New strategies in patients refractory to reversible EGFR TKIs

A patient with EGFR mutation who progresses to reversible EGFR TKI:
What should we do?

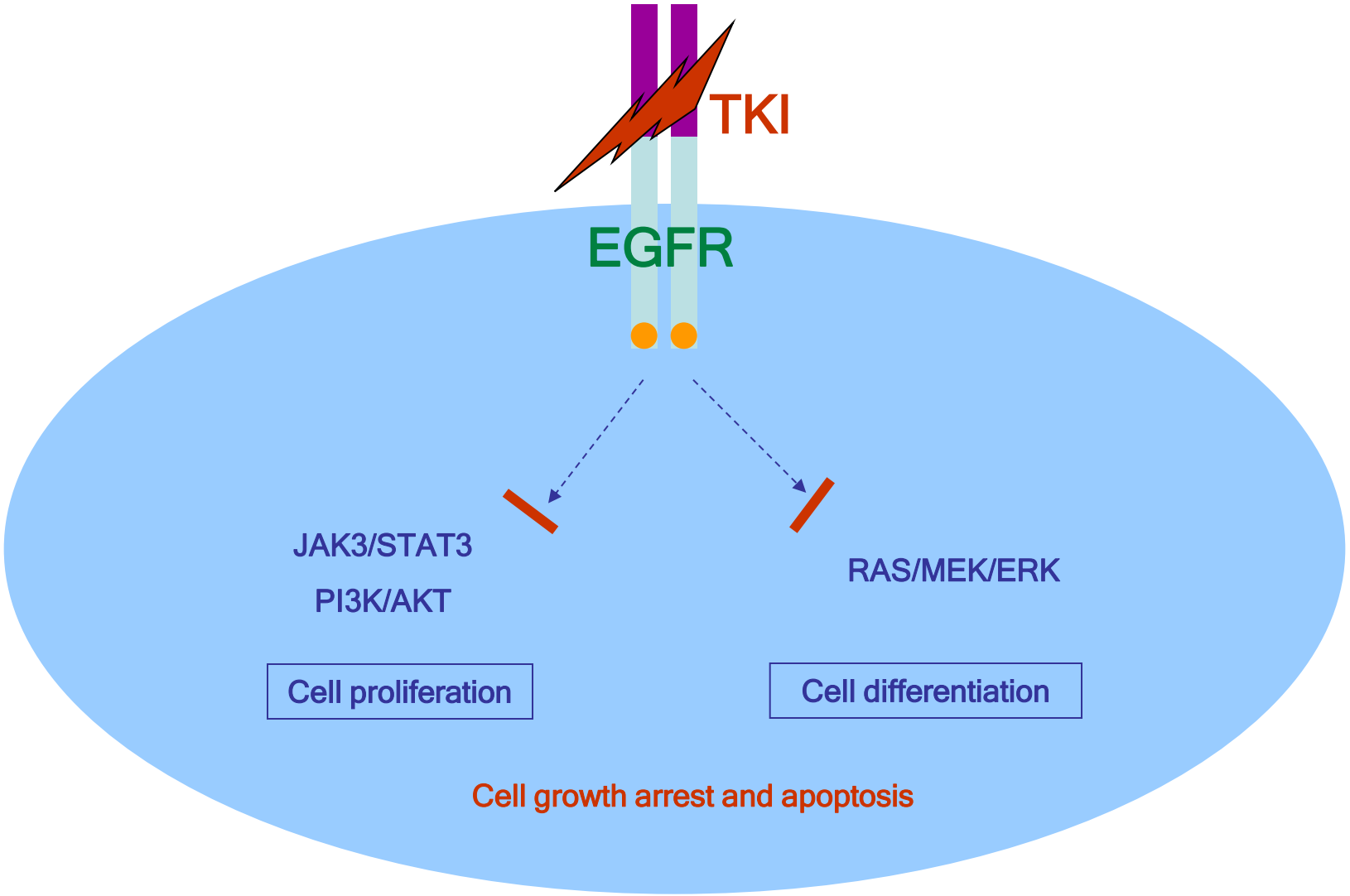
Teresa Morán, MD
ICO-Badalona, Hospital Universitari Germans Trias i Pujol
Badalona, Barcelona (Spain)

