ARS TOSCANA
agenzia regionale di sanità

Regione Toscana

• FIRENZE •
29 NOVEMBRE 2017

MEDICINA E ASSISTENZA DI PRECISIONE

COSA CAMBIA NELL'EPIDEMIOLOGIA,
NELLA GESTIONE CLINICA E VALUTAZIONE OUTCOME

Differenze genetiche e azioni dei farmaci

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Blood tests in the Unit of Clinical Pharmacology and Pharmacogenetics

- DPD and UGT genotyping for prevention and diagnosis of fluoropyrimidine and irinotecan toxicity in colorectal cancer
- EGFR/KRAS mutations for prediction of response/resistance to treatment in NSCLC
- ALK translocation and mutations for prediction of resistance to treatment in NSCLC
- RAS and BRAF mutations for prediction of resistance to treatment in colorectal cancer and pancreas cancer
- AR-V7 splice variant for prediction of resistance to treatment in prostate cancer

Background

- Safety is an important concern too often neglected – there are approximately 20.000 DPD-deficient patients, i.e., 3-5% of the approximately 450.000 patients diagnosed annually with colorectal cancer in Europe (Deenen MJ, Meulendijks D, Ann Onc 2016)

Characteristics of cohorts 1, 2 and 3

Characteristics	Cohort 1 N (%)	Cohort 2 N (%)	Cohort 3 N (%)
Patients	200	982	272
Gender (M/F)	113/87 (56.5/43.5)	392/590 (39.9/60.1)	147/125 (54/46)
Age (years, median)	58	65	59
Disease			
Colorectal cancer	150 (75)	740 (75,3)	130 (47,8)
Gastric cancer	40 (20)	195 (19,8)	12 (4,4)
Breast cancer	10 (5)	49 (5)	130 (47,8)
Treatment ([1])			
FU-LV (De Gramont regimen)	36 (18)	170 (17,3)	0 (0)
Capecitabine	40 (20)	210 (21,4)	80 (29,4)
FOLFIRI	26 (13)	182 (18,5)	0 (0)
FOLFOX-4	34 (17)	190 (19,3)	130 (47,8)
FOLFOXIRI	10 (5)	54 (5,5)	0 (0)
CAPOX	36 (18)	160 (16,3)	0 (0)
TPF	8 (4)	0 (0)	0 (0)
XELIRI	6 (3)	8 (0,7)	0 (0)
Epirubicin, oxaliplatin, capecitabine (EOX)	4 (2)	8 (0,8)	50 (18,4)

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Toxicity in cohorts 1 and 2

ADRs	Cohort 1	Cohort 2
Gastrointestinal	**Grade ≥2**	**Grade ≥2**
Nausea/Vomiting	21.5%	16%
Diarrhea	51%	39.7%
Stomatitis	19%	14%
Dermatological	**Grade ≥2**	**Grade ≥2**
Hand-foot syndrome	13%	9.3%
Hematological	**Grade ≥3**	**Grade ≥3**
Fever	4.5%	2.2%
Leucopenia	16.5%	12.3%
Neutropenia	21.5%	17.4%
Febrile neutropenia	7%	4.7%
Anemia	3.5%	4.2%
Thrombocytopenia	5%	5.8%

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Type and frequencies of *DPYD* genotypes in 1454 patients (C1: 200 pts; C2: 982 pts; C3: 272 pts)

	Wild-type (%)			Heterozygous (%)			Homozygous mut (%)		
Variant	Cohort 1	Cohort 2	Cohort 3	Cohort 1	Cohort 2	Cohort 3	Cohort 1	Cohort 2	Cohort 3
c.496A>G	79	76.2	82	20.2	22	16.5	0.8	1.8	1.5
c.1601G>A	91.5	90.7	93.8	8.5	9.1	6.3	0	0.2	0
c.1627A>G	68.6	67.4	60.3	28	29.1	34.2	3.4	3.5	5.5
c.1896T>C	97.5	96.5	95.2	2.5	3.5	4	0	0	0.7
c.1905+1G>A	95.8	93.8	100	3.4	6.1	0	0.8	0.1	0
c.2194G>A	81.3	80.2	88.2	15.3	18.4	10.7	3.4	1.3	1.1
c.2846A>T	99.2	97.6	100	0.8	2.3	0	0	0.1	0

