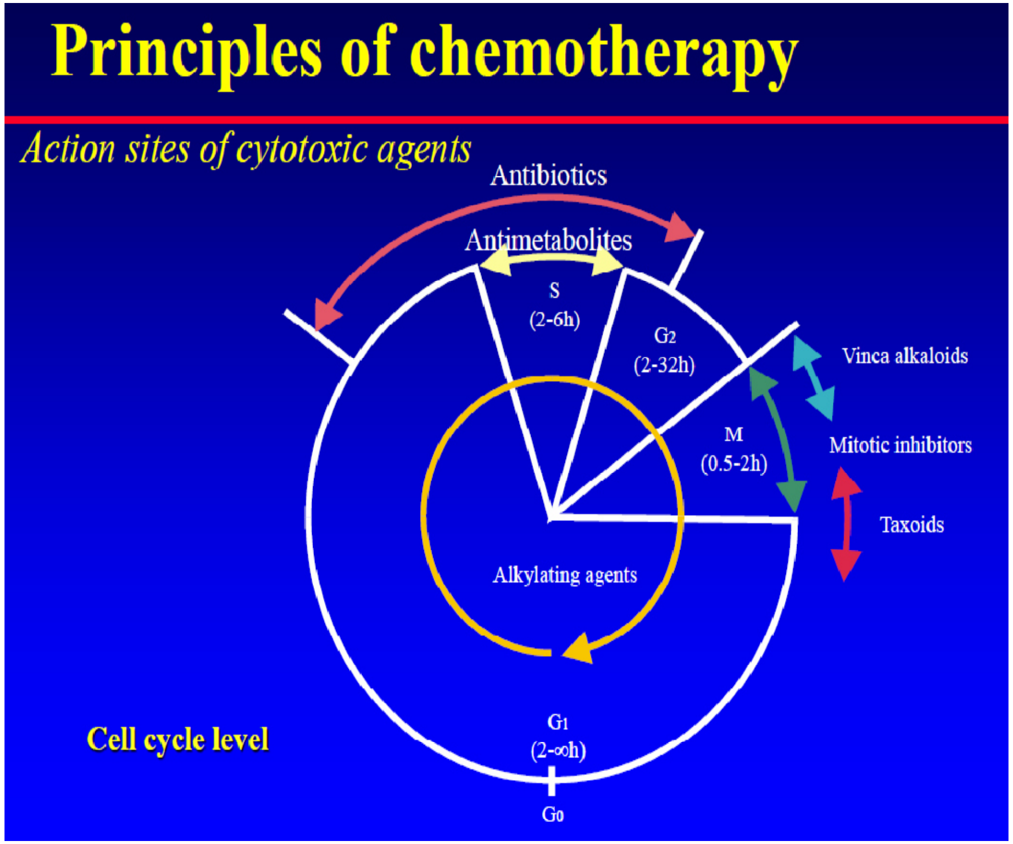
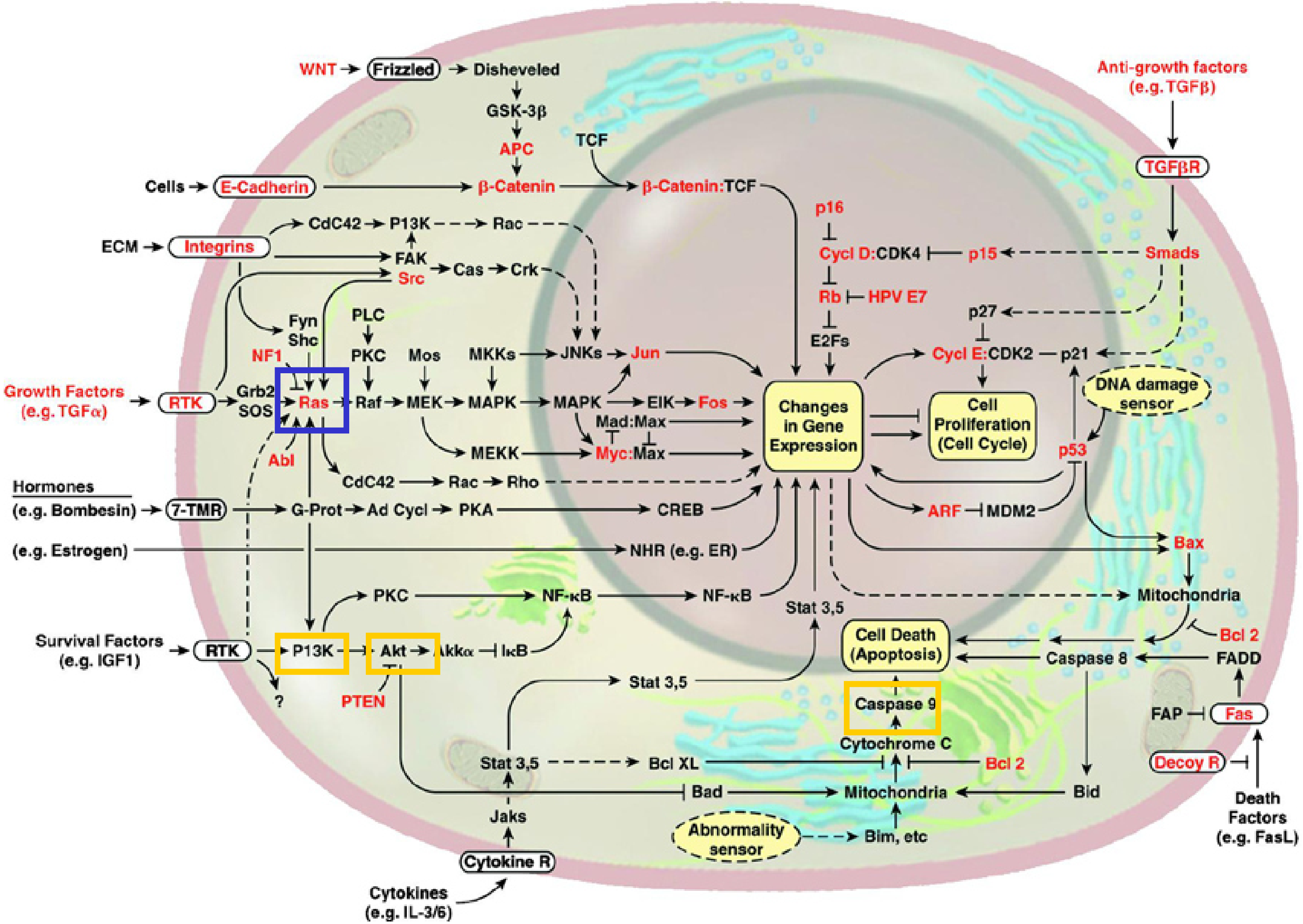
Dalla sola chemioterapia …..





