III SIMPOSIO
Biopsia líquida
EL CAMINO A LA ONCOLOGÍA DE PRECISIÓN
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Circulating tumor (ct)DNA captures intrapatient heterogeneity in metastatic colorectal patients progressing to FOLFIRI+panitumumab

J. Vidal, J.M. Viéitez, D. Paez, C. Santos, D. Azuara, A. Dalmases,
B. Bellosillo, R. Salazar, E. Aranda Aguilar, C. Montagut
On behalf of Grupo de Tratamiento de los Tumores Digestivos (TTD)

Background

- CRC cells evade EGFR blockade by monoclonal antibodies (mAbs) cetuximab/panitumumab by several mechanisms of acquired resistance, mainly due to mutations in *RAS/BRAF* or *EGFR* extracellular domain (ECD), and amplifications in *MET* or *ERBB2*[1,2].

- ctDNA is shed into the bloodstream by tumor cells and can be effectively used to track tumor heterogeneity and to evaluate acquired mutations at tumor progression[3,4]

1. Diaz, LA JCO 2014
2. Siravegna, S Nat.Med 2015
3. Arena S , CCR2015
4. Vidal J, Muinelo L, Ann Oncol 2017

Objective

- To analyze the acquisition of gene mutations in plasma ctDNA from patients with mCRC progressing to antiEGFR treatment and to correlate with laterality of primary tumor

Patients and Methods

- 16 Metastatic CRC patients treated within a fase II trial of FOLFIRI + panitumumab in irinotecan-refractory mCRC were included
- Plasma samples were collected at baseline and at the end of treatment and processed with the Oncomine ™ Colon cfDNA Assay
- The resulting library was sequenced in the ION PGM NGS System and analyzed with the Torrent Suite Software
- The detectable cutoff mutation was 0.1%
- Subclonal mutations were defined as mutations with mutant allele fraction (MAF) ≤ 20% of the highest somatic MAF in the sample

Oncomine™ Colon cfDNA Assay

GENE LIST

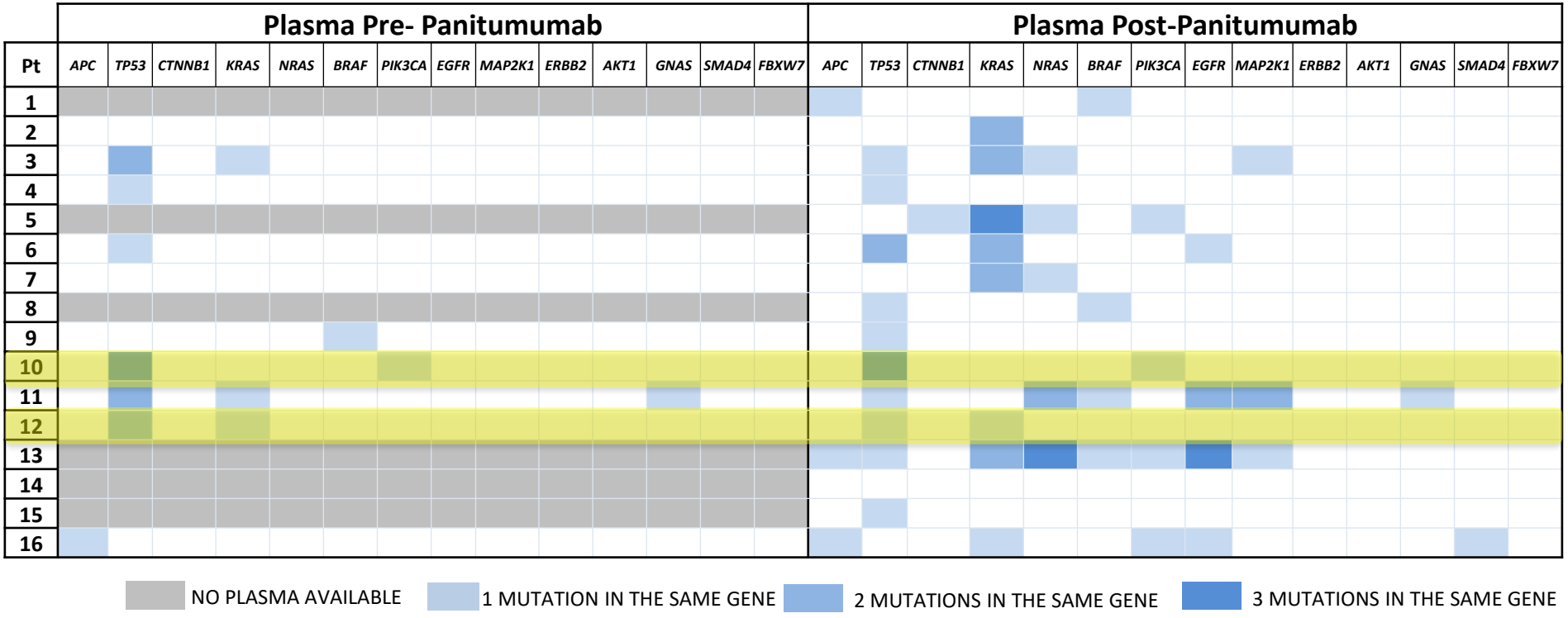
AKT1	*KRAS*
BRAF	*NRAS*
CTNNB1	*PIK3CA*
EGFR	*SMAD4*
ERBB2	*TP53*
FBXW7	*APC*
GNAS	
MAP2K1	