Del Re M et al. submitted 2017

Conclusions

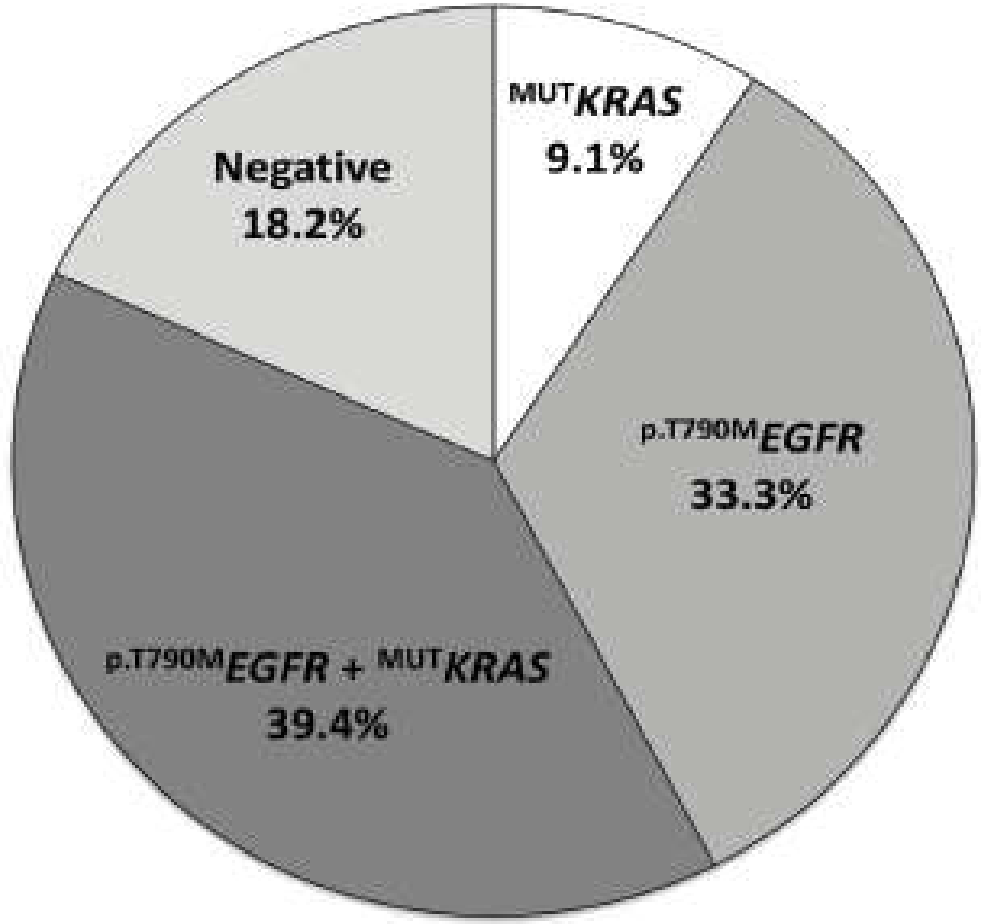
- PGx data are robust enough to support the introduction of DPD analysis in current practice
- The choice of DPYD variants should be made on the basis of functional data and population prevalence
- The utility of DPYD genotyping as pre-emptive screening of patients should be discussed between **clinical oncologists** and **experts in pharmacogenetics**
- The examination of more DPYD loci is helpful to improve the predictive value of PGx in fluoropyrimidine-based toxicities
- Avoiding risk of toxicity is a clinical commitment

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2016

Contribution of *KRAS* mutations and c.2369C > T (p.T790M) *EGFR* to acquired resistance to EGFR-TKIs in *EGFR* mutant NSCLC: a study on circulating tumor DNA

Marzia Del Re[1], Marcello Tiseo[2], Paola Bordi[2], Armida D'Incecco[3], Andrea Camerini[4], Iacopo Petrini[5], Maurizio Lucchesi[6], Alessandro Inno[7], Daniele Spada[8], Enrico Vasile[6], Valentina Citi[1], Giorgio Malpeli[9], Enrica Testa[8], Stefania Gori[7], Alfredo Falcone[6], Domenico Amoroso[4], Antonio Chella[10], Federico Cappuzzo[3], Andrea Ardizzoni[2], Aldo Scarpa[9], Romano Danesi[1]

