

Biomarcadores para avaliação de efectividade terapêutica no carcinoma colorectal

Objectivos do projecto

- Avaliar o valor predictivo de um conjunto de biomarcadores, relativamente à resposta à terapia em doentes com carcinoma colo-rectal metastático na população Portuguesa.

**IPATIMUP
IPO - Porto**

Investigação
fundamental e
aplicada
Genómica
Proteómica

Eurotrials

Metodologia de
Inv. clínica
Estratégia
regulamentar de
I&D

**HS João
IPO – Porto**

Coortes clínicas
Identificação de
necessidades
clínicas insatisfeitas

Plataforma de I&D oncológico

Estudos de translação, provas de conceito

Produtos

Genetest

Outros

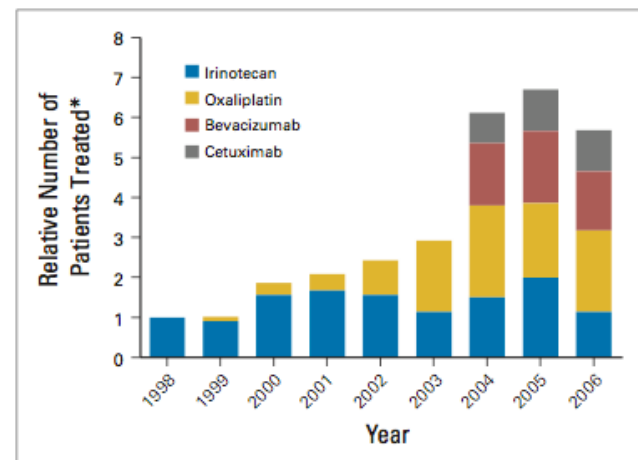
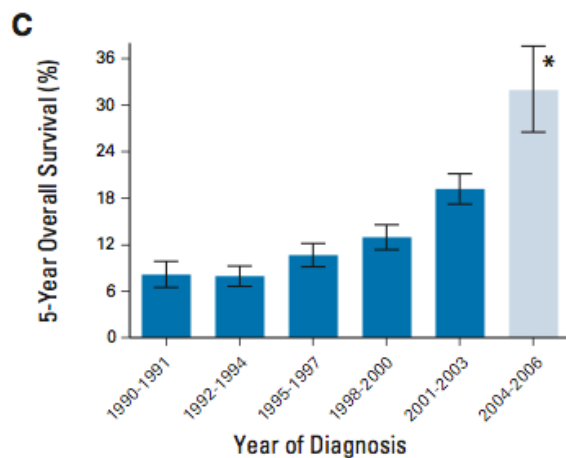
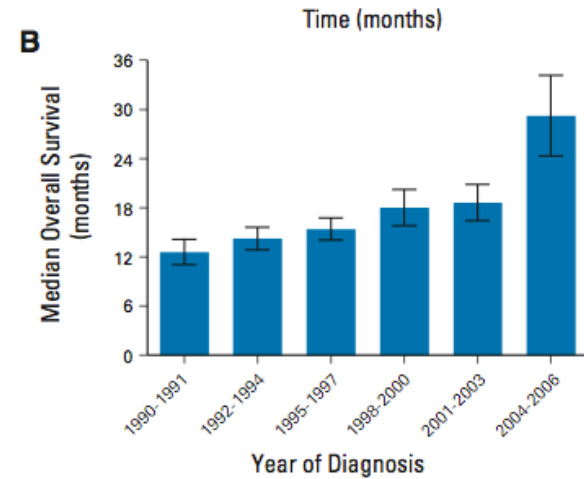
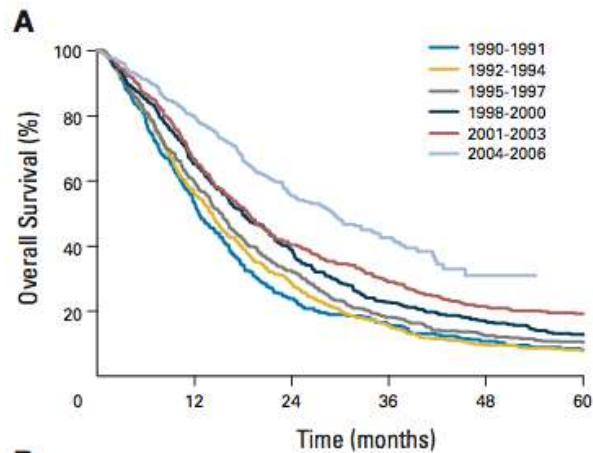
Desenho do estudo

- Coorte de 1000 casos de carcinoma colorectal – 800 incluídos num estudo retrospectivo e 200 incluídos num estudo prospectivo.
- Este estudo inclui os seguintes biomarcadores:
 - Mutações nos genes KRAS, NRAS e BRAF;
 - Pesquisa de instabilidade de microsatélites

