

Evoluzione del management e costi per il ca colon retto

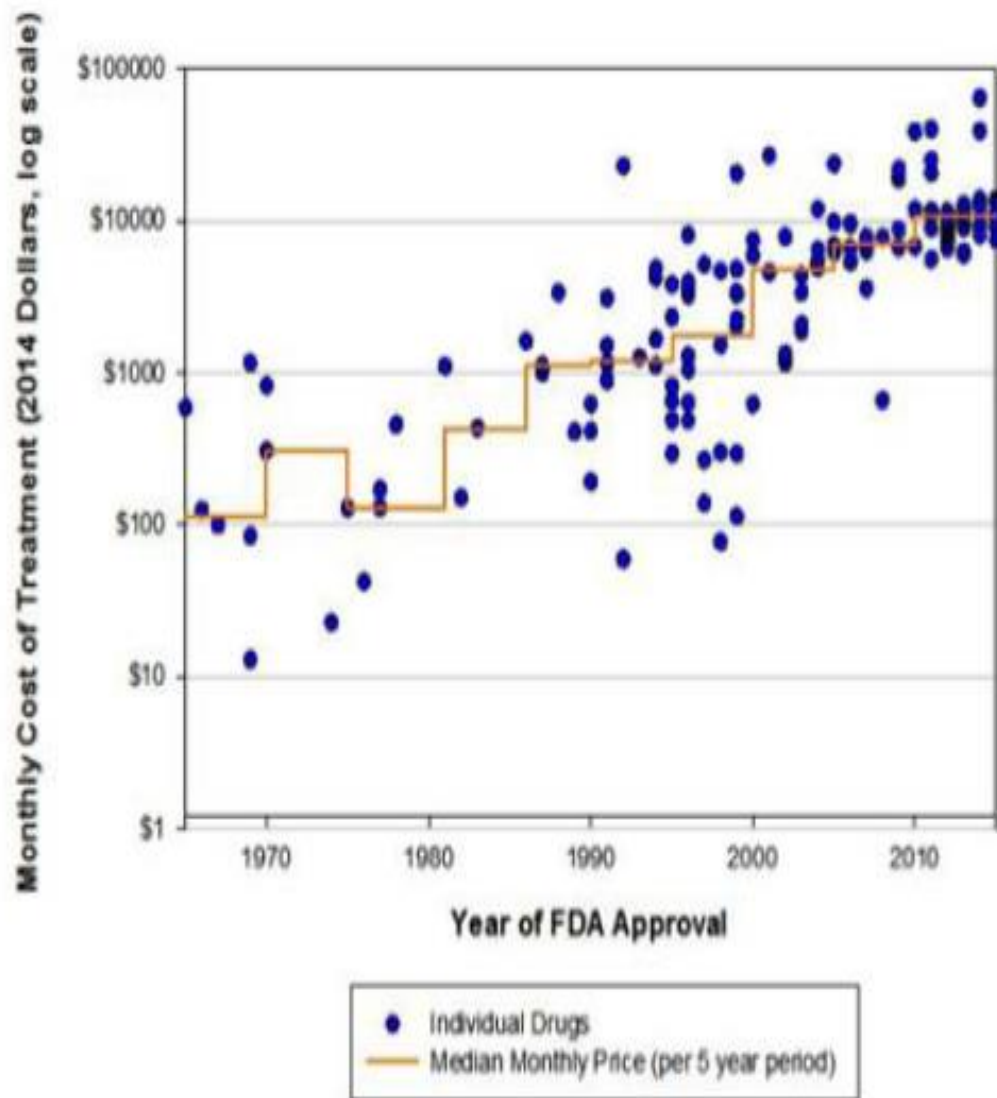
Alberto Sobrero

Policlinico IRCCS San Martino

II problema

- 1 **Cost of new drugs sky rocketing**
- 2 **Affordability gap : premium outpacing wages**
- 3 **If not affordable → useless**
- 4 **Problem in the problem: noone thinks it is his own responsibility**
- 5 **Prices must not be that crazy: more reasonable and homogeneous**
- 6 **Prices must be somehow linked to the benefit (corrected for GNP)**