Vienna, October 1st 2012

VIENNA 2012 ESMO congress

No disclosures

Cellular insights in the addicted cancer cells



Acquired resistance

Mechanisms of acquired resistance to TKI in EGFR mutant cancers

Secondary mutations

- T790M (50%)
- BRAF (1%)

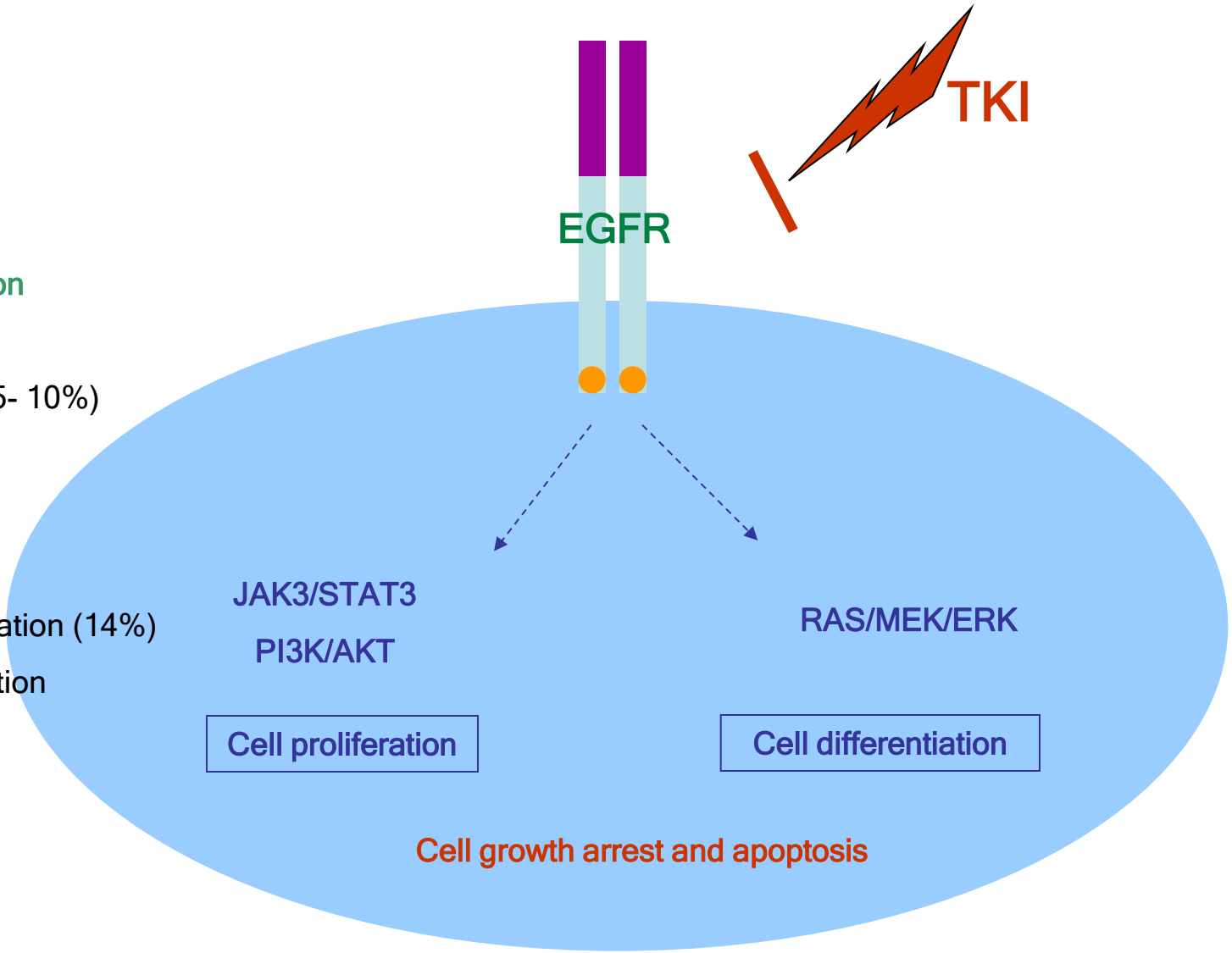
Bypass tracks activation

- EGFR (10%)
- MET by HER3 (5- 10%)
- PI3K (5%)
- AXL (20%)