Mechanisms of resistance in NSCLC

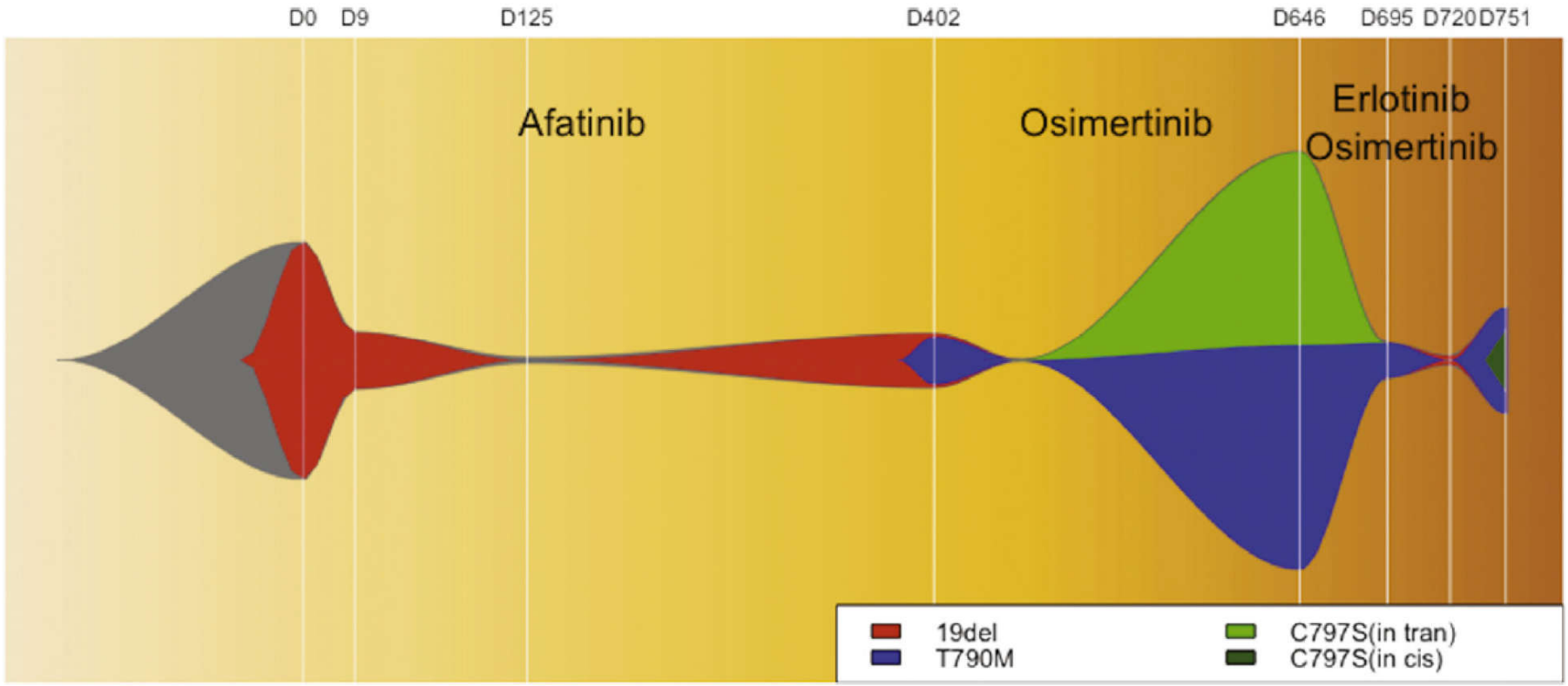


BRIEF REPORT

Lung Adenocarcinoma Harboring *EGFR* T790M and *In Trans* C797S Responds to Combination Therapy of First- and Third-Generation EGFR TKIs and Shifts Allelic Configuration at Resistance

Zhen Wang, MD, PhD,[a] Jin-Ji Yang, MD,[a] Jie Huang, MD, PhD,[a] Jun-Yi Ye, PhD,[b] Xu-Chao Zhang, PhD,[a] Hai-Yan Tu, MD,[a] Han Han-Zhang, PhD,[b] Yi-Long Wu, MD[a,*]