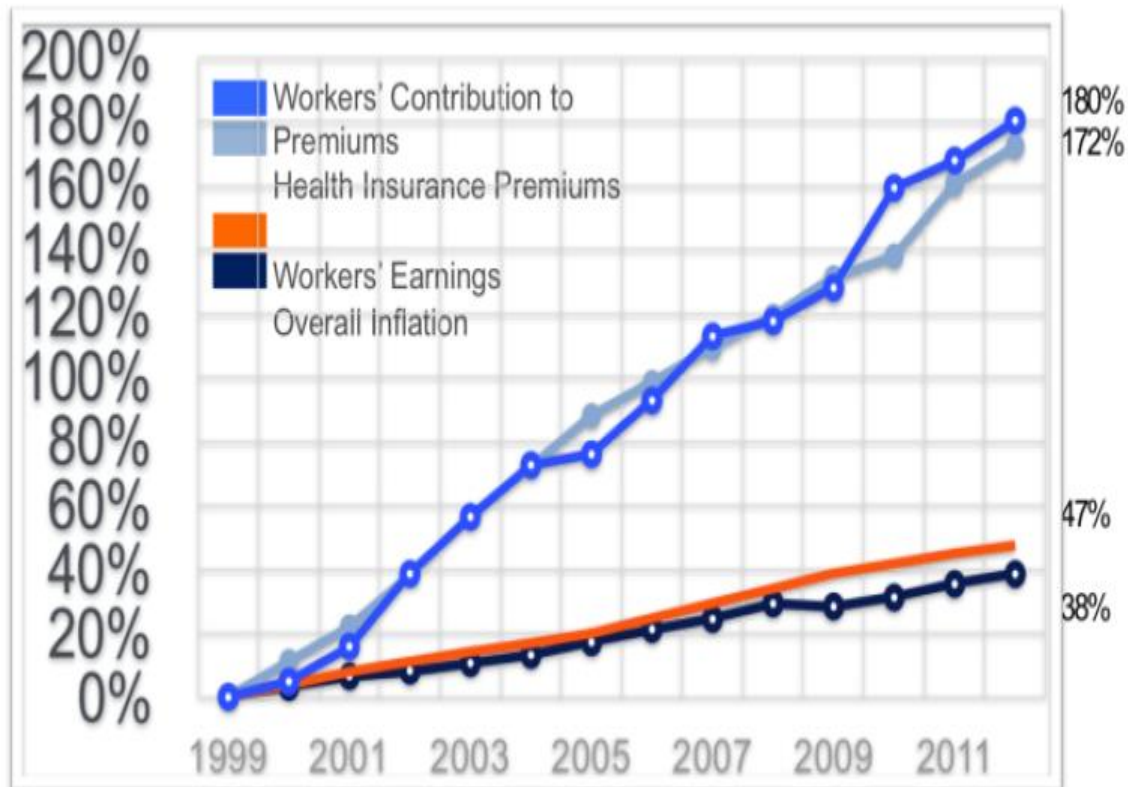
Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval 1965-2015



Source: Peter B. Bach, MD, Memorial Sloan-Kettering Cancer Center

Affordability Gap: Premiums Outpacing Wages, Inflation

Cumulative changes in components of U.S. national health expenditures and workers earnings



SOURCE: Kaiser/HRET Survey of Employer-Sponsored Health Benefits, 1999-2012. Bureau of Labor Statistics, Consumer Price Index, U.S. City Average of Annual Inflation (April to April), 1999-2012; Bureau of Labor Statistics, Seasonally Adjusted Data from the Current Employment Statistics Survey, 1999-2012 (April to April).