….. Alla terapia personalizzata



Il paradigma adenocarcinoma polmonare (1)

Lung Cancer Mutation Consortium-1 (LCMC-1)

1,000 Adenocarcinomas
13 US Institutions

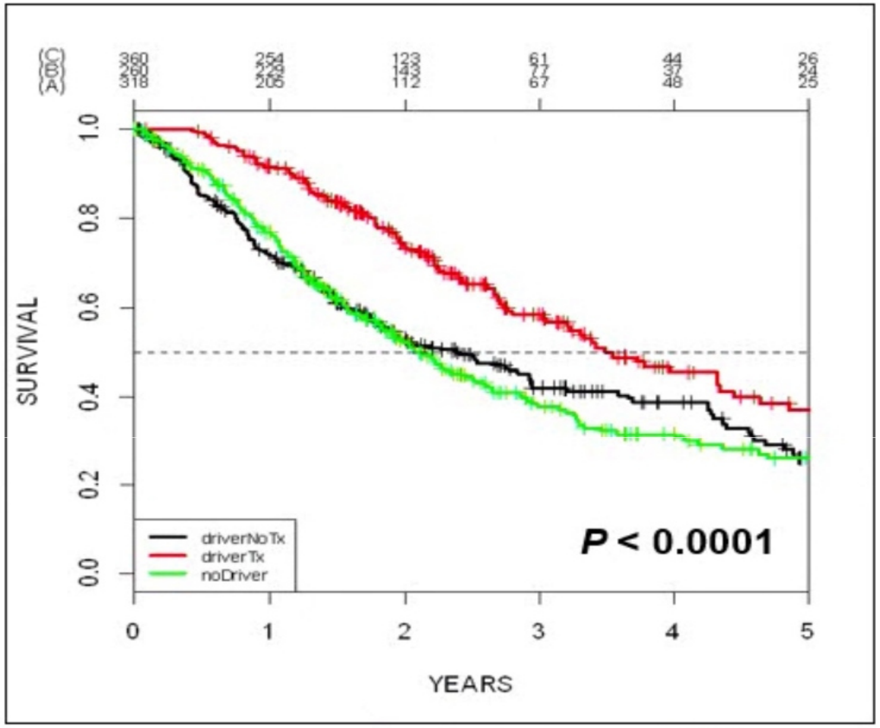
Mutations (8 genes/115 Assays)
Sequenom™ and Snap Shot™

- ***AKT1***
- ***BRAF***
- ***EGFR***
- ***HER2***
- ***KRAS***
- ***MEK1***
- ***NRAS***
- ***PIK3CA***

FISH (2 genes)

- ***MET* amplification**
- ***EML4-LK* fusion**

M Kris et al , JAMA, 2014



Group	N	Median Survival Yrs. (95% CI)
Driver, no targeted therapy (A)	318	2.4 (1.9-2.9)
Driver, targeted therapy (B)	260	3.6 (3.1-4.5)
No driver (C)	360	2.2 (1.8-2.5)

Il paradigma adenocarcinoma polmonare (2)

