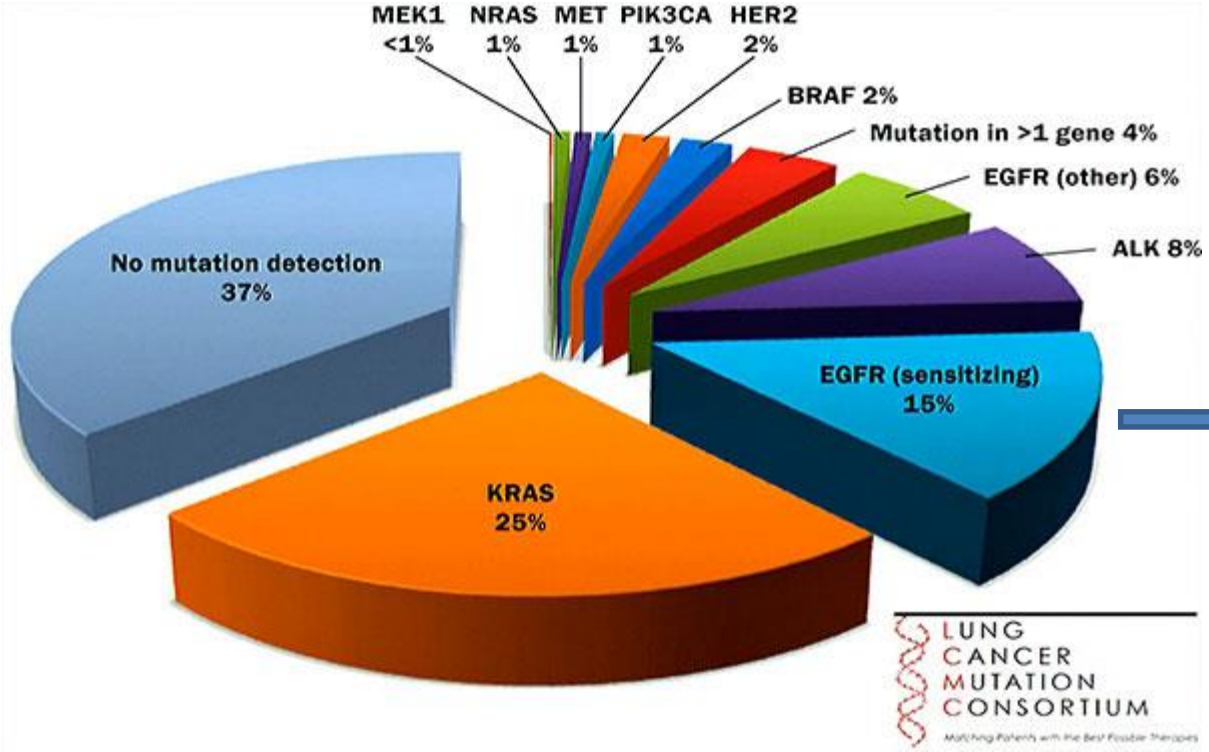
Role of *TP53* mutations in determining primary resistance to first-line tyrosine kinase inhibitors in *EGFR*-mutated NSCLC patients

Paola Ulivi[1], Matteo Canale[1], Angelo Delmonte[1], Elisabetta Petracci[1], Elisa Chiadini[1], Claudio Dazzi[2], Maximilian Papi[3], Laura Capelli[1], Claudia Casanova[2],Nicoletta De Luigi[1], Marita Mariotti[1], Alessandro Gamboni[4], Rita Chiari[5], Chiara Bennati[5], Daniele Calistri[1], Vienna Ludovini[5], Lucio Crinò[1], Dino Amadori[1]

[1]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola/Italy, [2]S. Maria delle Croci Hospital, Ravenna/Italy, [3]Infermi Hospital, Rimini/Italy, [4]Degli Infermi Hospital, Faenza/Italy,
[5]Medical Oncology, Santa Maria della Misericordia Hospital, Azienda Ospedaliera di Perugia, Perugia/Italy