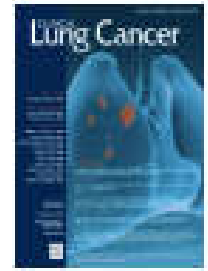
Sequential use of EGFR-TKI



Clinical Lung Cancer

Available online 18 May 2017

In Press, Corrected Proof

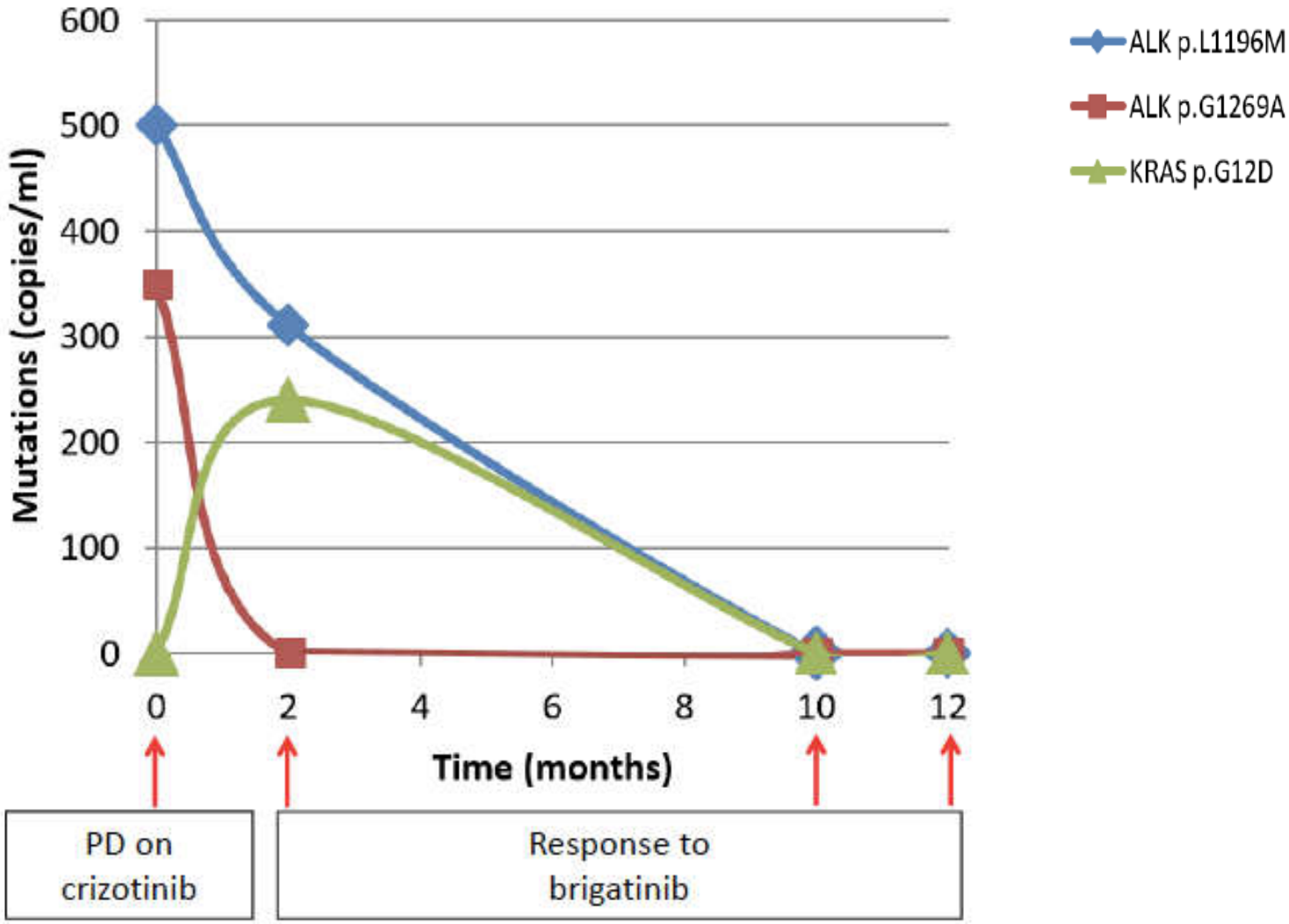


Original Study

Detection of *ALK* and *KRAS* Mutations in Circulating Tumor DNA of Patients With Advanced ALK-Positive NSCLC With Disease Progression During Crizotinib Treatment