Epidemiologia do carcinoma do cólon e recto

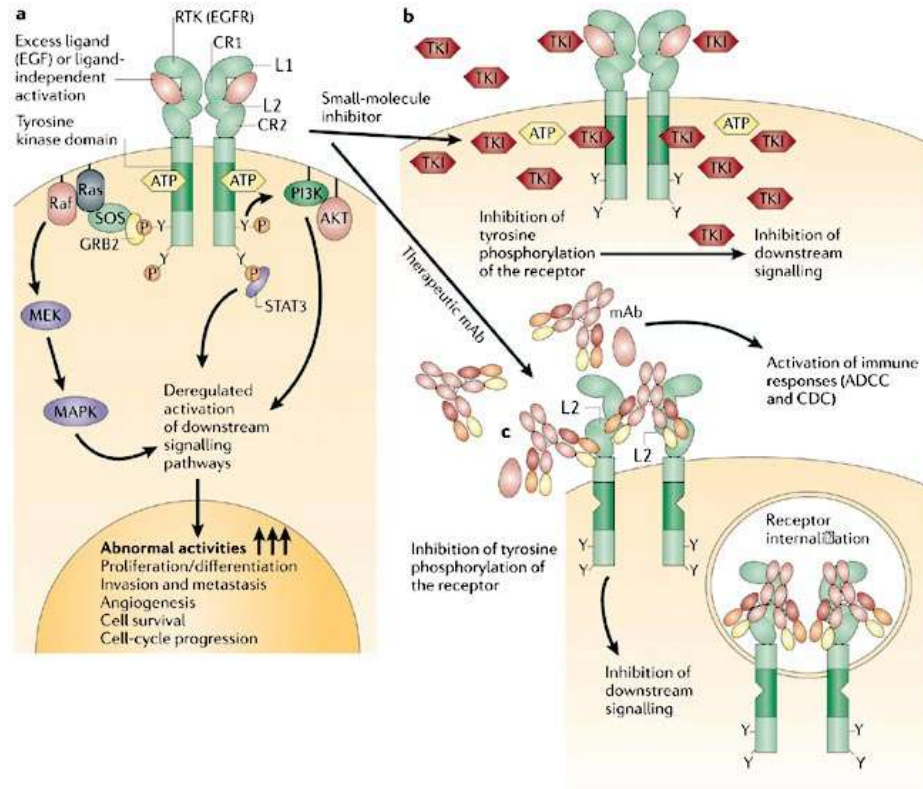
- Mais de 6000 novos casos por ano em Portugal.
- Mortalidade por CCR progrediu 5% ao ano nos últimos 10 anos.
- Sobrevida aos 5 anos para doentes com CCRm <3%.
- Quimioterapia convencional usada em CCRm apresenta grande toxicidade.

Overall survival for patients with metastatic colorectal cancer treated at the M.D. Anderson Cancer Center and the Mayo Clinic by year of diagnosis.



Targeted Chemotherapy - antibody and small molecule mechanisms of action

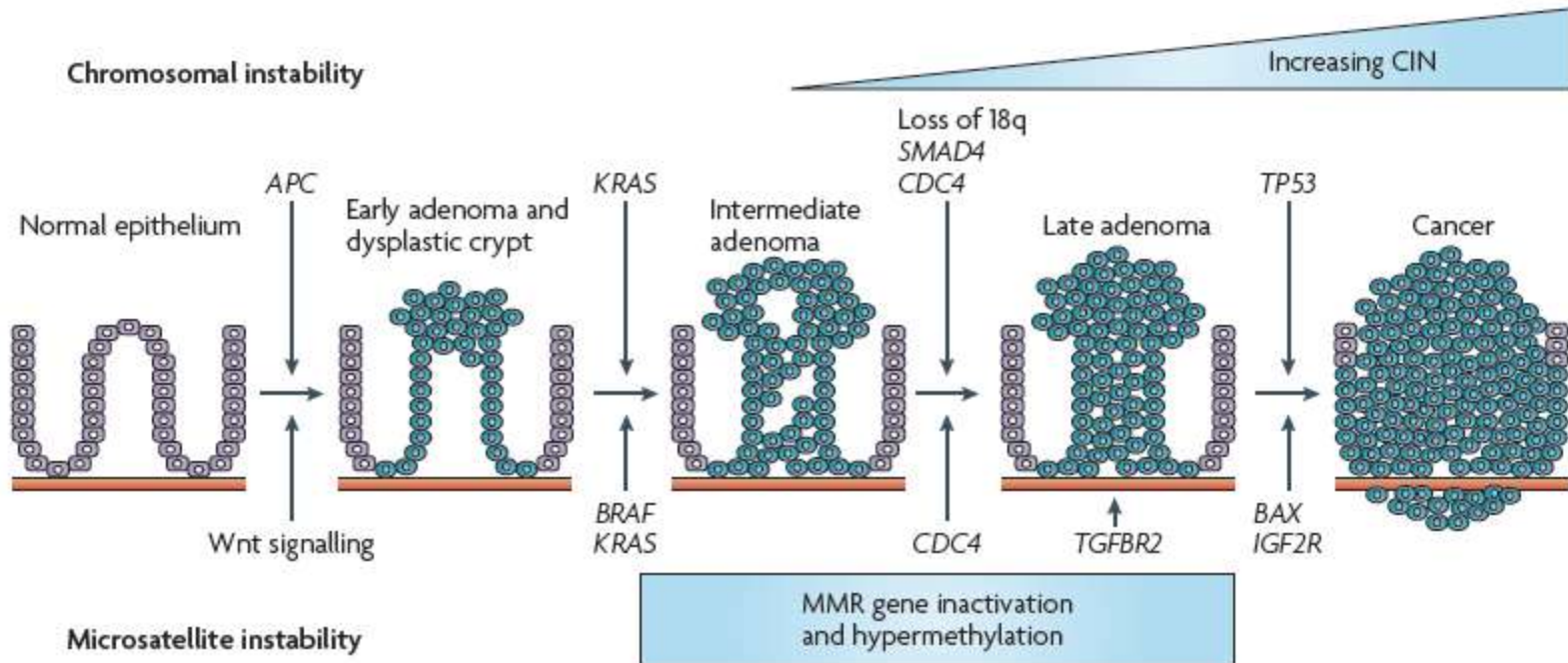
L1, L2 : ligand-binding domains
CR1, CR2 : cystein-rich domains
Y : Tyrosine