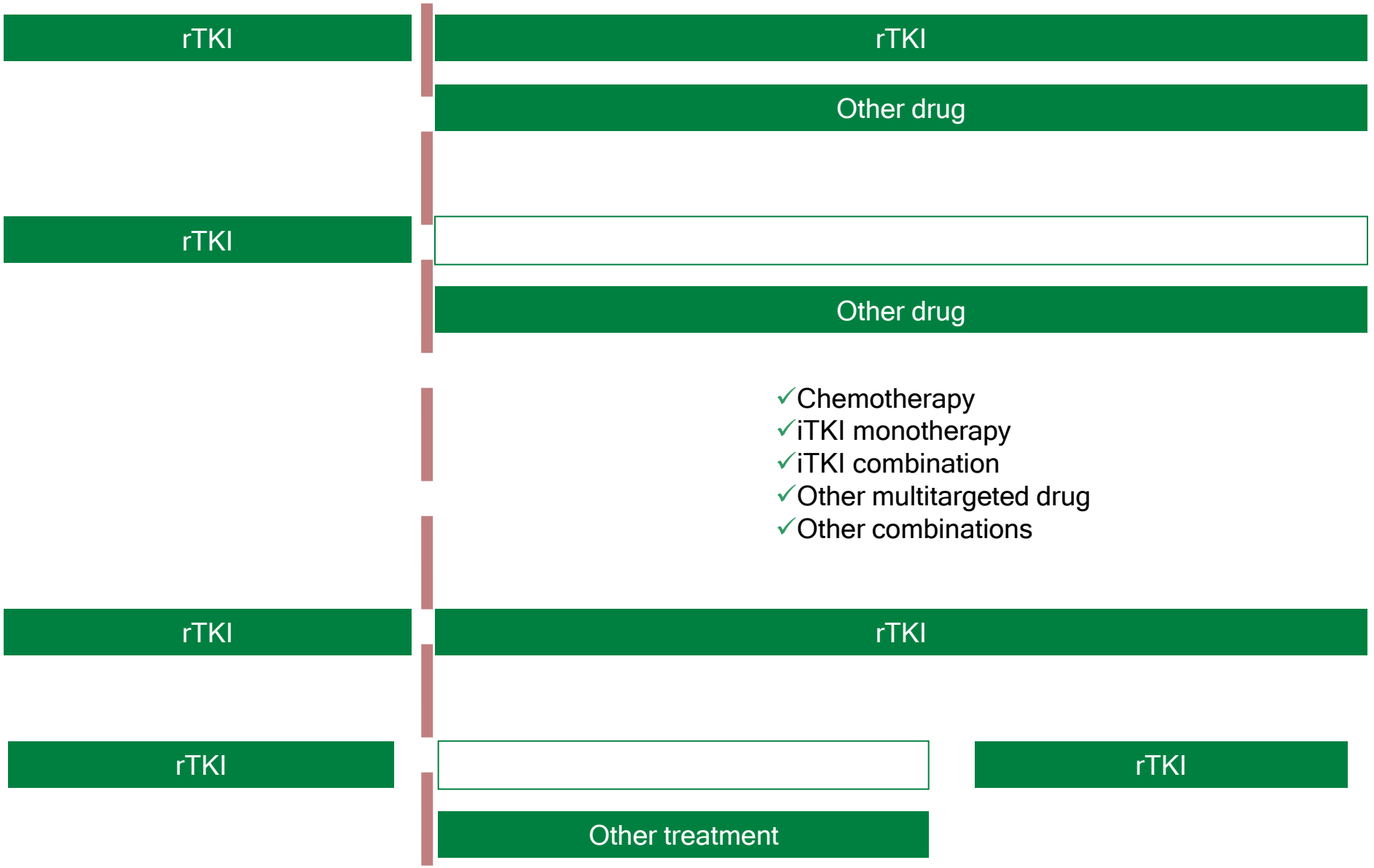
Other mechanisms

- SCLC transformation (14%)
- EMT transformation
- Loss of BIM

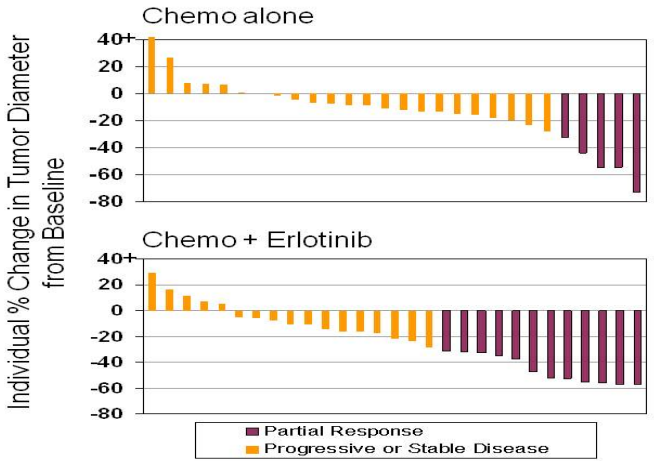
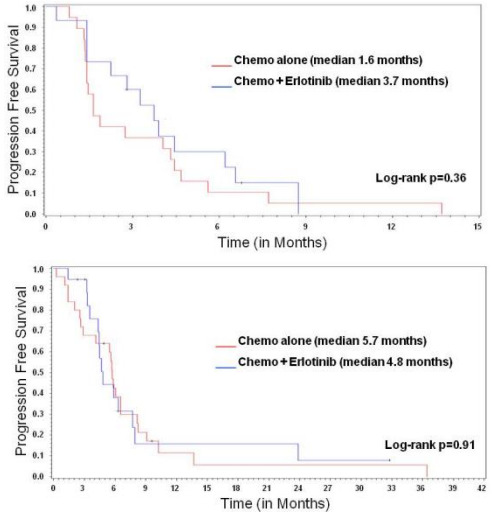
Unknown



Options for acquired resistance to TKI in EGFR mutant cancers



Strategy 1A Add CT to the rTKI

rTKI	rTKI Chemotherapy
Goldberg 2012  	
NCT00660816	pII erlotinib plus CT vs CT alone EGFR+ CT based pemetrexed or docetaxel

Strategy 1B. Add “anything” but CT

rTKI

rTKI

Other drug (try to revert the resistance)

		EGFR mut resist	Known mec	RR	SD	PFS	OS
Gefitinib plus everolimus (Price 2010)	responders to TKI	none	NA	13%			
prior CT				16%	61%	4 m	27 m
no prior CT				9.6%	55%	4 m	11 m
Erlotinib/dasatinib (Johnson 2011)	responders to TKI	none		0%	0.9 m		
dasatinib				0%	0.5 m		
Sunitinib plus erlotinib (Scagliotti 2012)	Unselected	none	NA				
Sunitinib plus erlotinib				10.6%	32.3%	3.6 m	9 m
erlotinib				6.9%	28.1%	2 m	8.5 m
Elotinib plus cetuximab (Janjigian 2011)	responders to TKI		12 of 19	0%	17%	3 m	NR
E100 + C 250, 375, 500 mg/kg							
Erlotinib plus vorinostat (Reguart 2010)	EGFR mut			0%	28%	1.8 m	10.3 m
Erlotinib plus onartuzumab (Spigel 2011)	Unselected	none	NA				
EP				NR		2.6 m	7.4 m
EM				NR		2.2 m	8.9 m
	MET+						
EP				NR		1.5 m	3.8 m
EM				NR		2.9 m	12.6 m
Gefitinib plus MK2206 (AKTi)	**AKTi**						
Erlotinib plus BKM120	**Pi3K i**						
Erlotinib plus bortezomib	**proteosome i**						
Erlotinib plus MM121	**HER3**						

Strategy 2A. Changing gears

rTKI

Other therapy (include TKI in the strategy)