Paola Bordi [1], Marcello Tiseo [1] ✉, Eleonora Rofi [2], Iacopo Petrini [3], Giuliana Restante [2], Romano Danesi [2], Marzia Del Re [2]

Monitoring or ALK mutations in plasma



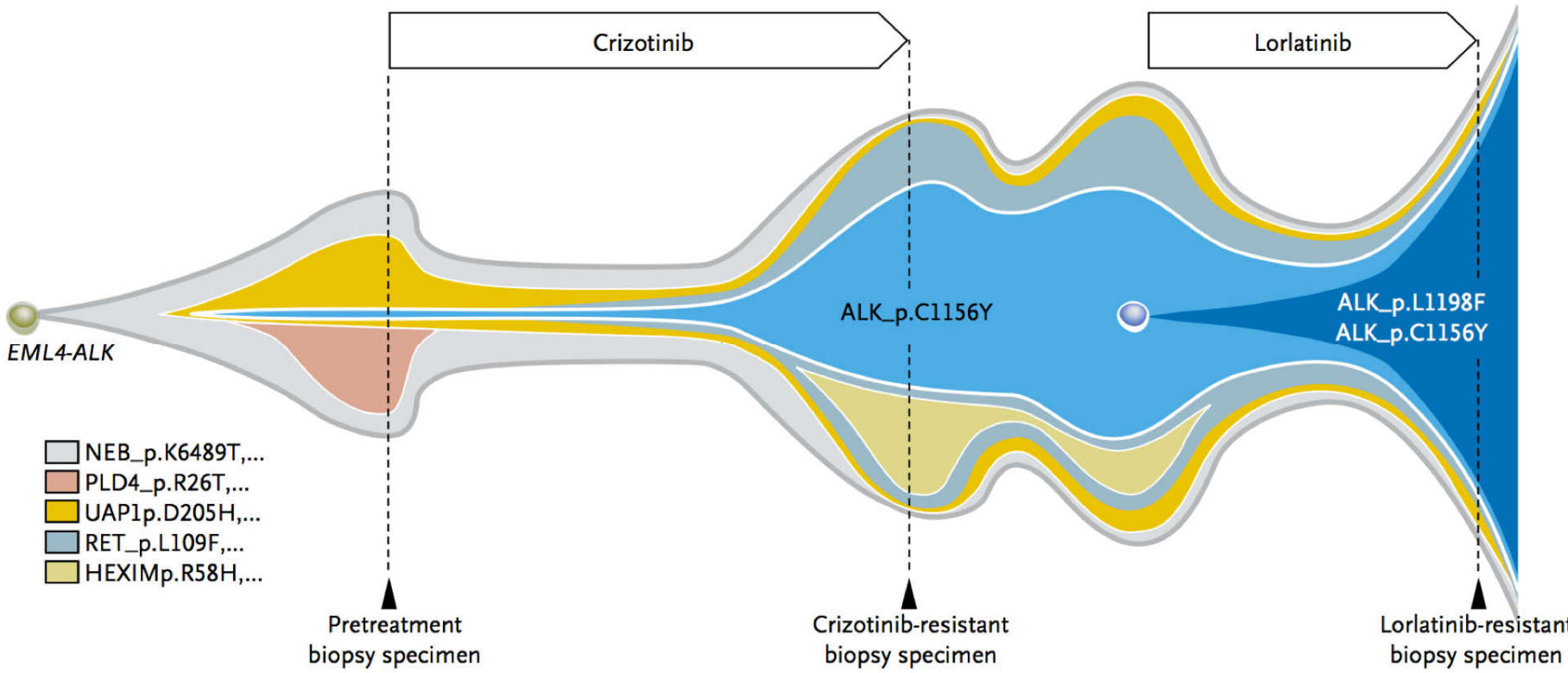
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Resensitization to Crizotinib by the Lorlatinib *ALK* Resistance Mutation L1198F