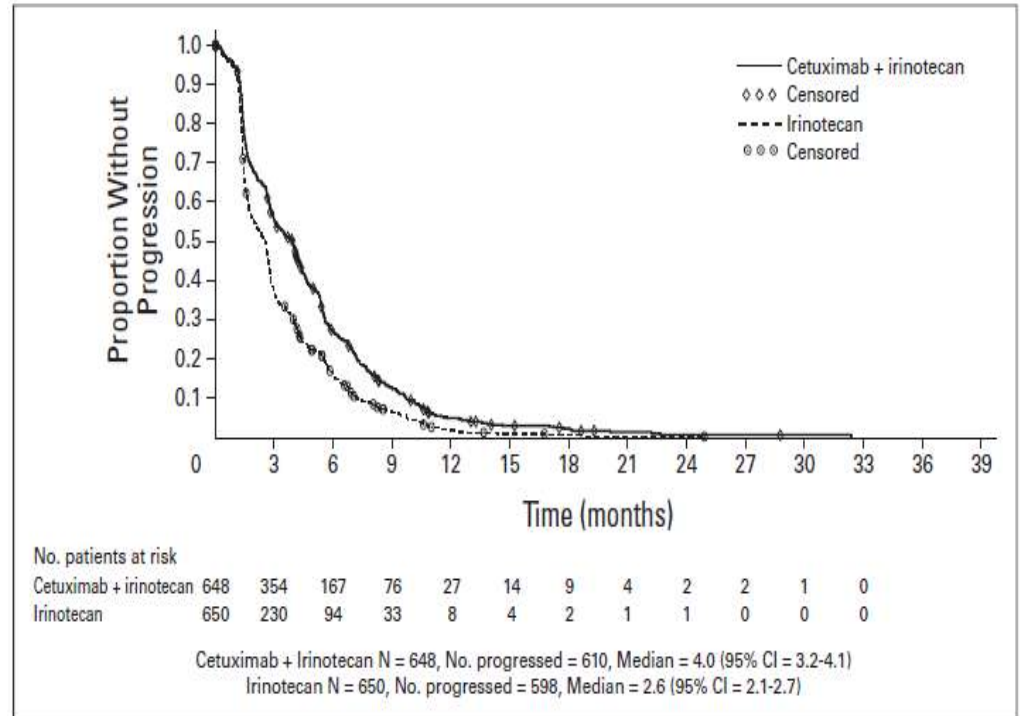
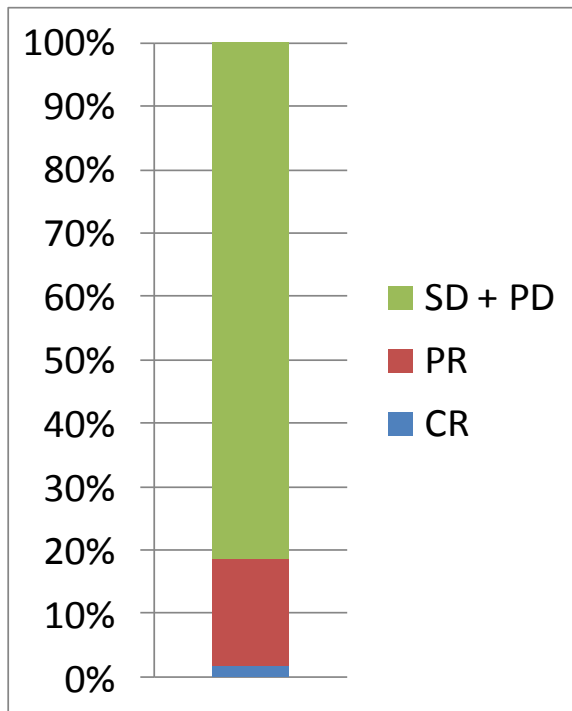
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Nature Reviews | Cancer

Imai and Takaoka *Nature Reviews Cancer* 6, 714–727 (September 2006) | doi:10.1038/nrc1913