		EGFR mut resist	Known mec	RR	SD	PFS	OS
Neratinib (Sequist 2010)	EGFR mut and WT	91 of 167	9 of 88	3%	50%	<4 m	NR
XL647 (Pietanza 2012)	responders to TKI	14 of 41	10 of 40	3%	64%	3.5 m	16.1 m
Afatinib (Miller 2012)	Unselected	(96/141 asses)	NR				
afatinib				7%	51%	3.3 m	10 m
placebo				<1%	18%	1.1 m	12 m
Dacomitinib (Ramalingan 2012)	Unselected	none	NA				
dacomitinib				17%	12.8%	2.8 m	9.53 m
erlotinib				5.3%	9.6%	1.9 m	7.44 m
dacomitinib	EGFR (16%)	none	NA	NR	NR	7.4 m	
erlotinib				NR	NR	7.4 m	
Afatinib plus cetuximab (Janjigian 2011)	**responders to TKI**	47 of 51	27 of 51	51%	40%	NR	NR
Crizotinib plus dacomitinib	**MET, panHER**						
BMS-690514	**panHER, VEGFR2i**						
XL-647 (cabozantanib)	**MET, RET, VEGFR**						
INC280	**MET**						

Strategy 2A. Changing gears

rTKI

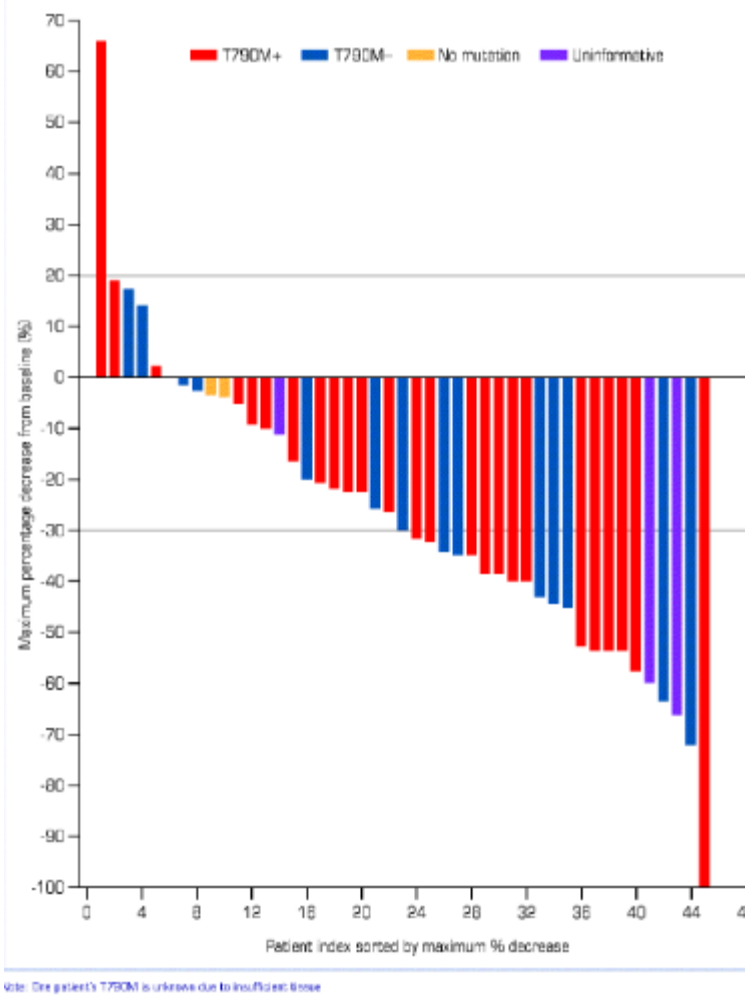
Other therapy (include TKI in the strategy)

Table 2: Afatinib + cetuximab at MTD: responses by mutation

	T790M positive	T790M negative	T790M unknown	No EGFR mutation	Total
Total treated	27	15	3	2	47
Evaluable for efficacy†	26	14	3	2	45
Best response	**n (%)**				
Any PR	13 (50)	8 (57)	2 (67)		23 (51)
Confirmed PR	9 (35)	7 (50)	2 (67)		18 (40)
SD	11 (42)	5 (36)	1 (33)		19 (42)
Clinical response (any PR + SD)	24 (92)	13 (93)	3 (100)	2 (100)	42 (93)
Progression of disease	2 (8)	1 (7)			3 (7)

PR = partial response; SD = stable disease

†Two patients were not evaluable for efficacy



Janjigian 2011

Strategy 2A. Changing gears

rTKI

Other therapy (include TKI in the strategy)