Lung Cancer Targeted Therapy Landscape Change – 2016

• Adenocarcinoma	% Prevalence	Available TKIs
- *EGFR* mutation	15%	Erlotinib/Gefitinib/Afatinib
- *ALK-EML4* fusion	4%	Crizotinib/Ceritinib
- *ROS1-FIG* fusion	2%	Crizotinib
- *MET* amplification	5%	Met inhibitors
- *KIF5B-RET* fusion	2%	Ret inhibitors
- *PI3KCA* mutation	5%	PI3K inhibitors
- *HER2* mutation	1%	Her2 inhibitors
- *MET exon14* splice site	1%	Capmatinib
• Squamous Cell Carcinoma		
- *FGFR1* amplification	22%	FGFR TKIs
- EGFRvIII mutation	5%	EGFR TKIs
- *PI3KCA* mutation	4%	PI3KCA inhibitors
- *DDR2* mutation	3%	Dasatinib & Nilotinib

Il paradigma adenocarcinoma polmonare (3)

EGFR Inhibitors are Standard First-Line Therapies for Patients with Sensitizing EGFR Mutations

			RR	(%)	Median PFS (mo)		Median OS (mo)	
Country	Trial	Agent	TKI	Chemo	TKI	Chemo	TKI	Chemo
	IPASS Mut +	gefitinib	71.2	47.3	9.5	6.3	21.6	21.9
	First-SIGNAL Mut +	gefitinib	84.6	37.5	8.4	6.7	30.6	26.5
	WJTOG	gefitinib	62.1	32.2	9.2	6.3	30.9	NR
	NEJ002	gefitinb	73.7	30.7	10.8	5.4	27.7	26.6
	OPTIMAL	erlotinib	83	36	13.7	4.6	22.6	28.8
	EURTAC	erlotinib	58	15	9.7	5.2	19.3	19.5
	LUX-Lung 3	afatinib	56.1	22.6	11.1	6.9	NR	NR
	LUX-Lung 6	afatinib	66.9	23.0	11.0	5.6	NR	NR

Il paradigma adenocarcinoma polmonare (3)

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	LUX-Lung 6	afatinib	66.9	23.0	11.0	5.6	NR	NR

Il paradigma adenocarcinoma polmonare (4)

Crizotinib versus Chemotherapy in Advanced *ALK*-Positive Lung Cancer

	Pemetrexed/Taxotere	Crizotinib	P-value
N° of patients	174	173	
RR%	20	65	<0.001
mPFS (months)	3	7.7	<0.001
mOS (months)	22.8	20.3	NS
Time to sympt. deterioration (months)	1.4	4.5	<0.001

Shaw et al, NEJM'13

Il paradigma adenocarcinoma polmonare (5)

First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

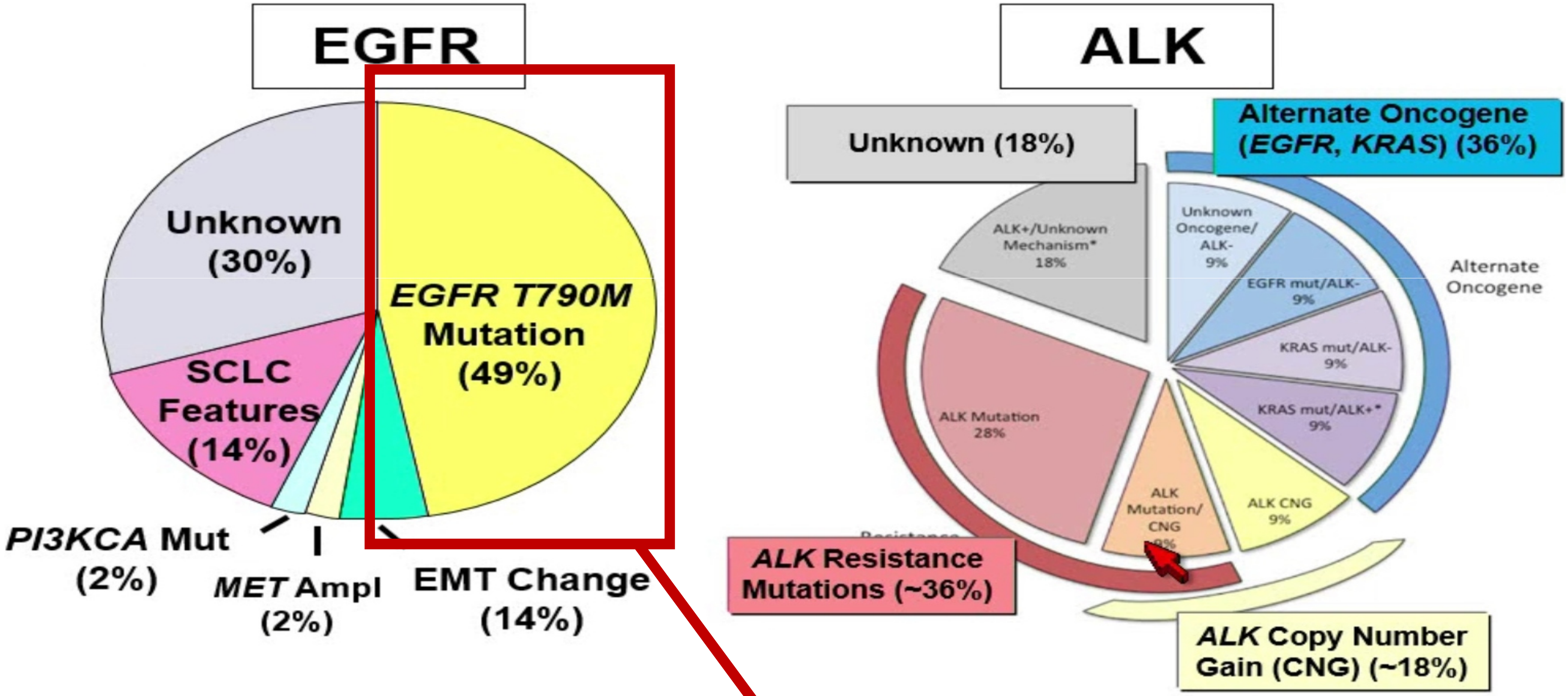
Table 2. Response to Treatment in the Intention-to-Treat Population.*