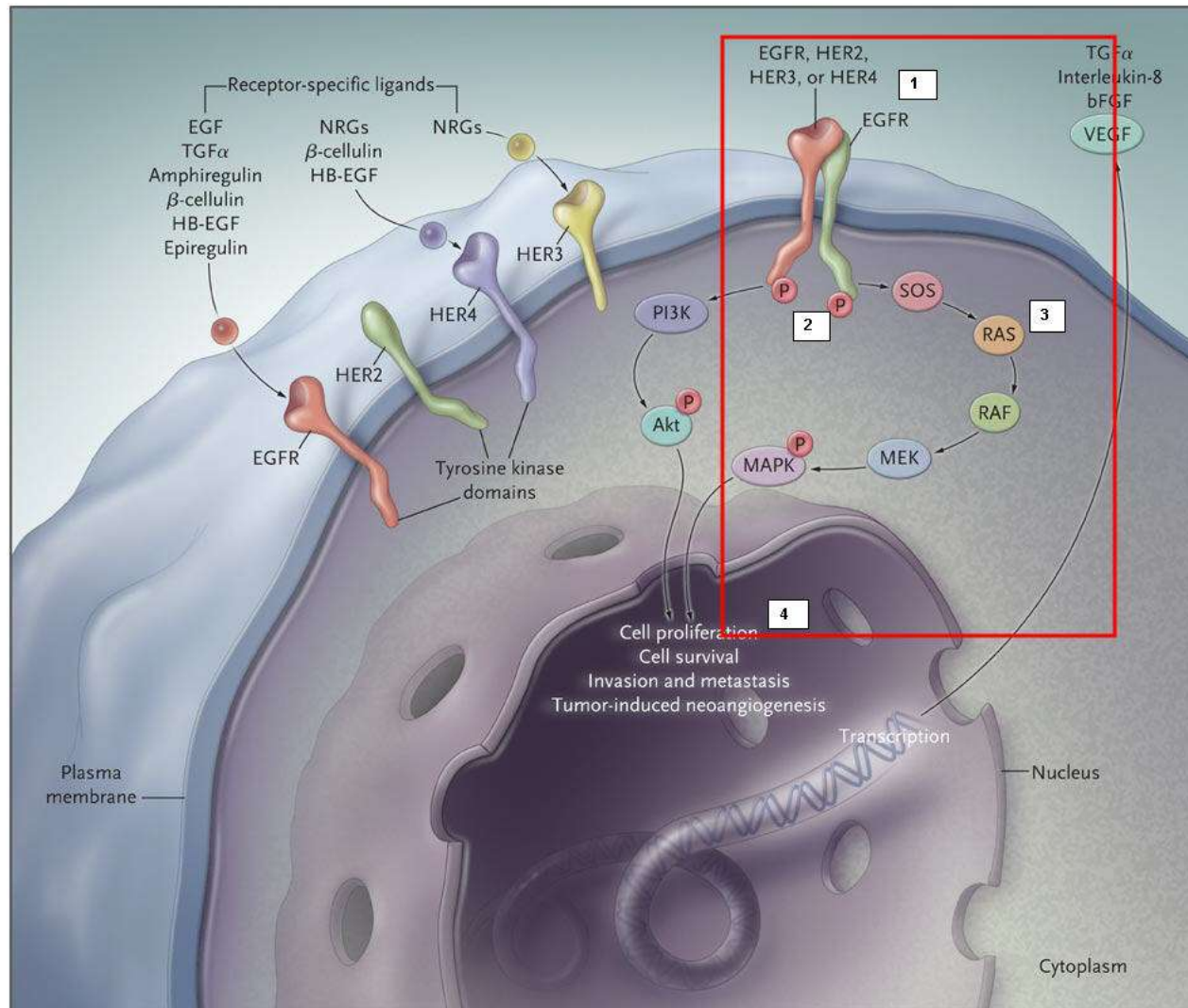
Colorectal carcinogenesis



Need for predictive markers

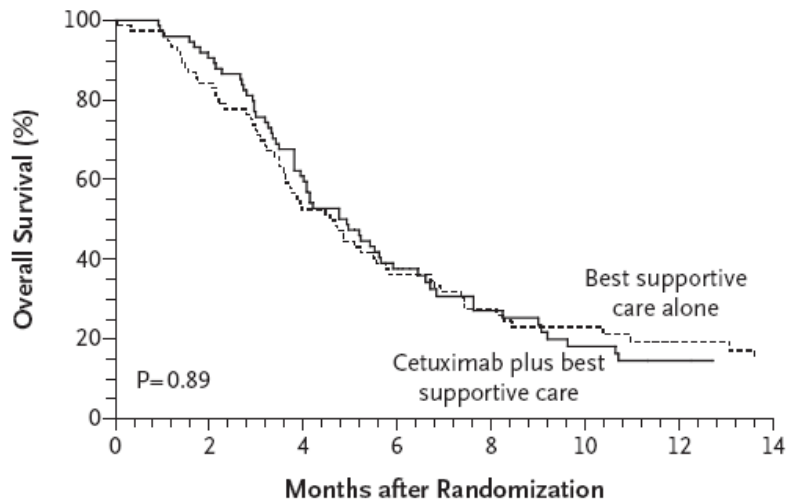


Resistance to EGFR Inhibitors



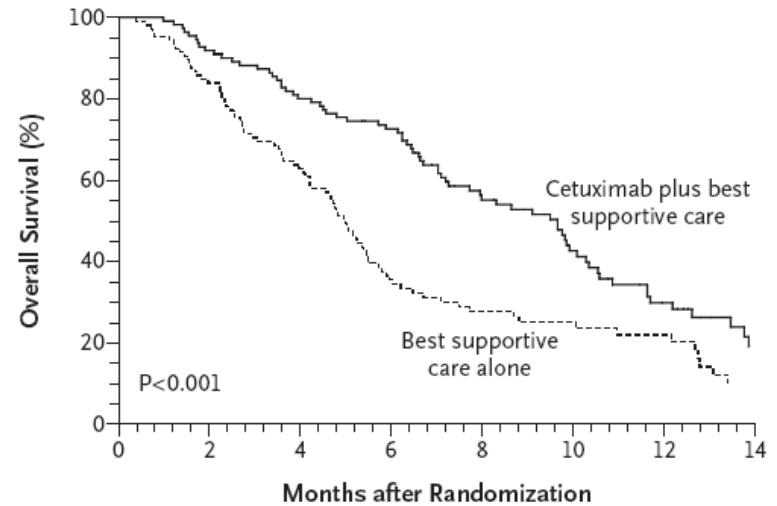
Influence of KRAS mutation status on treatment outcome