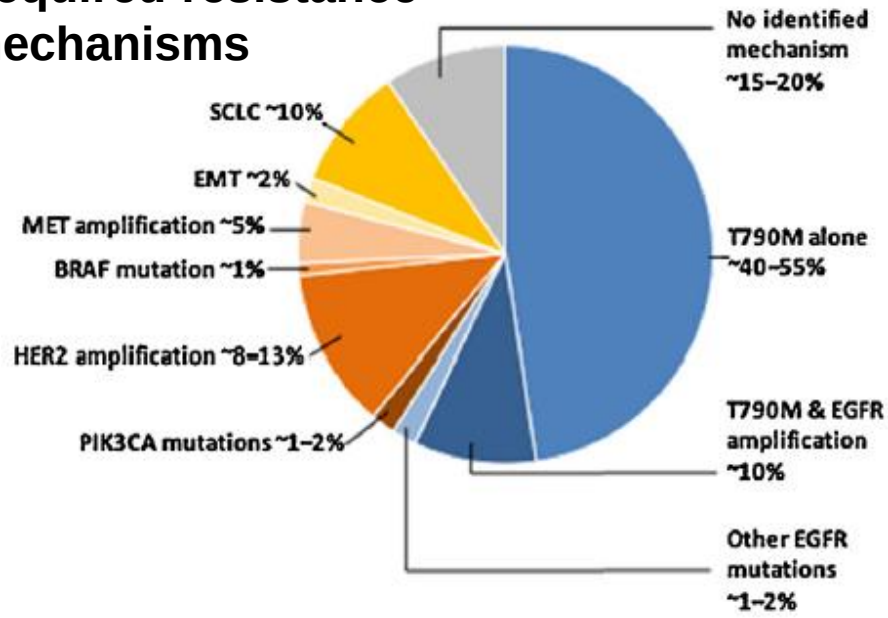


Response to TKIs (gefitinib, erlotinib, afatinib)

EGFR mutated patients treated with a TKI

About 70% response rate

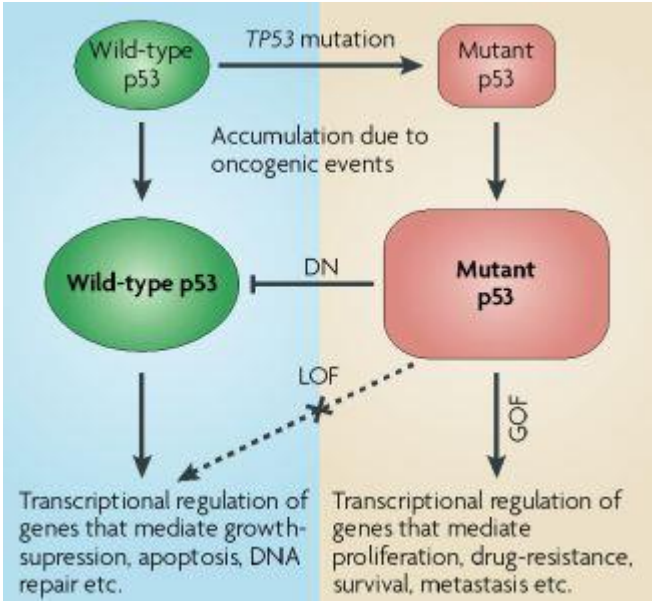
Acquired resistance mechanisms



About 30% of patients show primary resistance

?