Response	Crizotinib (N=172)	Chemotherapy (N=171)
Type of response — no. (%)		
Complete response	3 (2)	2 (1)
Partial response	125 (73)	75 (44)
Stable disease	29 (17)	63 (37)
Progressive disease	8 (5)	21 (12)
Could not be evaluated†	7 (4)	10 (6)
Objective response rate — % (95% CI)‡	74 (67–81)	45 (37–53)
Time to response — mo§		
Median	1.4	2.8
Range	0.6–9.5	1.2–8.5
Duration of response — mo¶		
Median	11.3	5.3
95% CI	8.1–13.8	4.1–5.8

Solomon et al, NEJM'14

Il paradigma adenocarcinoma polmonare (6)

Mechanisms of Resistance to EGFR and ALK TKIs in Lung Adenocarcinoma



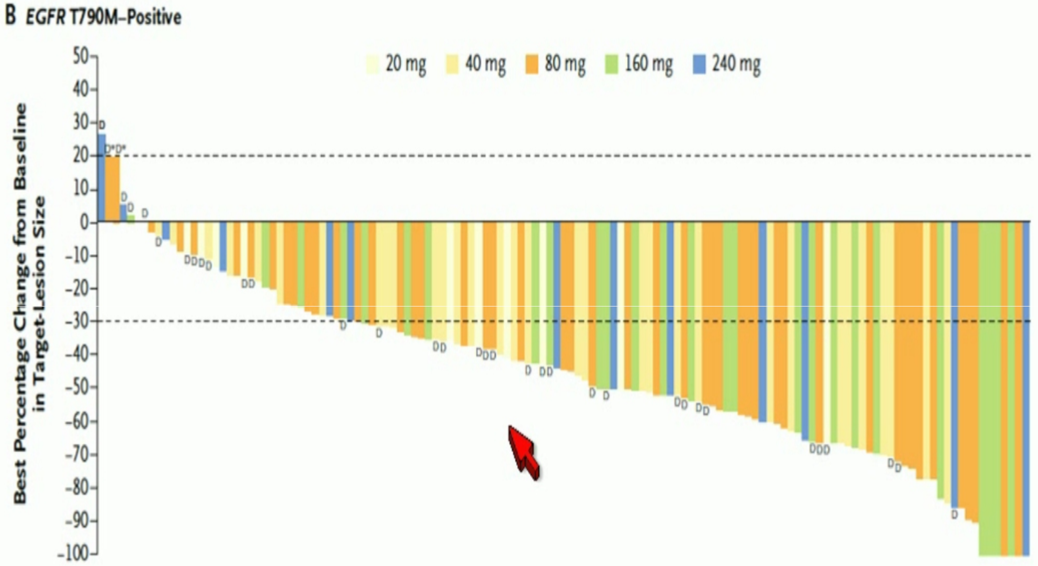
Modified from Sequist L V et al. Sci Transl Med 2011;

Doebele RC et al, Clin Cancer Res, 2012

Re-biopsy

Il paradigma adenocarcinoma polmonare (7)

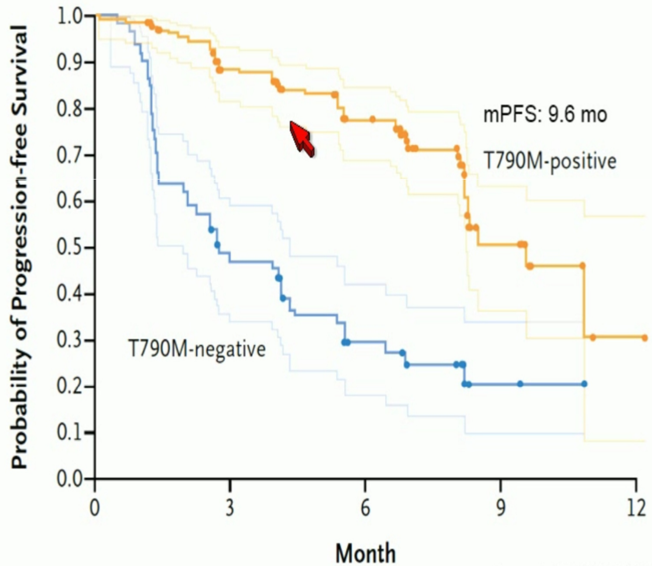
Clinical Activity of Osimertinib in Advanced EGFR Mutant T790M+ NSCLC