Alice T. Shaw, M.D., Ph.D., Luc Friboulet, Ph.D., Ignaty Leshchiner, Ph.D., Justin F. Gainor, M.D., Simon Bergqvist, Ph.D., Alexei Brooun, Ph.D., Benjamin J. Burke, Ph.D., Ya-Li Deng, B.S., Wei Liu, M.A., Leila Dardaei, Ph.D., Rosa L. Frias, B.A., Kate R. Schultz, M.A., Jennifer Logan, M.S.N., Leonard P. James, M.D., Ph.D., Tod Smeal, Ph.D., Sergei Timofeevski, Ph.D., Ryohei Katayama, Ph.D., A. John Iafrate, M.D., Ph.D., Long Le, M.D., Michele McTigue, Ph.D., Gad Getz, Ph.D., Ted W. Johnson, Ph.D., and Jeffrey A. Engelman, M.D., Ph.D.

Clonal evolution in ALK-mut NSCLC and drug sensitivity

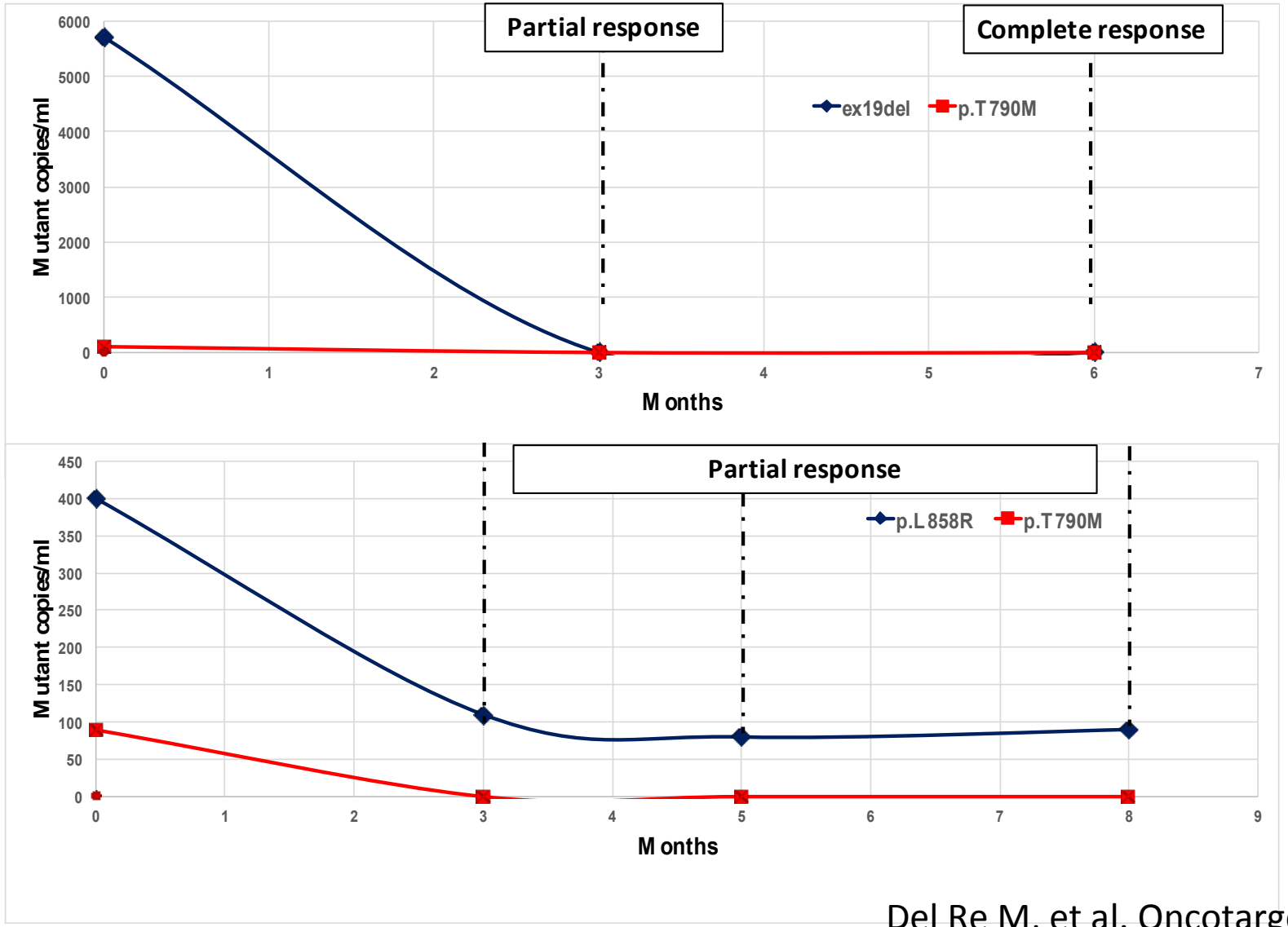


www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2017

Patients with NSCLC may display a low ratio of p.T790M *vs.* activating EGFR mutations in plasma at disease progression: implications for personalised treatment

Marzia Del Re[1,*], Paola Bordi[2,*], Iacopo Petrini[3,*], Eleonora Rofi[1], Francesca Mazzoni[4], Lorenzo Belluomini[5], Enrico Vasile[3], Giuliana Restante[1], Francesco Di Costanzo[4], Alfredo Falcone[3], Antonio Frassoldati[5], Ron H.N. van Schaik[6], Christi M.J. Steendam[7], Antonio Chella[8], Marcello Tiseo[2], Riccardo Morganti[9] and Romano Danesi[1]