Patients and Methods

Patient Characteristics	STUDY pts N 16 (%)	ULTRA pts N 72 (%)
Age median (range)	61 (42-83)	62 (38-83)
Gender		
Male	11 (68.8%)	51 (70.8%)
Female	5 (31.3%)	21 (29.2%)
Stage at diagnoses		
III	2 (12.5%)	20 (27.8%)
IV	14 (87.5%)	52 (72.2%)
Primary site of disease		
Right colon	4 (25%)	10 (24.4%)
Left colon / Rectum	12 (75%)	62 (75.6%)
Surgery of primary tumor		
Yes	10 (62.5%)	53 (73.6%)
No	6 (37.5%)	19 (26.4%)
Adjuvant QT		
Yes	3 (18.7%)	30 (41.7%)
No	13 (81.3%)	42 (58.3%)
Number of metastatic sites		
1	8 (50%)	22 (30.6%)
2	5 (31.3%)	27 (37.5%)
3 or more	3 (18.8%)	23 (31.9%)
Metastasis Location		
Liver	13 (81.3%)	46 (63.9%)
Lung	4 (25%)	34 (47.2%)
Peritoneum	1 (6.3%)	11 (15.3%)
Node	4 (25%)	26 (36.1%)
Others	1 (6.3%)	19 (26.4%)

RESULTS

Heterogeneity and co-existence of mutations at progression of Panitumumab based treatment



- At least one mutation was detected in 80% of pts (8/10)
- Median mutations per sample was 1.8 (range 1 - 4)

- At least one mutation was detected in 94% of pts (15/16)
- Median mutations per sample were 2.5 (range 1 -13)

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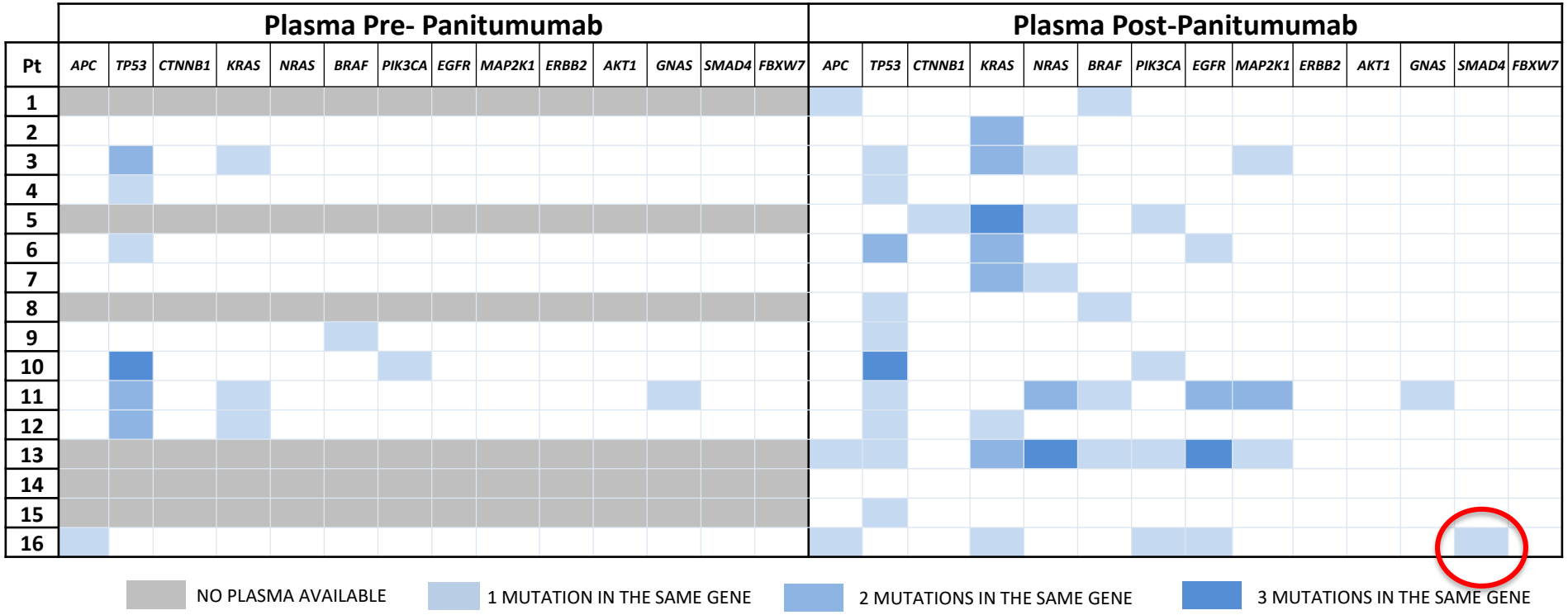