Objective response rate (N=127): 61% (95% CI, 52-70)

Janne et al., NEJM 372: 1689-99, 2015

Progression-free Survival in T790M+ Subgroup (central test; N=138)



Janne et al., NEJM 372: 1689-99, 2015

Immunoterapia: nuovi «drivers» (1)

Intra-tumoral PD-L1 expression and response to PD-1/PD-L1 blockade

	Nivolumab Solid Tumors (Topalian et al. NEJM 2012)	Nivolumab Melanoma (Weber ASCO 2013)	Nivolumab Melanoma (Grosso et al. ASCO 2013)	MPDL3280a Solid Tumors (Herbst et al ASCO 2013)	MPDL3280a Melanoma (Hamid et al ASCO 2013)	MPDL3280a NSCLC (Sorial et al ECC 2013)	Pembrolizumab Melanoma (Daud et al AACR 2014)	Pembrolizumab NSCLC (Gandhi et al AACR 2014)	MPDL3280a Bladder (Powels et al ASCO 2014)	Pembrolizumab Head & Neck (Selwert et al ASCO 2014)	Pembrolizumab Melanoma (Ribas et al ASCO 2014)
n=	42	44	34	94	30	53	113	129	65	55	411
Response Rates											
Unselected	21%	32%	29%	22%	23%	23%	40%	19%	26%	18%	40%
PD-L1 +	36%	67%	44%	39%	27%	46%	49%	37%	43%	46%	49%
PD-L1 −	0%	19%	17%	13%	20%	15%*	13%	11%	11%	11%	13%

ASCO

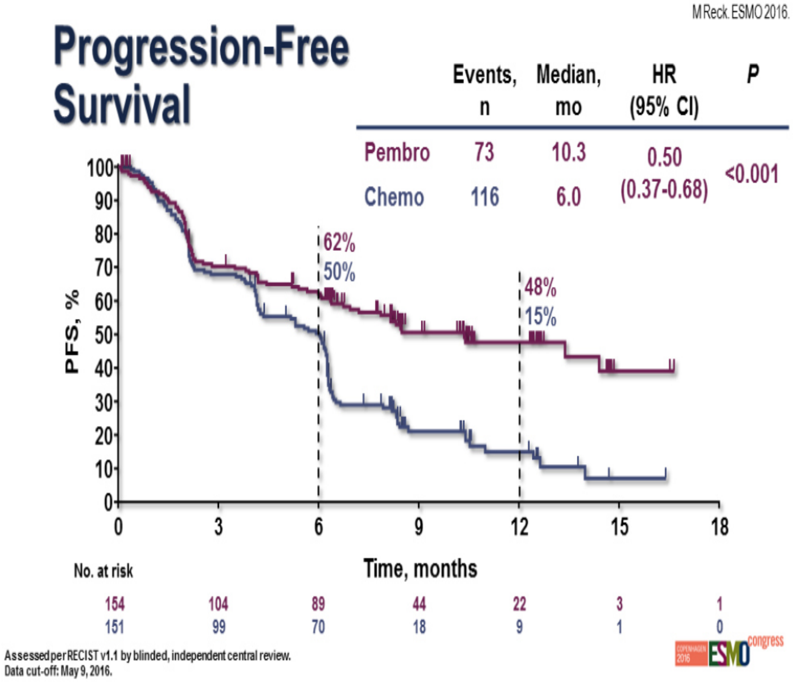
Immunoterapia: nuovi «drivers» (2)

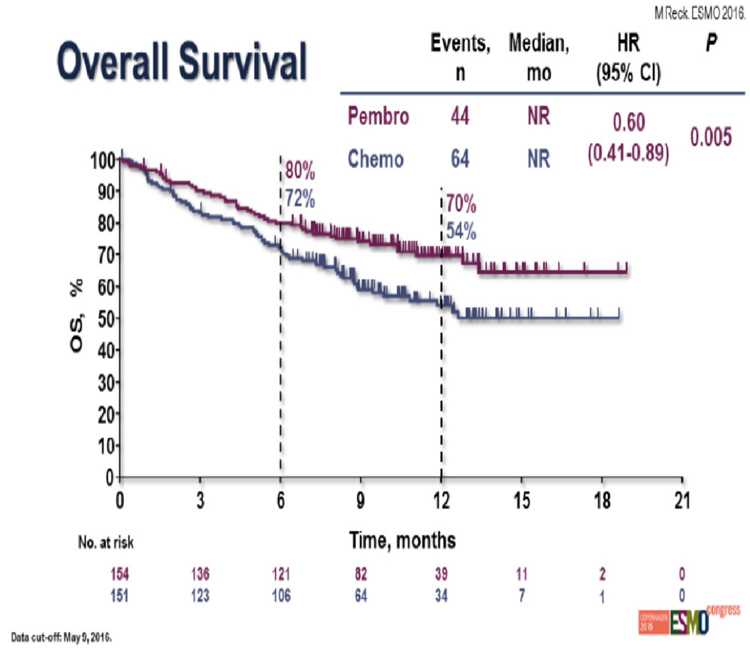
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