EGFR mutations clearence during osimertinib treatment



Del Re M, et al. Oncotarget 2017

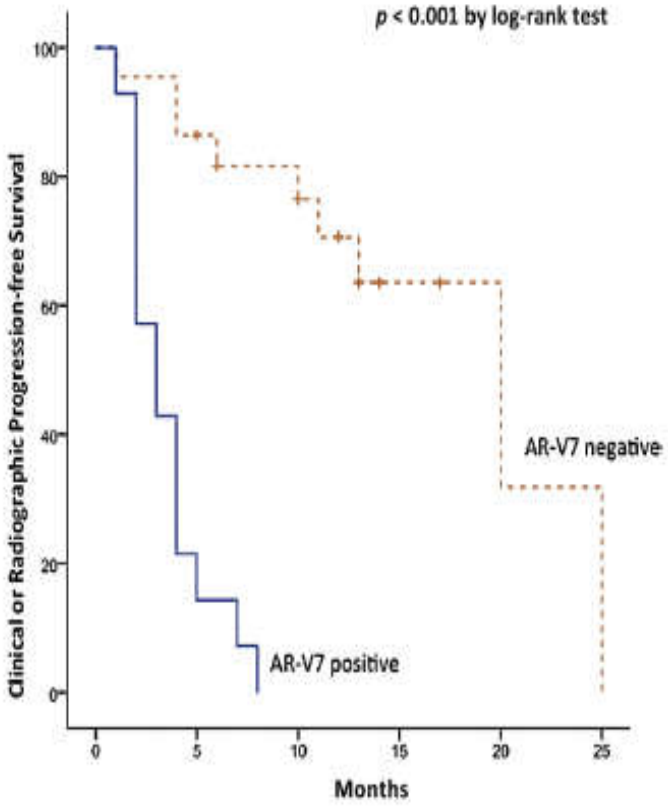
European Association of Urology

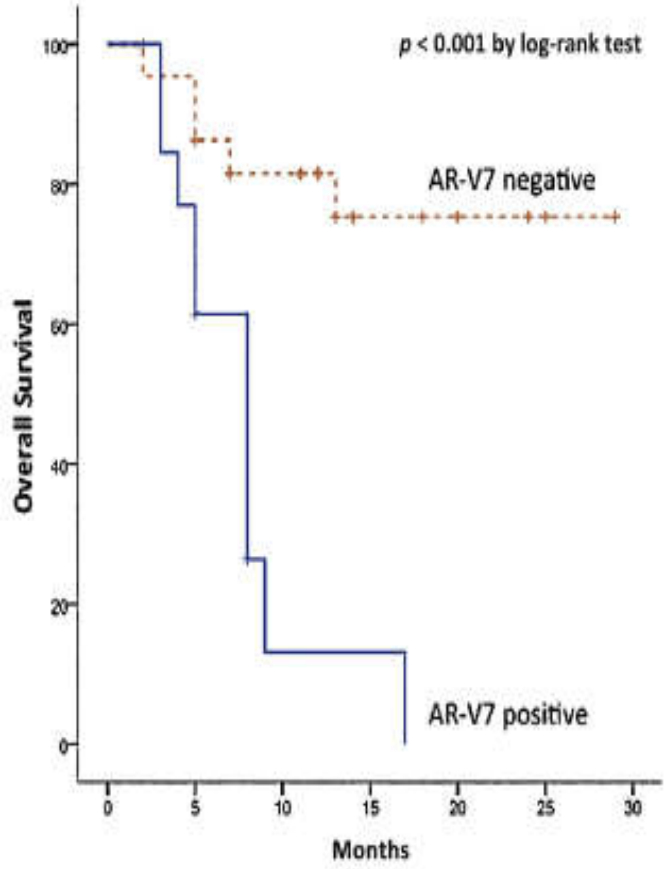
From Lab to Clinic

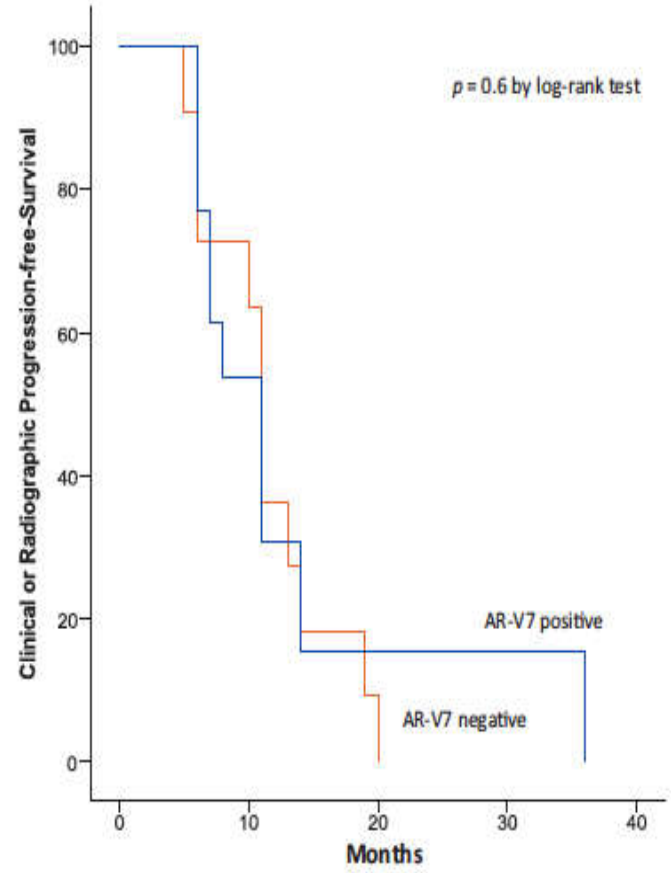
The Detection of Androgen Receptor Splice Variant 7 in Plasma-derived Exosomal RNA Strongly Predicts Resistance to Hormonal Therapy in Metastatic Prostate Cancer Patients

Marzia Del Re[a,*], *Elisa Biasco*[b], *Stefania Crucitta*[a], *Lisa Derosa*[b,†], *Eleonora Rofi*[a], *Cinzia Orlandini*[b], *Mario Miccoli*[c], *Luca Galli*[b], *Alfredo Falcone*[b], *Guido W. Jenster*[d], *Ron H. van Schaik*[e], *Romano Danesi*[a]

AR-V7 effect on survival







www.nature.com/scientificreports

OPEN

Early changes in plasma DNA levels of mutant KRAS as a sensitive marker of response to chemotherapy in pancreatic cancer

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Marzia Del Re[1], Caterina Vivaldi[2], Eleonora Rofi[1], Enrico Vasile[2], Mario Miccoli[3], Chiara Caparello[2], Paolo Davide d'Arienzo[2,4], Lorenzo Fornaro[2], Alfredo Falcone[2] & Romano Danesi[1]