Patient Spending on Deductibles Outpacing Wages

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Prices for Nivolumab and Ipilimumab

(First Quarter, 2015)

Drug	Vial Size	AWP	\$/mg
Nivolumab	100mg	\$2,878	\$29
Ipilimumab	200mg	\$31,491	\$157

outline

- 1** risultati
- 2** Contributo incrementale dei vari farmaci
- 3** Le 4 terapie di attacco di oggi
- 4** Il mantenimento
- 5** Le seconde linee
- 6** rego and TAS102
- 7** Pembro-Nivo,
- 8** Her-2
- 9** altro

outline

1 Risultati

40 anni fa	6 mesi
30 anni fa	12 mesi
20 anni fa	18 mesi
10 anni fa	24 mesi
ora	30 mesi

Simplification of the incremental overall benefit of the antineoplastic agents in advanced CRC (34 trials)

Agent	gain in median OS
FU	6 mo +
Oxali irino	6 mo
Anti VEGF	6 mo
Anti EGFR	6 mo +

The L and R story as an aid to uniformity

		R	L
CALGB	CET vs BEV	- 8 (-19)	+ 5
FIRE III	CET vs BEV	- 6	+ 11
PEAK	PANI vs BEV	- 4	+ 11

R bev better than anti EGFR by 4 to 8 (19) mo

L anti EGFR better than BEV by 5 to 11 mo

TRIBE trial: final OS results

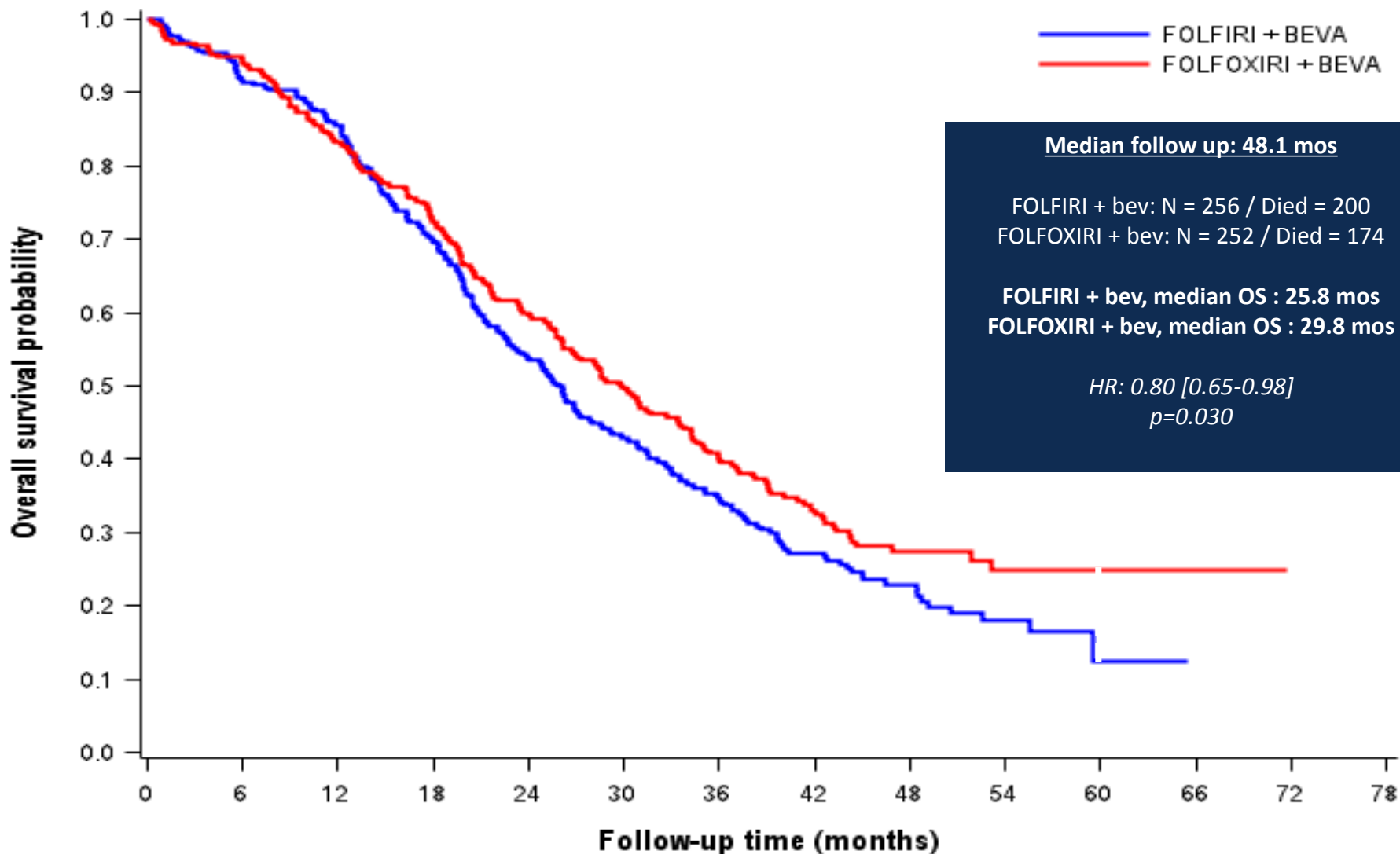
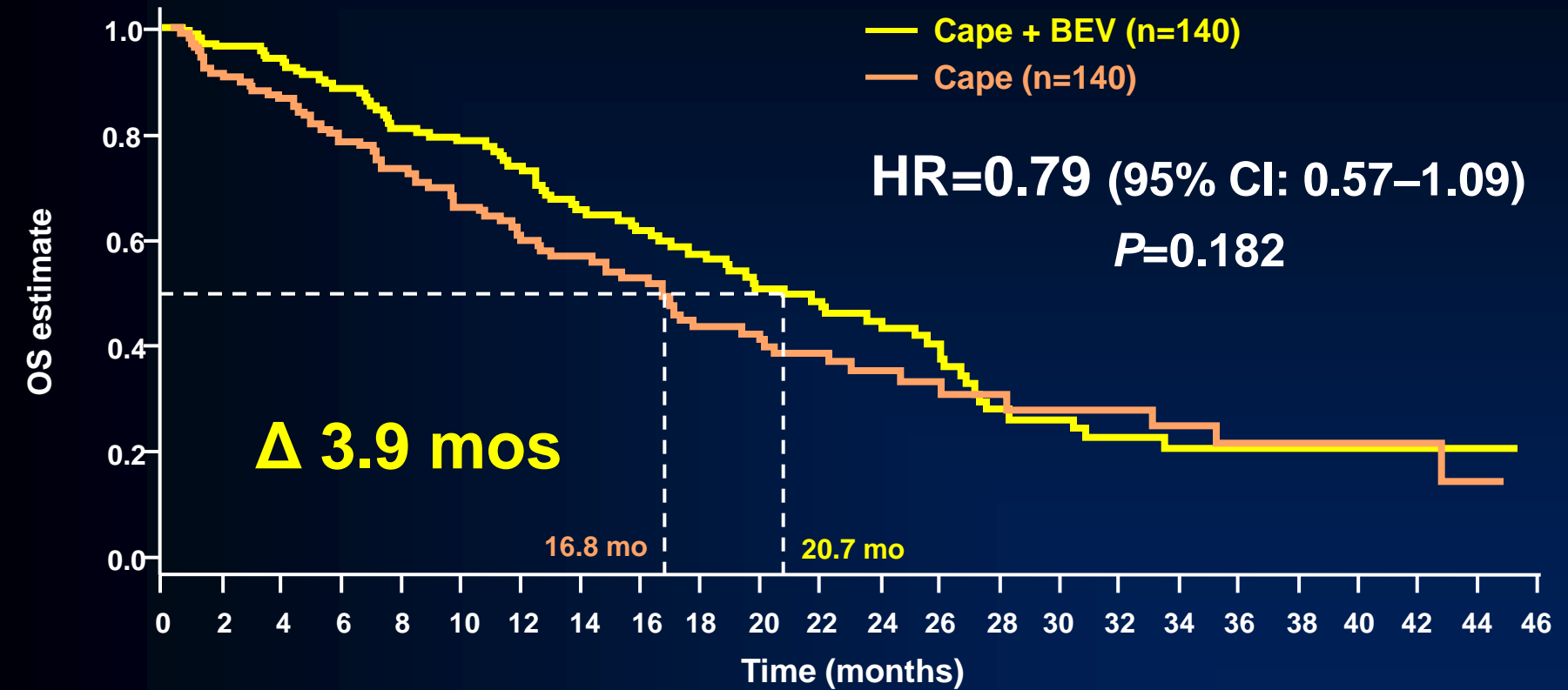