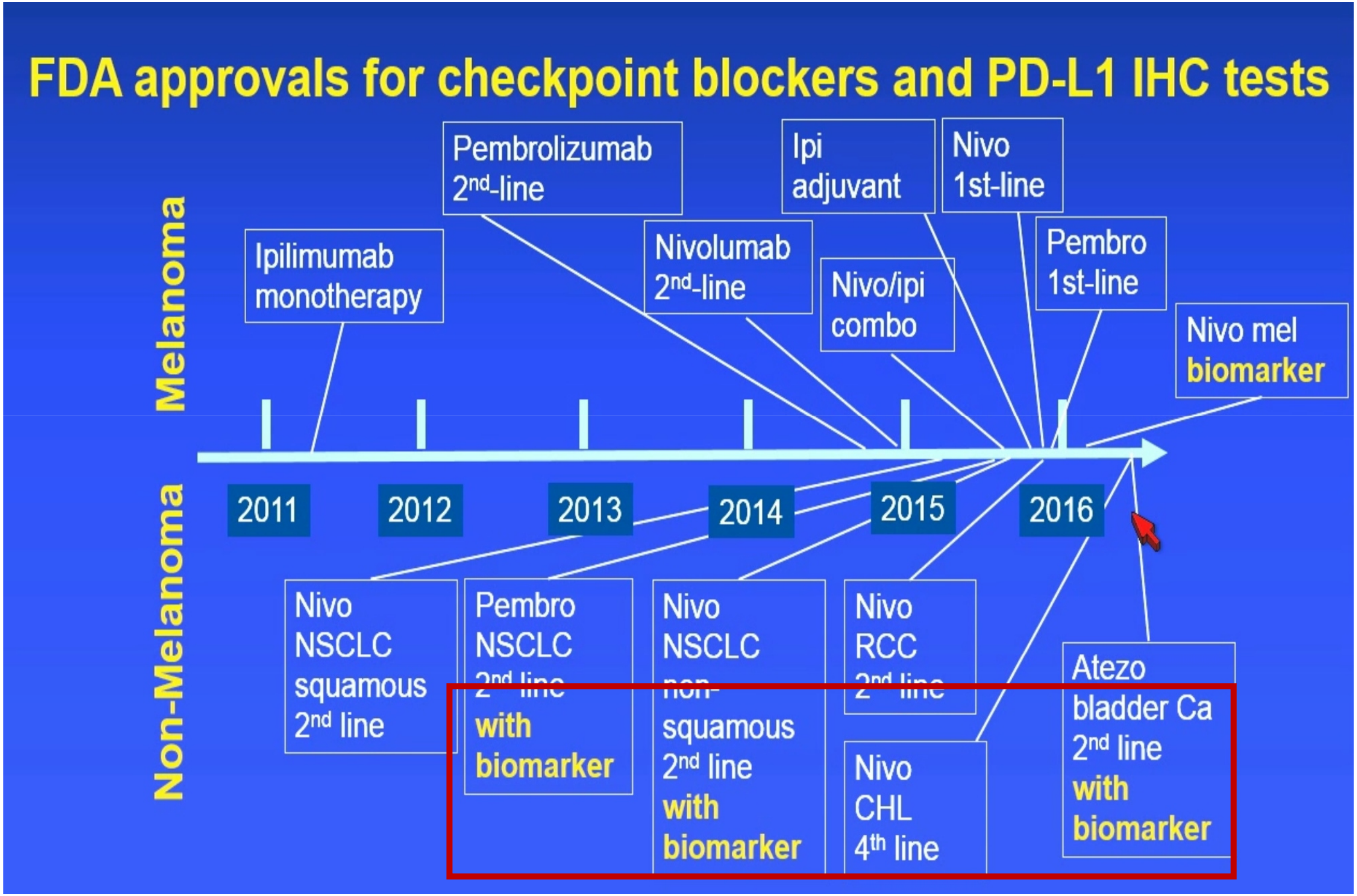
Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D.,





Immunoterapia: nuovi «drivers» (3)



Altre neoplasie con possibili alterazioni molecolari predittive di risposta a trattamenti oncologici «personalizzati»

- **ER, HER2** = **tumore della mammella in fase adiuvante e avanzata**
- **HER2** = **tumore dello stomaco in fase avanzata**
- **RAS family** = **tumore del colon in fase avanzata**
- **BRAF** = **melanoma avanzato**