KRAS monitoring in PaCa

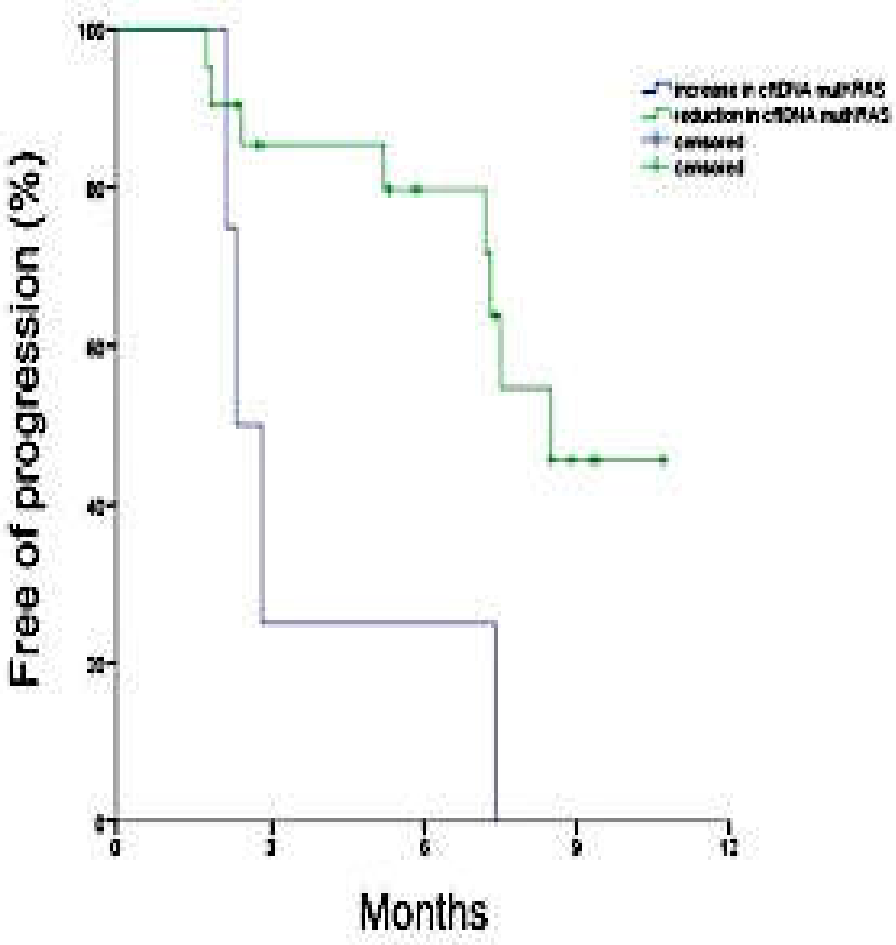
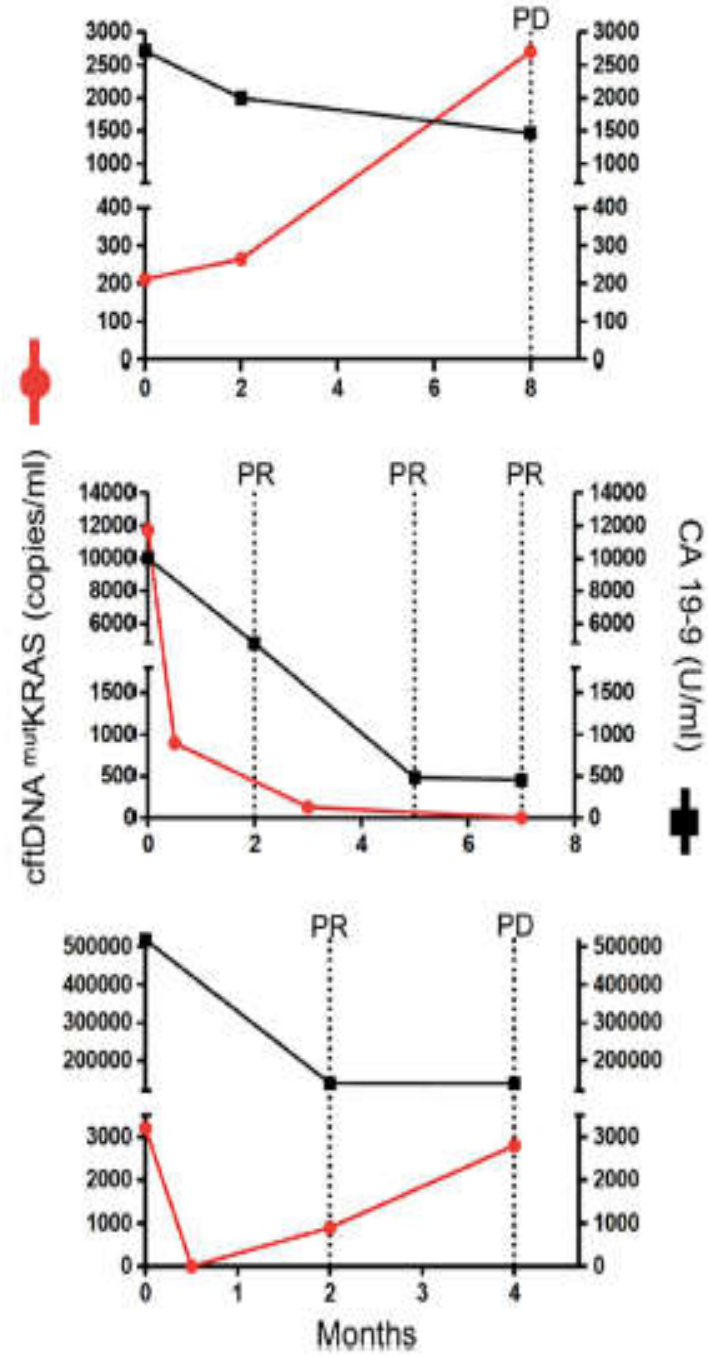


Figure 1. PFS according to early ^{mut}KRAS cfDNA variation (increase vs. reduction).



Conclusions

- cftDNA is a powerful tool to monitor tumor evolution and clonal heterogeneity induced by treatment

- Application of cftDNA monitoring to treatment selection may help improve appropriateness of therapeutic choices