Table 3. Most Common Grade 3 or 4 Adverse Events.*

Event	FOLFIRI plus Bevacizumab (N= 254)	FOLFOXIRI plus Bevacizumab (N= 250)	P Value
	<i>no. (%)</i>		
Neutropenia	52 (20.5)	125 (50.0)	<0.001
Febrile neutropenia	16 (6.3)	22 (8.8)	0.32
Diarrhea	27 (10.6)	47 (18.8)	0.01
Stomatitis	11 (4.3)	22 (8.8)	0.048
Nausea	8 (3.2)	7 (2.8)	1.00
Vomiting	8 (3.2)	11 (4.4)	0.49
Asthenia	23 (9.1)	30 (12.0)	0.31
Peripheral neuropathy	0	13 (5.2)	<0.001
Hypertension	6 (2.4)	13 (5.2)	0.11
Venous thromboembolism	15 (5.9)	18 (7.2)	0.59
Serious adverse events	50 (19.7)	51 (20.4)	0.91

AVEX - Overall survival



	Number at risk																							
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Cape + BEV	140	126	120	106	95	89	81	67	60	51	44	40	34	24	16	15	12	10	8	6	5	4	2	0
Cape	140	120	108	94	85	73	62	57	49	37	33	23	19	13	11	10	9	7	6	5	5	3	1	0

KRAS WT Colorectal Cancer Bevacizumab vs. Cetuximab

Mean Cost Differences- Alliance/SWOG 80405

	Bevacizumab N=559	Cetuximab N=578
FOLFOX/ FOLFIRI	\$2,894	\$2,616
Antibody Rx	\$33,500	\$71,718
Hospital/ Acute Care	\$28,951	\$29,494

Schrag D: Proc ASCO 2015

Maintenance

<u>STUDY</u>	<u>AGENTS</u>	<u>OUTCOME</u>
MACRO	bevacizumab	slightly inferior to contin CT + bev
MACRO II	cetuximab	gain in PFS
CAIRO-3	bev + cape	PFS1 and 2 gain vs nothing
SAKK	bevacizumab	minor PFS and OS gain vs nothing
AIO 207	cape+bev / bev	minor gains in os



Hard to run trials: actually trials mirror practice
Substantial gain in PFS1
Minimal gain in OS usually non significant

The Price of (PFS) Stability: Bevacizumab alone on AIO 0207

- 1.2 m PFS improvement (investigator-adjudicated) over observation (3.6 m vs. 4.7 m)
- No Rx for 3.6 months = 15.5 weeks
- 2.5 mg/kg/week x 80 kg x 15.5 weeks = 3100mg
- Bev ASP (2nd quarter, 2014) = \$6.19/mg
- 3100 mg x \$6.19/mg = **\$19,189** per patient



PRESENTED AT:

The Price of (PFS) Stability: Bevacizumab alone on AIO 0207

- **\$19,189** ASP + 4% = \$20,000
- ~ 40,000 met CRC patients per year in U.S.
- Bev market penetration ~ 70%

- $40,000 \times 0.70 = 28,000$ patients
- 55% assessed for eligibility were randomized
- $28,000 \times 0.55 = 15,400$ patients
- $15,400 \times \$20,000 = \mathbf{\$308,000,000}$ per year