A Mutated K-ras



No. at Risk		0	2	4	6	8	10	12	14
Cetuximab plus best supportive care	75	67	45	26	15	10	7	4	
Best supportive care alone	76	64	39	26	19	12	10	7	

B Wild-type K-ras



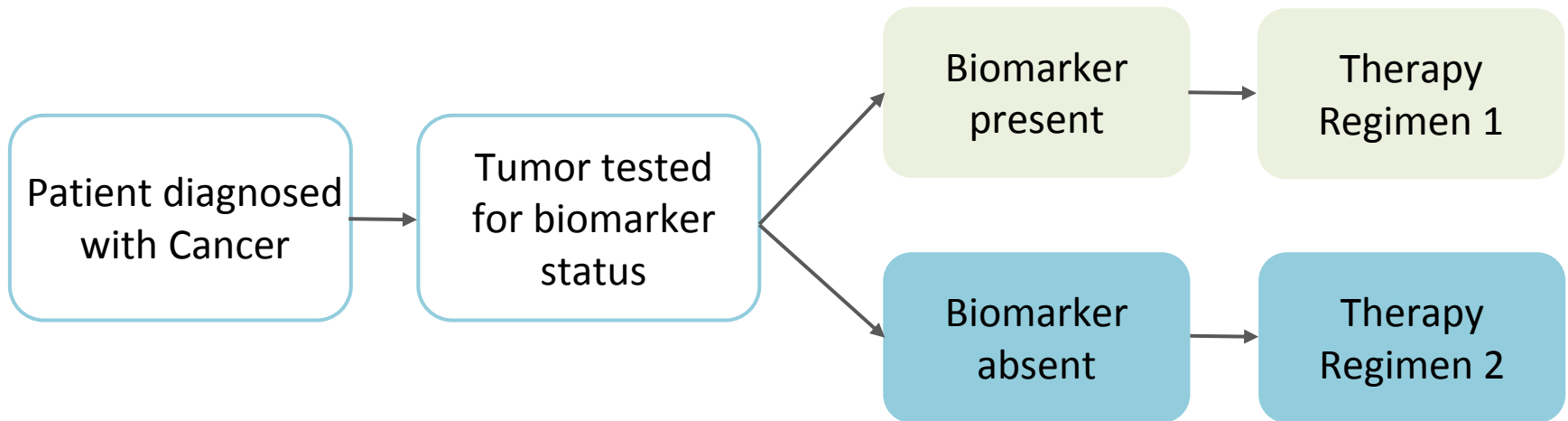
No. at Risk		0	2	4	6	8	10	12	14
Cetuximab plus best supportive care	110	101	88	75	48	31	19	8	
Best supportive care alone	105	88	65	34	23	17	12	5	