TP53 is mutated in about 30% of NSCLC



***TP53* GOF mutations are able to:**

- Increase tumorigenicity
- Increase growth rate and motility
- Increase metastasis and invasiveness

- Up-regulate the expression of Axl
- Induce the EMT process

Both implicated in TKIs resistance

We analyzed the status of TP53 in relation to response to first-line TKIs in EGFR-mutated patients

Clinical-pathological characteristics of patients

	n (%)
Gender	
F	102 (75.0)
M	34 (25.0)
Age at start of first-line of therapy, years	
Mean ± sd	70.4 ± 10.7
Smoking status	
Never smoker	62 (59.0)
Former smoker	28 (26.7)
Current smoker	15 (14.3)
Missing	31
Histology	
Adenocarcinoma	134 (98.5)
Poorly differentiated carcinoma	2 (1.5)
EGFR mutation	
Exon 18 point mutation	6 (4.4)
Exon 19 deletion	74* (54.4)
Exon 21 point mutation	56 (41.2)
L858R	49 (36.0)
L861Q	7 (5.1)
Type of first-line therapy	
Gefitinib	104 (76.5)
Erlotinib	27 (19.8)
Afatinib	3 (2.2)
Dacomitinib	2 (1.5)
Therapy response	
CR	4 (3.0)
PR	71 (52.6)
SD	37 (27.4)
PD	23 (17.0)

123 patients underwent TP53 mutation analysis:

37 (30%) mutated:
- 27% exon 5
- 16% exon 6
- 24% exon 7
- 33% exon 8

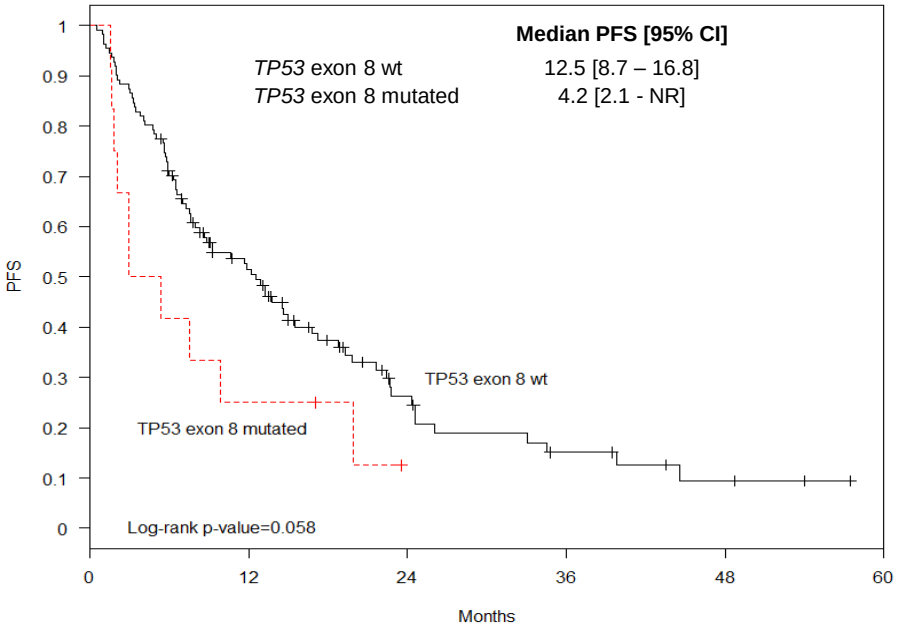
Canale M et al, Clin Cancer Res, October 2016

Disease Control Rate (DCR) in relation to the different types of *TP53* mutations