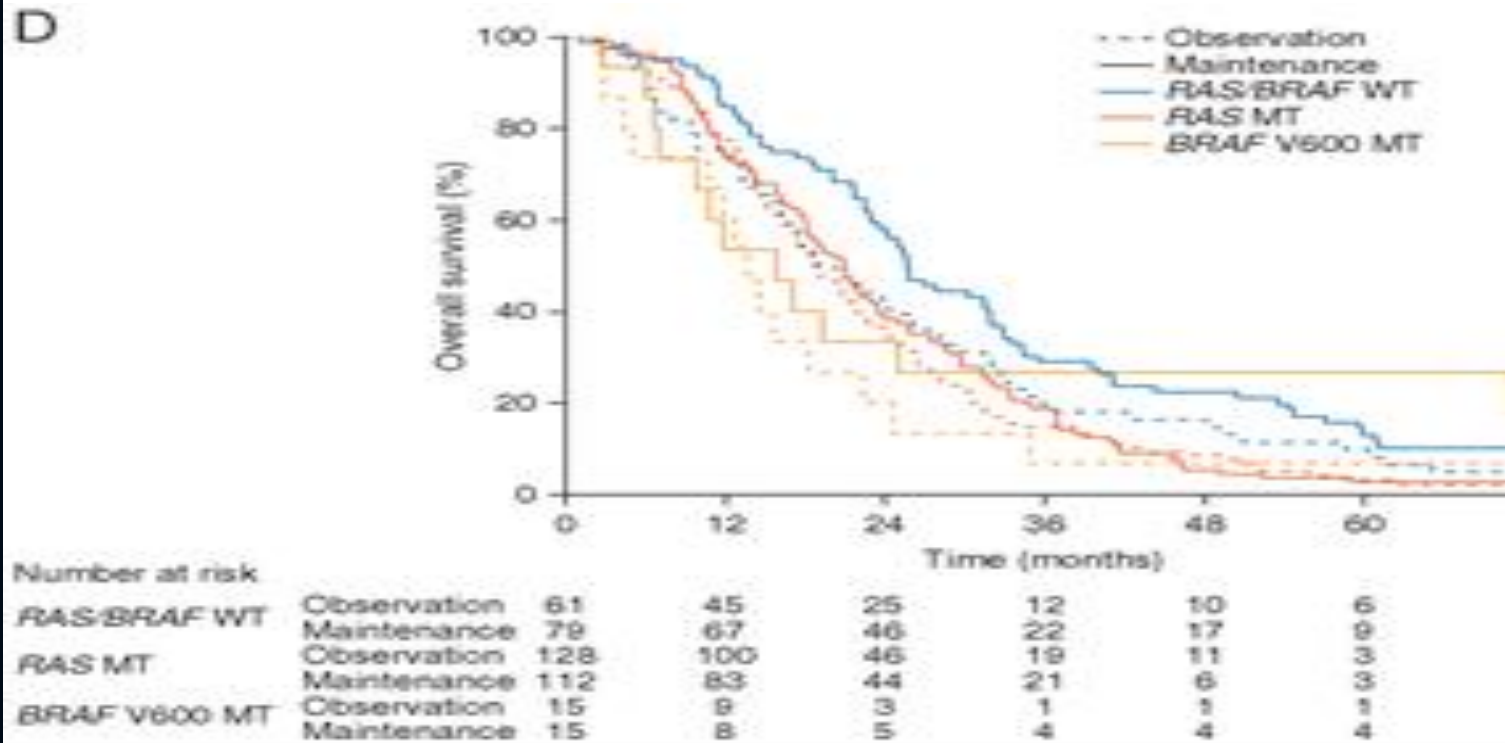


PRESENTED AT:

Maintenance treatment with capecitabine and bevacizumab versus observation in metastatic colorectal cancer: updated results and molecular subgroup analyses of the phase 3 CAIRO3 study