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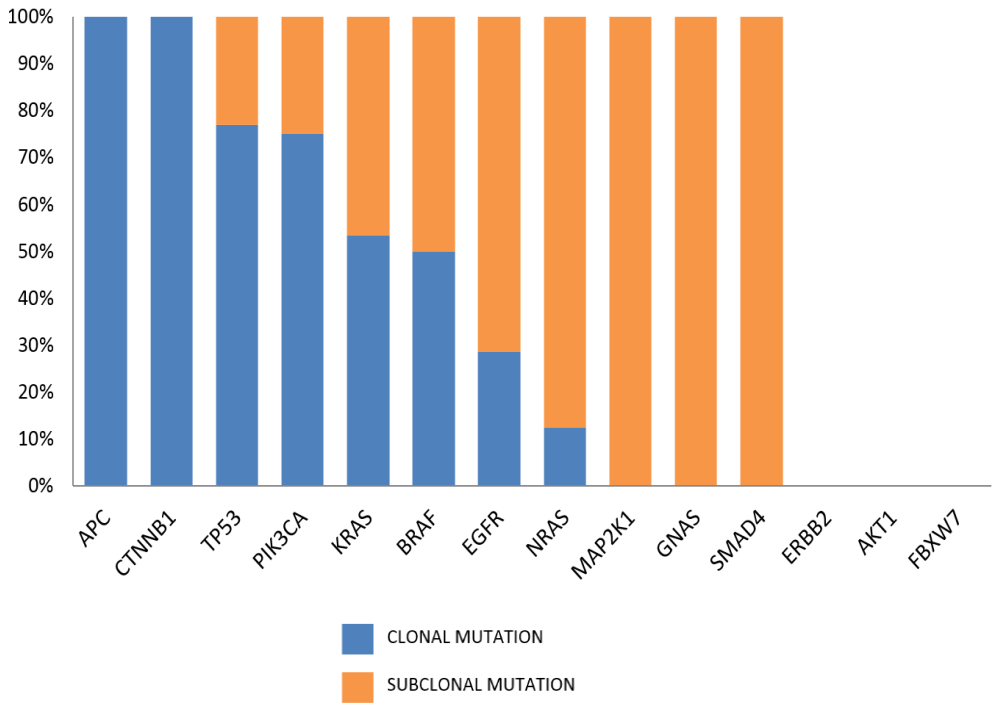
RESULTS

Genomic heterogeneity at tumor progression according to ctDNA mutant allele fraction (MAF)

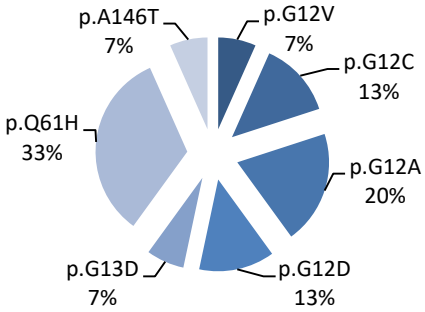


- Mutations most likely to be clonal: *APC* (100%), *CTNNB1* (100%), *TP53* (77%) and *PIK3CA* (75%)
- 53% of mutations in *KRAS* were clonal, while most *NRAS* mutations were subclonal (87.5%)
- *EGFR* ECD mutations were most likely to be detected as subclonal (71%)
- All *MAP2K1* mutations detected were subclonal
- No *ERBB2*, *AKT1* or *FBXW7* mutations were detected