		EGFR mut resist	Known mec	RR	SD	PFS	OS
Neratinib (Sequist 2010)	EGFR mut and WT	91 of 167	9 of 88	3%	50%	<4 m	NR
XL647 (Pietanza 2012)	responders to TKI	14 of 41	10 of 40	3%	64%	3.5 m	16.1 m
Afatinib (Miller 2012)	Unselected	(96/141 asses)	NR				
afatinib				7%	51%	3.3 m	10 m
placebo				<1%	18%	1.1 m	12 m
Dacomitinib (Ramalingan 2012)	Unselected	none	NA				
dacomitinib				17%	12.8%	2.8 m	9.53 m
erlotinib				5.3%	9.6%	1.9 m	7.44 m
dacomitinib	EGFR (16%)	none	NA	NR	NR	7.4 m	
erlotinib				NR	NR	7.4 m	
Afatinib pus cetuximab (Janjigian 2011)	**responders to TKI**	47 of 51	27 of 51	51%	40%	NR	NR
Crizotinib plus dacomitinib	**MET, panHER**						
BMS-690514	**panHER, VEGFR2i**						
XL-647 (cabozantanib)	**MET, RET, VEGFR**						
INC280	**MET**						

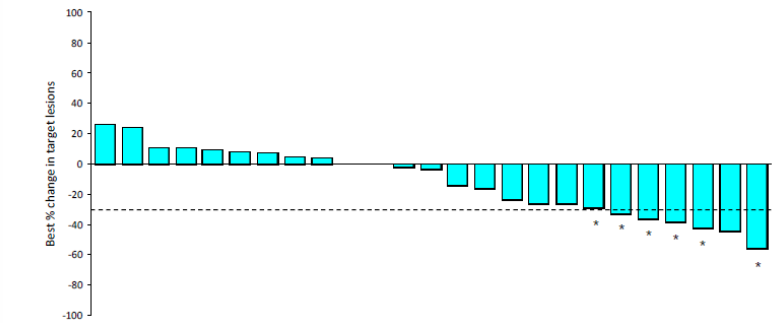
Strategy 2B. Changing gears

rTKI

Other therapy (without TKI)

AUY992 (Felip ESMO 2012)

EGFR-mutant (n=35)	
ORR (any PR)	7 (20%)‡
DCR (CR/PR or SD)	20 (57%)
PFS (18 weeks [95% CI]), %	35.2 (18.7, 52.2)



AP26113 pI/II ALK and EGFR inhibitor

1. ALK positive, ALKi-naïve
2. ALK positive, resistant to ALKi
3. **EGFR mutant, resistant to TKI**
4. Other tumors expressing ALK.

Strategy 3. Continue the rTKI despite PD

rTKI | rTKI

	PPS	Time to new M1 sites	PPS with TKI	PPS without TKI
Oxnard 2010				
T790M+	19 m	14 m		
T790M-	12 m	4 m		
			NA	NA
Hata 2012				
T790M+	34 m	NR		
T790M-	14.5 m	NR		
			23.4 m	10.4 m

	PPS	Time to new M1 sites
Yu 2012	10 m	22 m
Weickhardt 2012	6.2 m	NR
CNS	7.1 m	
eCNS	4 m	

Oxnard 2012	n= 19 delayed > 3 m	n=23 < 3 m	
del 19	74%	39%	p=0.03
mPFS	15 m	13 m	
New M1 sites	11%	30%	
related symptoms	11%	43%	p=0.04
mPPS	29 m		
delayed > 12 m	19%		

Strategy 4 TKI re-challenge after a *holiday* period:

rTKI | | rTKI

Other treatment

Benefits: re-induction of response and PPFS

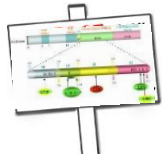
		n	DCR	RR	SD	PPFS	PPOS
Cho 2007	Unselected (5 mut)	21	28.6%	9.5%	19.1%	2 m	5.2 m
Lee 2008	Unselected	23	8.7%	4.3%	4.4%	NR	NR
Watabe 2011	Unselected (3 mut, 8 UK)	11	73%	9%	64%	2 m	7.3 m
Hata 2011	Unselected (7 mut)	125	44%	9%	35%	2 m	11.8 m
	imm vs delayed		72%	25%	47%	3.4 m	11.8 m
Oh 2012	Unselected (56% mut)		84%	21.5%	62.5%	>3 m	11.4 m
Heon 2012	selected	19	79%	5%	74%	4.4 m	NR