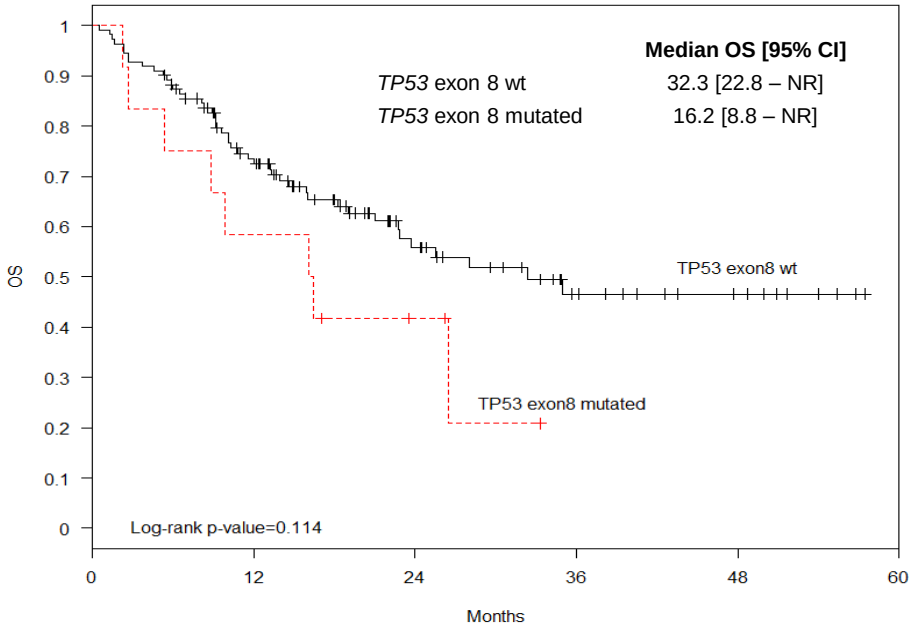
	DCR, n (%)		Unadjusted	
***TP53* mutation**	No (n=22)	Yes (n=101)	RR [95% CI]	P
All mutations				
Wt	10 (11.8)	75 (88.2)	1	0.019
Mut	11 (29.7)	26 (70.3)	3.17 [1.21 - 8.48]	
Exon 5				
Wt	18 (16.1)	94 (84.0)	1	0.2745
Mut	3 (30.0)	7 (70.0)	2.24 [0.45 - 8.92]	
Exon 6				
Wt	20 (17.2)	96 (82.8)	1	0.971
Mut	1 (16.7)	5 (83.3)	0.96 [0.05 - 6.39]	
Exon 7				
Wt	21 (18.4)	93 (81.6)	1	-
Mut	-	9 (100)	-	
Exon 8				
Wt	14 (12.7)	96 (87.3)	1	< 0.001
Mut	7 (58.3)	5 (41.7)	9.6 [2.71- 36.63]	
Disr/Non disr				
Wt	10 (11.7)	75 (88.2)	1	
Disruptive	3 (25.0)	9 (75.0)	2.25 [0.25- 8.94]	0.273
Non-disruptive	8 (33.3)	16 (66.7)	3.75 [1.26 - 11.07]	0.016

PFS and OS in *TP53* exon 8-mutated patients compared to *TP53* exon 8 wt patients