Novo cenário em Oncologia: Biomarcadores predictivos

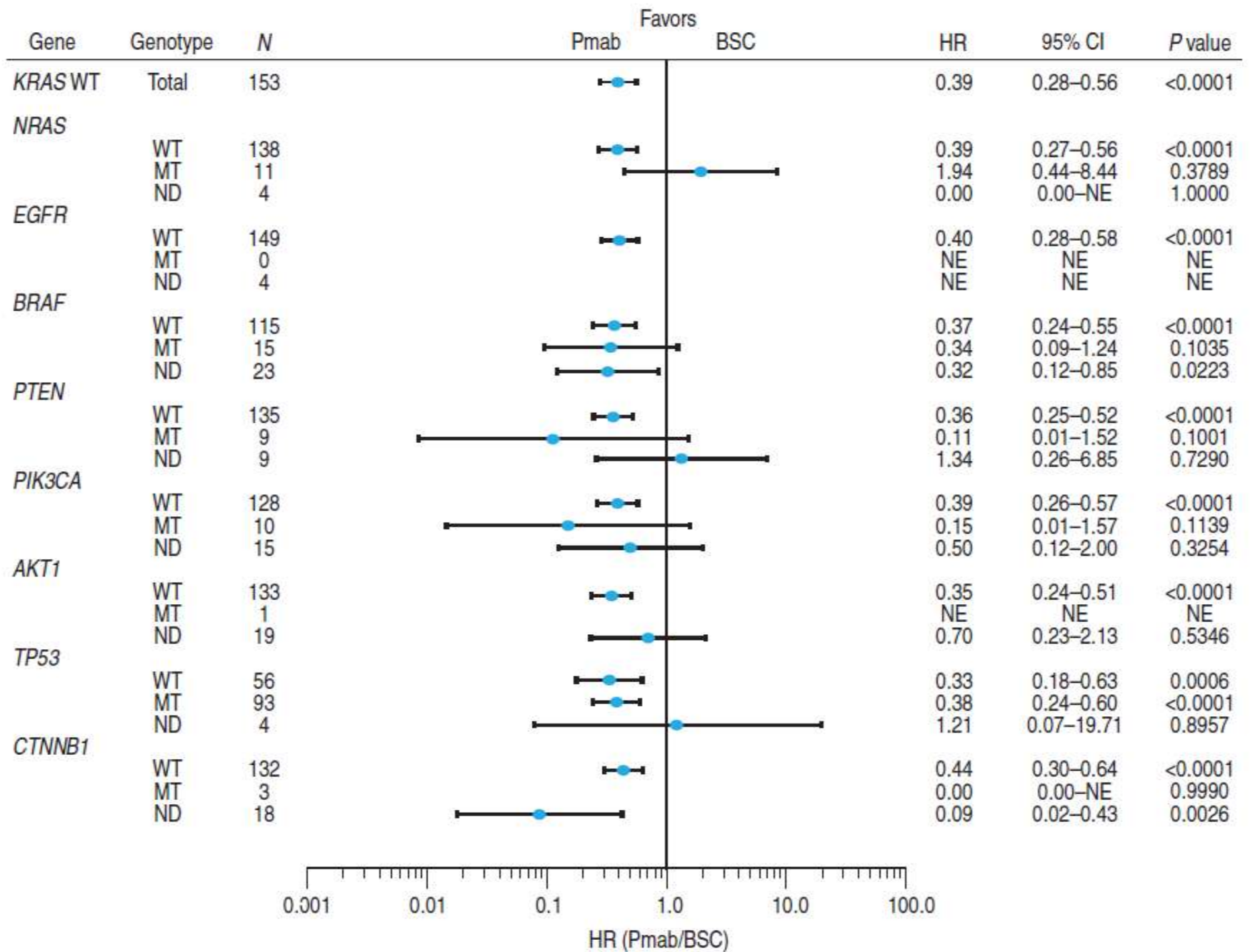
Utilidade dos Biomarcadores

1. Evitar toxicidades não necessárias
2. Evitar custos adicionais
3. Aumentar a eficácia

Biomarkers for therapy selection



Cancer	Drug	Biomarker	% eligible
Breast	Trastuzumab	HER2 gene amplification	30%
Lung	Gefitinib/Erlotinib	EGFR mutation	12%
Lung	Crizotinib	EML4-ALK translocation	5%
Colon	Cetuximab/Panitumumab	KRAS mutation	55%
CML	Imatinib	BCR-ABL translocation	95%
GIST	Imatinib	KIT/PDGFR mutation	90%
Gastric	Trastuzumab	HER2 gene amplification	20%
Melanoma	Vemurafenib	BRAF mutation	42%



Genotipagem retrospectivo concluído

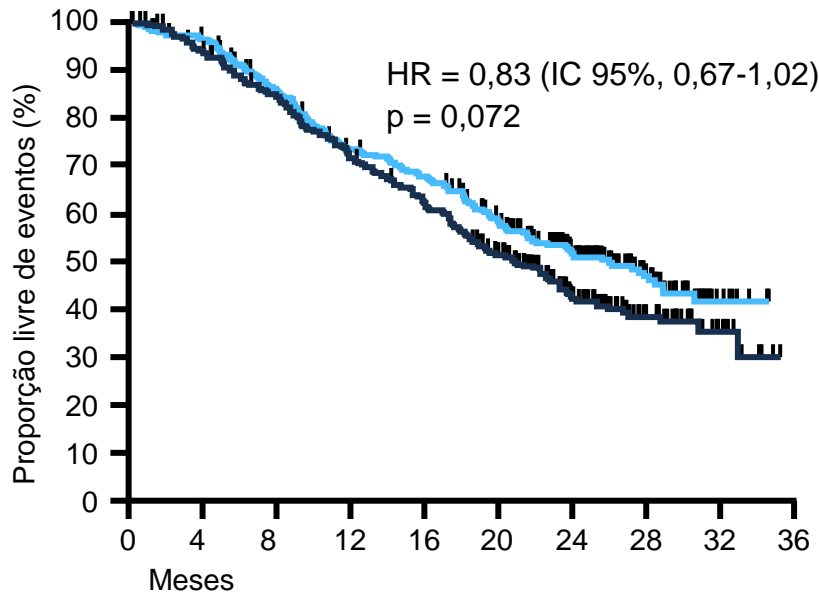
KRAS e NRAS têm valor predictivo de resposta ao tratamento com inibidores do EGFR. Os restantes biomarcadores avaliados não demonstraram valor predictivo.

Mutação	IPO Porto (n=400)	Ipatimup – HS João (n=400)	Total (n=800)
KRAS exão 2	157 (39,3%)	164 (41,0%)	321 (40,1%)
KRAS exões 3 e 4	12 (3,0%)	16 (4,0%)	28 (3,5%)
NRAS	21 (5,3%)	13 (3,3%)	34 (4,3%)
BRAF	10 (2,5%)	8 (2,0%)	18 (2,3%)
Total	200 (50,0%)	201(50,3%)	401(50,1%)