✓ICARUS TRIAL= Gefitinib rechallenge *(NCT01530334)*

Risks: Disease flare

Rieley 2007 (n=13) Discontinuation and reinitiation	Increase tumor size Increase tumor uptake Worsens symptoms
Chaft 2011 (n= 61) Discontinuation due to wash out period	23% flare Median 8 days Pleural effusion, CNS M1, shorter TTP TKI Independently T790M status

Decision making in every day clinical practice



Indolent behavior?

Explosive behavior?

Overall progressive disease?

New lesions but previous sites under control?

Repeat biopsy

rTKI

Local therapy

Treatment modification

Change to CT

Clinical trial

Add CT

Clinical trial (adding "whatever" to the rTKI)

Clinical trial

Do not forget…

EGFR mutant patients are currently more frequently identify since screening platforms are widespread available, but when relapse occurred

1. Importance of repeat biopsies in growing lesions
   - ✓ Understand the underlying biology
   - ✓ Direct our patients to the appropriate clinical trials

2. " Have mutation, will travel" *(West and Camidge 2012)*

Case report 1

	Apr-05	Sep-05	Aug-07	Jul-08	Jun-09	Aug-09
Histology	adeno			SCLC	adeno	
M1 sites	lung, liver	lung, liver	adrenal	adrenal, lung	CNS, abdomen	
Molecular profile		del 19		del 19; T790M -	del 19; T790M -	
TKI		Gefitinib				
Chemotherapy	carbo/ paclitaxel x4		Cis-Docetaxel x 4	Carbo-VP16 x 6	pemetrexed x2	
Other treatments					WCRT	
Rebiopsy			No	Yes	Yes	
Response	SD	CR	CR	PR	NE	

1. TKI: Continuous administration *vs*. holiday period
2. Role of repeat biopsies
3. Value of clinical trials

Case report 2

	Oct-07	Feb-08	Oct-09	May-10	Oct-10	Apr-12	Oct-12
Histology	adeno						
M1 sites	lung	lung	lung	lung	lung		
Molecular profile	del 19; T790M -						
TKI		erlotinib	afatinib	erlotinib		erlotinib	
Chemotherapy	Cis-gem				cis-pem x4, pem x12		
Other treatments			sirolimus	vorinostat			
Rebiopsy			no	no	no		
Response	SD	PR	SD	SD	PR	SD	

1. Changing a rTKI to an iTKI
2. Re challenging rTKI
3. Role of repeat biopsies
4. Combining targeted therapy at recurrence

Acknowledgements

ICO-Badalona

Rafael Rosell

Enric Carcereny

Erika Mijangos

Ana Montañés

Cristina Bugés

Sara Cros

Laia Capdevila

Olga Fernández

Miquel Tarón

Cristina Queralt

Itziar de Aguirre

MGH

Lecia Sequist

Jeff Engelman

	abr-05	sep-05	ago-07	jul-08	jun-09	ago-09
Histology	adeno			SCLC	adeno	
M1 sites	lung, liver	lung, liver	adrenal	adrenal, lung	CNS, abdomen	
Molecular profile	del 19; T790M -			del 19; T790M -	del 19; T790M -	
TKI		Gefitinib				
Chemotherapy	carbo/ paclitaxel x4		Cis-Docetaxel x 4	Carbo-VP16 x 6	pemetrexed x2	
Other treatments					WCRT	
Rebiopsy			no	Yes	Yes	
Response	SD	CR	CR	PR	NE	

	oct-07	feb-08	oct-09	may-10	oct-10	abr-12	oct-12
Histology	adeno						
M1 sites	lung	lung	lung	lung	lung		
Molecular profile	del 19; T790M -						
TKI		erlotinib	afatinib	erlotinib		erlotinib	
Chemotherapy	Cis-gem				cis-pem x4, pem x12		
Other treatments			sirolimus	vorinostat			
Rebiopsy			no	no	no		
Response	SD	PR	SD	SD	PR	SD	