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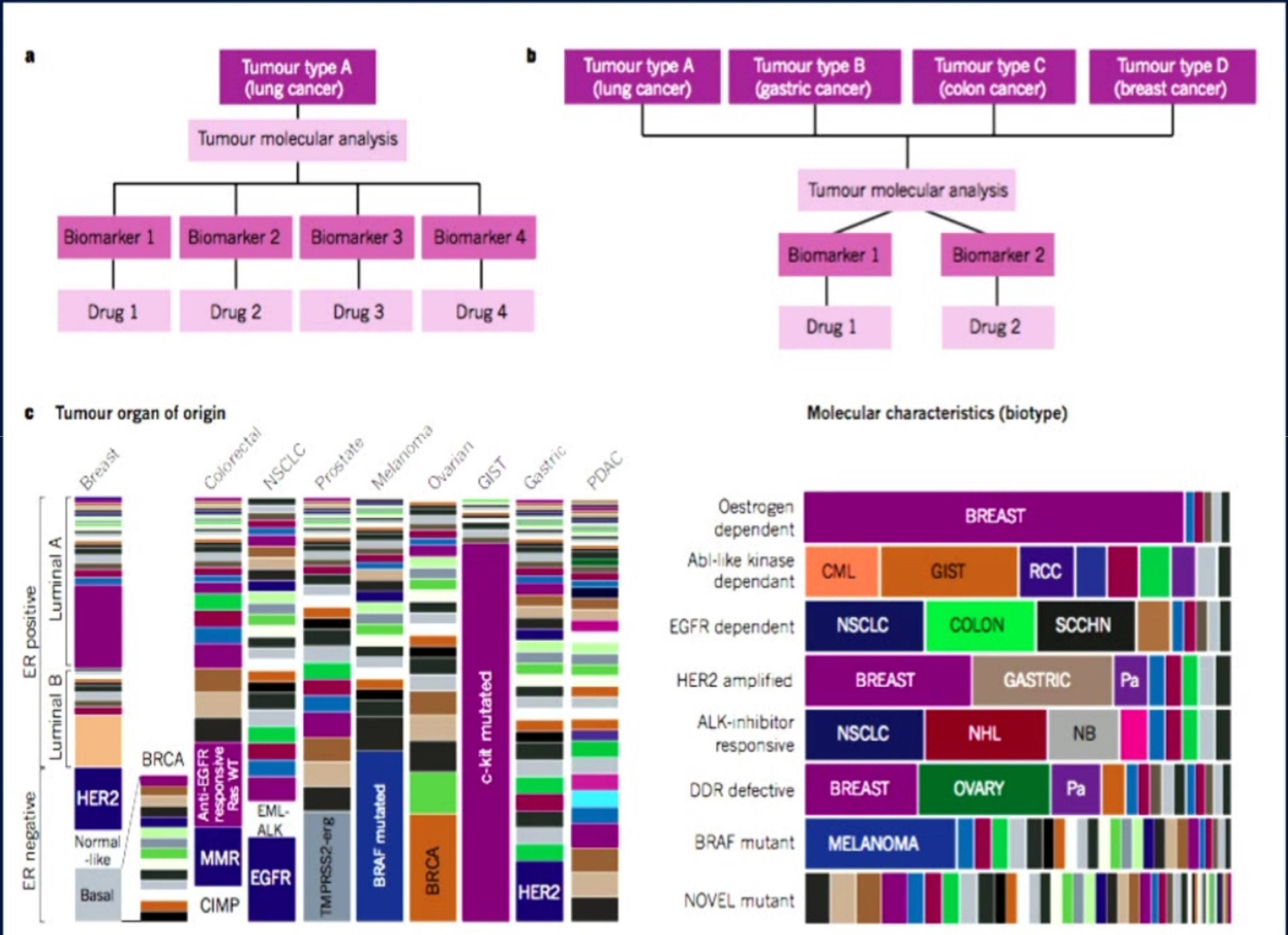
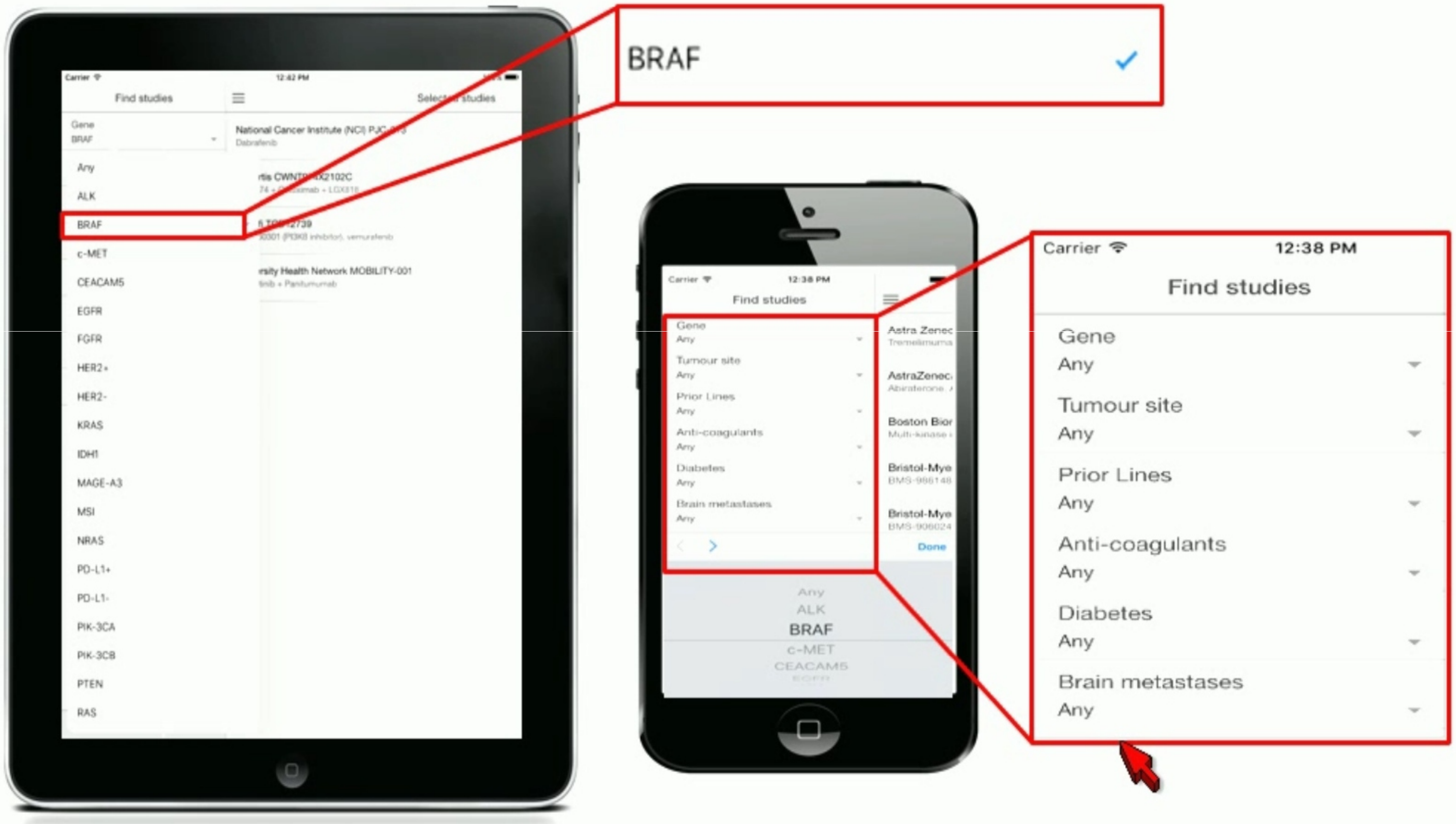
Non c'è studio clinico di fase precoce che non abbia il seguente criterio di inclusione…..