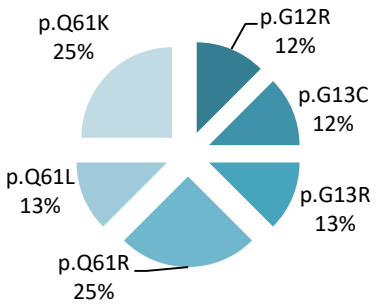
RESULTS

Frequency of mutations at tumor progression detected in gene hotspots

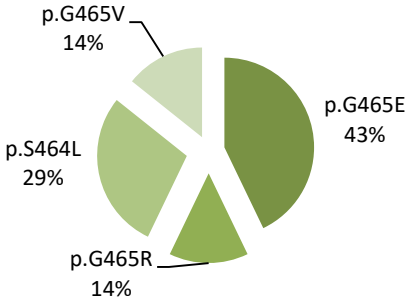
KRAS acquired mutations (N=15)



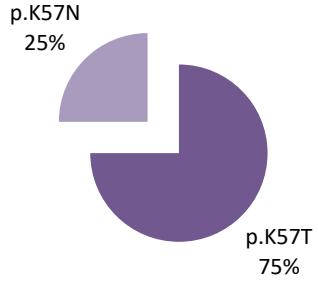
NRAS acquired mutations (N=8)



EGFR ECD acquired mutations (N=7)



MAP2K1 acquired mutations (N=4)

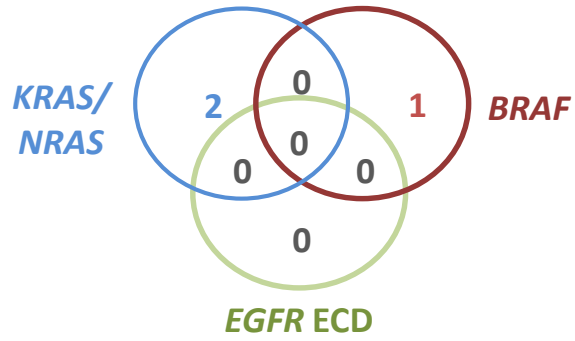


RESULTS

Genomic heterogeneity according to sidedness of primary tumor

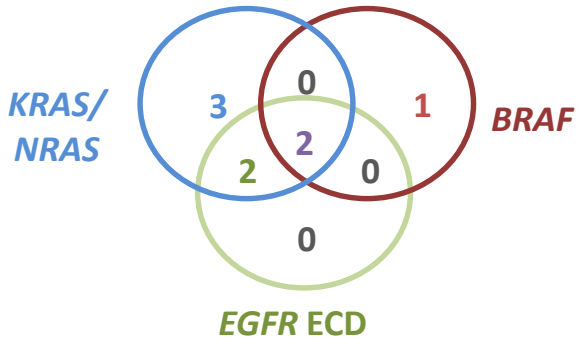
Right colon

Median mutations 2.5 range 1-6
All *RAS/BRAF* mutations were clonal
No EGFR ECD mutation was detected



Left colon

Median mutations 6 (range 3-13)
50% of *RAS/BRAF* mutations were clonal
only one patient with EGFR ECD mutations were clonal



Efficacy data	N 4 (%)
Best Response	
Partial Response	1 (25%)
Stable Disease	2 (50%)
Progression Disease	1 (25%)
Progression Free Survival	
median month (range)	6.18 (2.5-7.63)
Overall Survival	
median (range)	13.96 (3.82-17.04)

Efficacy data	N 12 (%)
Best Response	
Partial Response	7 (59%)
Stable Disease	4 (33%)
Progression Disease	1 (8 %)
Progression Free Survival	
median month (range)	8.52 (1.36-14.3)
Overall Survival	
median (range)	24.29 (3.22-28.85)

Conclusions

- ctDNA analysis captured intrapatient heterogeneity which developed as a result of EGFR inhibition

- All *EGFR* ECD mutations emerged in the left colon and always co-existed with several other mechanisms of acquired resistance, reflecting genomic complexity

- More acquired mutations were detected in left CRC compared to right primary tumors (6 vs. 2.5 respectively)

Muchas gracias!

jvidal@parcdesalutmar.cat