a



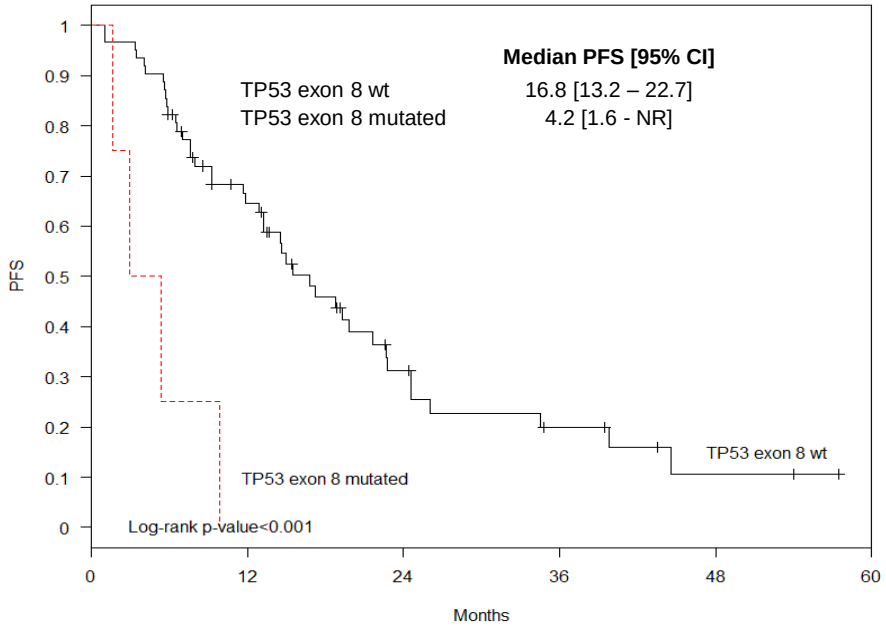
b



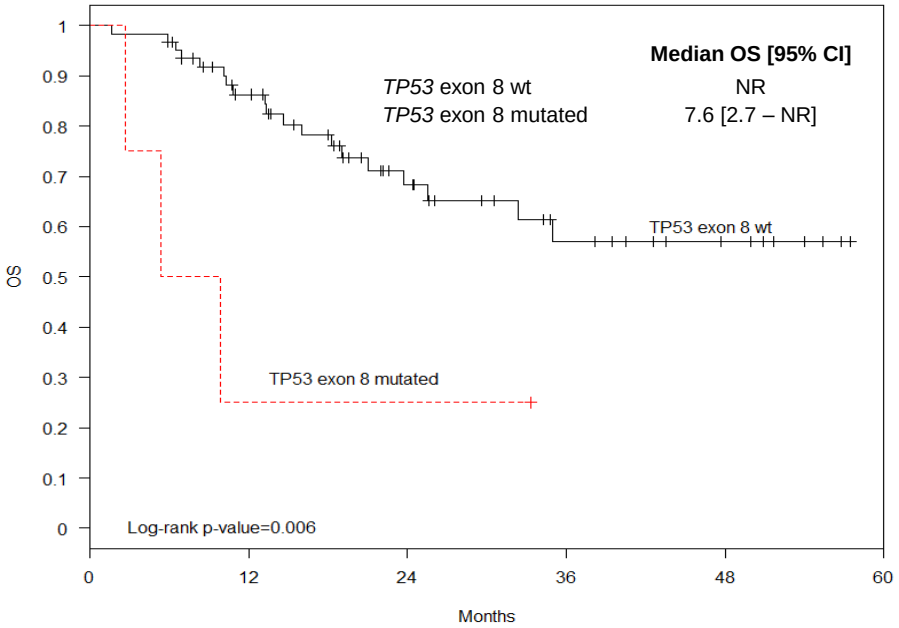
Canale M et al, Clin Cancer Res, October 2016

PFS and OS in *TP53* exon 8-mutated patients compared to *TP53* exon 8 wt patients in the subgroup of *EGFR* exon 19 deleted patients

c



d



Canale M et al, Clin Cancer Res, October 2016

Risk of PFS and OS in relation to *TP53* exon 8 mutations in the subgroup of patients with *EGFR* exon 19 deletion

	PFS		OS	
	HR [95% CI]	p	HR [95% CI]	p
***TP53* mutation**				
wt	1		1	
mut	1.74 [0.92 – 3.29]	0.086	1.58 [0.64 – 3.87]	0.321
***TP53* exon 8 mutation**				
wt	1	0.006	1	0.013
mut	6.99 [2.34-20.87]		4.75 [1.38-16.29]	

Canale M et al, Clin Cancer Res, October 2016

CONCLUSIONS

- ***TP53*** **mutations were associated with a significantly lower DCR in *EGFR*-mutated patients treated with first-line TKIs**

- ***TP53*** **exon 8 mutations were those associated with the lowest DCR**

- ***TP53*** **exon 8 mutations were associated with a significantly shorter PFS and OS in the subgroup of patients carrying *EGFR* exon 19 deletion**

- **Once confirmed in a larger independent case series, these results could lead to a more accurate selection of *EGFR*-mutated NSCLC patients who could benefit from treatment with first-line TKIs**

Thank you for your attention!!!