Patient must have a site of disease amenable to biopsy, and be a candidate for tumor biopsy according to the treating institution's guidelines. Patient must be willing to undergo a new tumor biopsy at baseline, and during therapy on this study. For patients in the phase

Umbrella and Basket Trials



Mobile Application

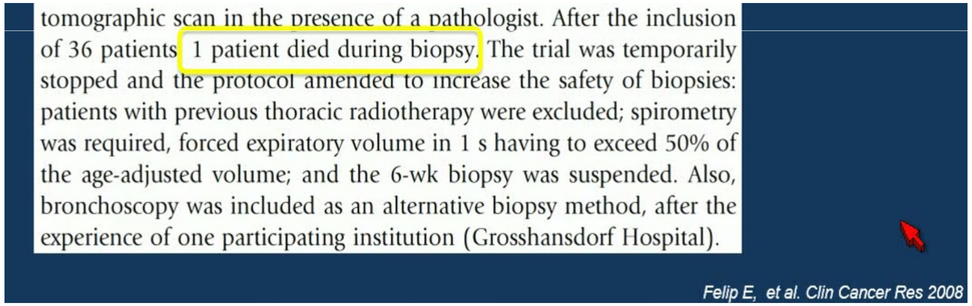


La biopsia: le riflessioni dell’oncologo

Quale sito biopsiabile? E con quale metodica?
(guida ecografica vs TC vs endoscopica)

Quale procedura?
(citologia con FNA vs biopsia tissutale)

Quale finalità?
(diagnostica vs sperimentale)


tomographic scan in the presence of a pathologist. After the inclusion of 36 patients 1 patient died during biopsy. The trial was temporarily stopped and the protocol amended to increase the safety of biopsies: patients with previous thoracic radiotherapy were excluded; spirometry was required, forced expiratory volume in 1 s having to exceed 50% of the age-adjusted volume; and the 6-wk biopsy was suspended. Also, bronchoscopy was included as an alternative biopsy method, after the experience of one participating institution (Grosshansdorf Hospital).

Felip E, et al. Clin Cancer Res 2008

E se non è fattibile con le metodiche standard?
Quale ruolo per la biopsia liquida?