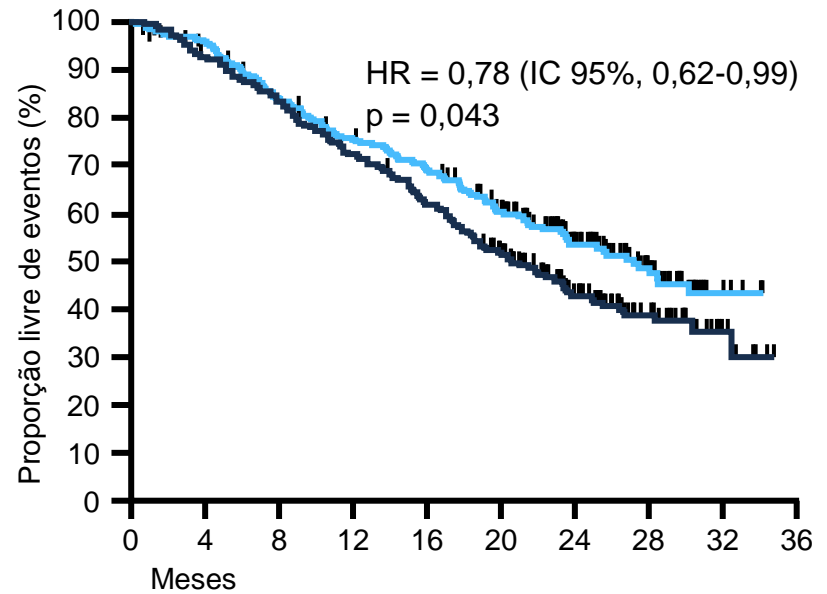
Estudo PRIME - Análise RAS

OS (análise primária)

KRAS exão 2 não mutado¹



RAS não mutado²



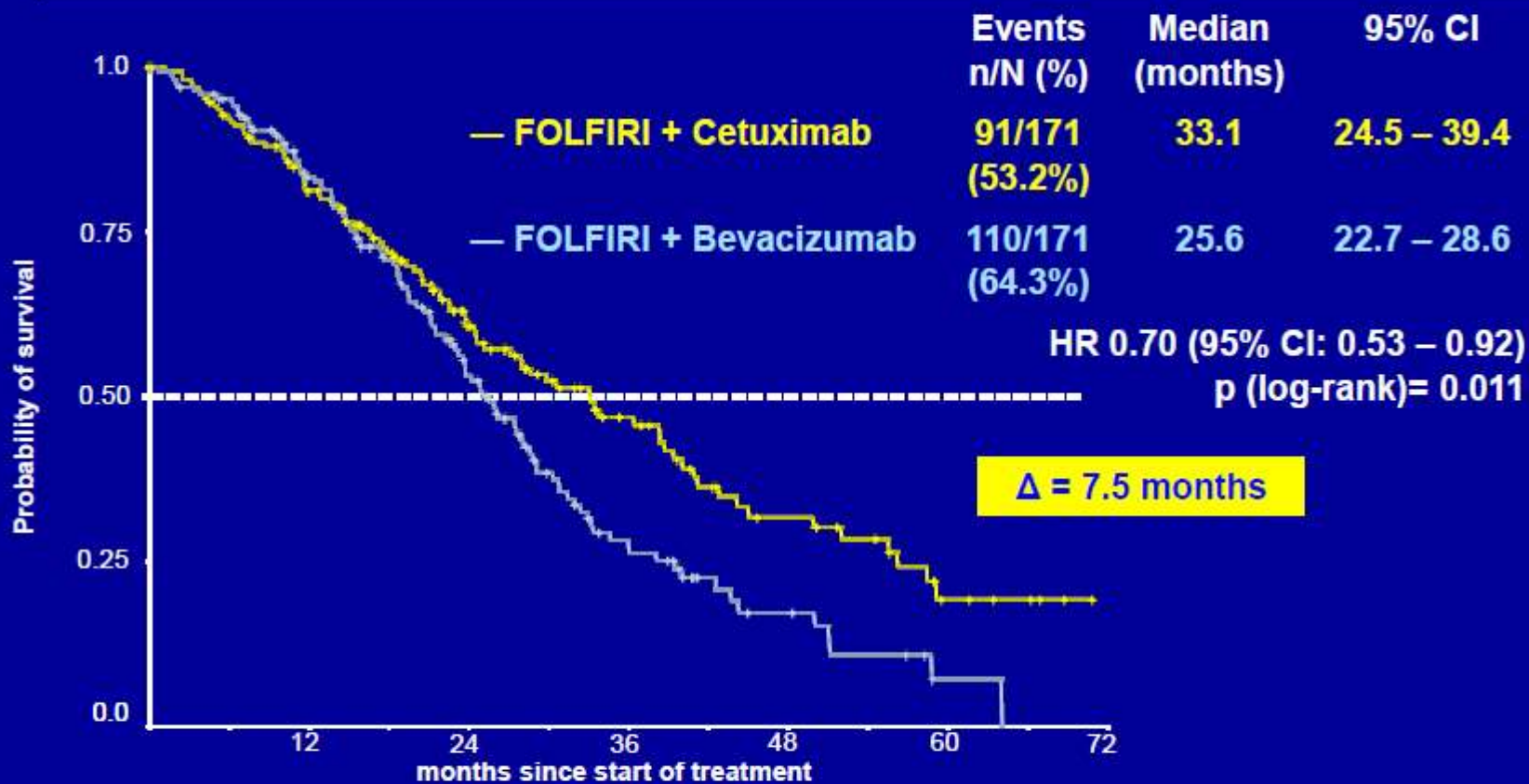
	Eventos n (%)	Mediana (IC 95%) meses
— Panitumumab + FOLFOX4 (n = 325)	165 (51)	23,9 (20,3-28,3)
— FOLFOX4 (n = 331)	190 (57)	19,7 (17,6-22,6)

	Eventos n (%)	Mediana (IC 95%) meses
— Panitumumab + FOLFOX4 (n = 259)	128 (49)	26,0 (21,7-30,4)
— FOLFOX4 (n = 253)	148 (58)	20,2 (17,7-23,1)

1. Douillard JY, et al. J Clin Oncol 2010;28:4697-705;
2. Douillard JY, et al. N Engl J Med 2013; 369:1023-34.

RAS não mutado, KRAS & NRAS não mutados exões 2/3/4
(inclui 7 doentes com mutações codão 59 KRAS/NRAS)

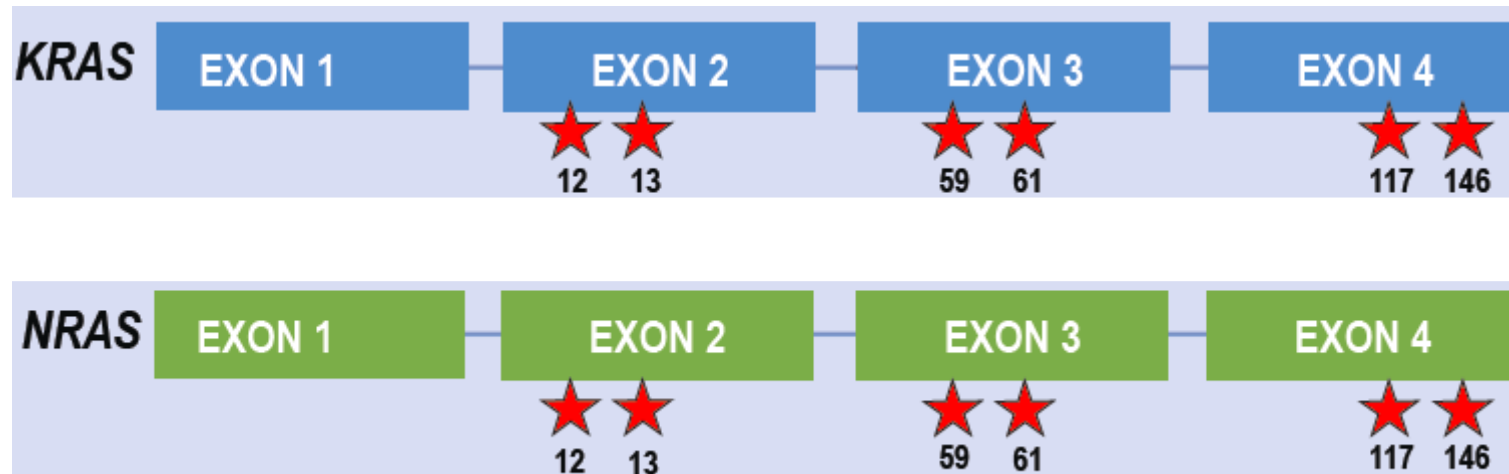
Overall survival RAS* wild-type



No. at risk	171	128	71	39	20	6
risk	171	127	68	26	9	1

* KRAS and NRAS exon 2, 3 and 4 wild-type

Mutações a analisar



Método

- Localmente validado e acompanhado de controlo de qualidade externo.

Publicações

1. Pinto P, et al. Comparison of methodologies for KRAS mutation detection in metastatic colorectal cancer. *Cancer Genetics* 204:439-446, 2011.
2. Costa JL, Sousa S, Justino A, Kay T, Fernandes S, Cirnes L, Schmitt F, Machado JC. Non Optical Massive Parallel DNA Sequencing of BRCA1 and BRCA2 Genes in a Diagnostic Setting. *Hum Mutat* 34:629-35, 2013.
3. Castro AS, Parente B, Gonçalves I, Antunes A, Barroso A, Conde S, Neves S, Machado JC. Epidermal Growth Factor Receptor mutation study for 5 years, in a population of patients with non-small cell lung cancer. *Rev Port Pneumol* 19:7-12, 2013.
4. Guedes JG, et al. High resolution melting analysis of KRAS, BRAF and PIK3CA in KRAS exon 2 wild-type metastatic colorectal cancer. *BMC Cancer* 13:169, 2013.
5. Rossi ED, Gerhard R, Cirnes L, Machado JC, Schmitt F. Detection of Common and Less Frequent EGFR Mutations in Cytological Samples of Lung Cancer. *Acta Cytol* 58:275-80, 2014.
6. Vissers LE, Bonetti M, Paardekooper Overman J, Nillesen WM, Frints SG, de Ligt J, Zampino G, Justino A, Machado JC, Schepens M, Brunner HG, Veltman JA, Scheffer H, Gros P, Costa JL, Tartaglia M, van der Burgt I, Yntema HG, den Hertog J. Heterozygous germline mutations in A2ML1 are associated with a disorder clinically related to Noonan syndrome. *Eur J Hum Genet* (in press).
7. Schmitt F, Machado JC. Ancillary Studies, Including Immunohistochemistry and Molecular Studies, in Lung Cytology. *Surgical Pathology* (in press).

Deliverables

- Teste genético - ✓
- Matriz de decisão terapêutica - ✓

Teste genético – Life(TermoFisher)



The advertisement features a photograph of four diverse scientists in white lab coats smiling in a laboratory setting. A white ribbon, a symbol for cancer awareness, is overlaid on the left side of the image. In the top right corner of the photo, the text 'LIFE TECHNOLOGIES' and 'CANCER RESEARCH' is visible. Below the photo, the word 'Prevail' is written in a large, white, sans-serif font. Underneath 'Prevail', the text 'with Ion Torrent™ next-generation sequencing (NGS)' is written in a smaller, white, sans-serif font.

Prevail
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Ion AmpliSeq™ Colon and Lung Cancer Research Panel v2 and
Ion AmpliSeq™ RNA Fusion Lung Cancer Research Panel