K. K. H. Goey, S. G. Elias, H. van Tinteren, M. M. Laclé, S. M. Willems, G. J. A. Offerhaus, W. W. J. de Leng, E. Strengman, A. J. ten Tije, G.-J. M. Creemers ... Show more

Annals of Oncology, Volume 28, Issue 9, 1 September 2017, Pages 2128–2134, <https://doi.org/10.1093/an->

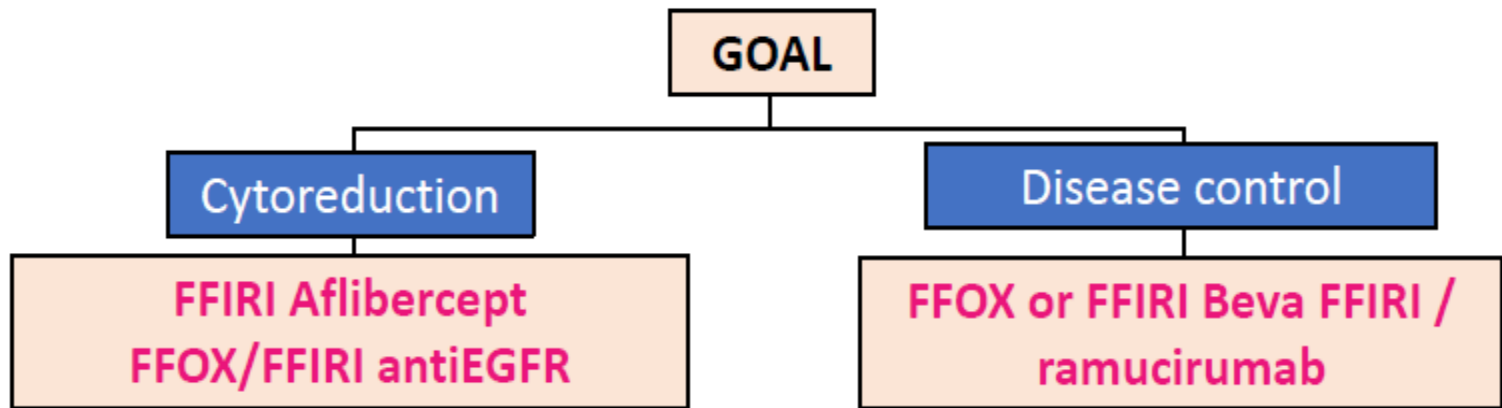


Maintenance therapy in advanced colorectal cancer, yes or no? Ask the laboratory

A. Sobrero ✉, A. Damiani

Annals of Oncology, Volume 28, Issue 9, 1 September 2017, Pages 2043–2044, <https://doi.org/10.1093/>

True second lines : options



1. Symptoms
2. Clinical course
3. Impending complications
4. Patient attitude
5. Resectability

Are we worried for the clinical development of the disease ?

Colorectal Cancer - Comparison of Anti-VEGF Agents

	OS Chemo + Placebo	OS Chemo + Anti VEGF	Survival Benefit	Percent Increase in OS	Hazard Ratio
Bevacizumab	9.8 m	11.2 m	1.4 m (43 days)	14%	0.83
Ziv-aflibercept	12.1 m	13.5 m	1.4 m (43 days)	12%	0.82
Ramucirumab	11.7 m	13.3 m	1.6 m (49 days)	14%	0.84

Drug name (Generic)	Drug name (Brand)	Price Information Source	Price/mg	Price of 100 mg vial	Standard treatment dose	Price of a single 2-week dose (75 kg patient)
Bevacizumab	Avastin	Oct 2015 ASP	\$6.96	\$696.03	5 mg/kg	\$2784
Ziv-Aflibercept	Zaltrap	Oct 2015 ASP	\$8.32	\$831.50	4 mg/kg	\$2495
Ramucirumab	Cyramza	Oct 2015 NOC	\$10.79	\$1,079.42	8 mg/kg	\$6477

CONCLUSIONS: REGO vs TAS

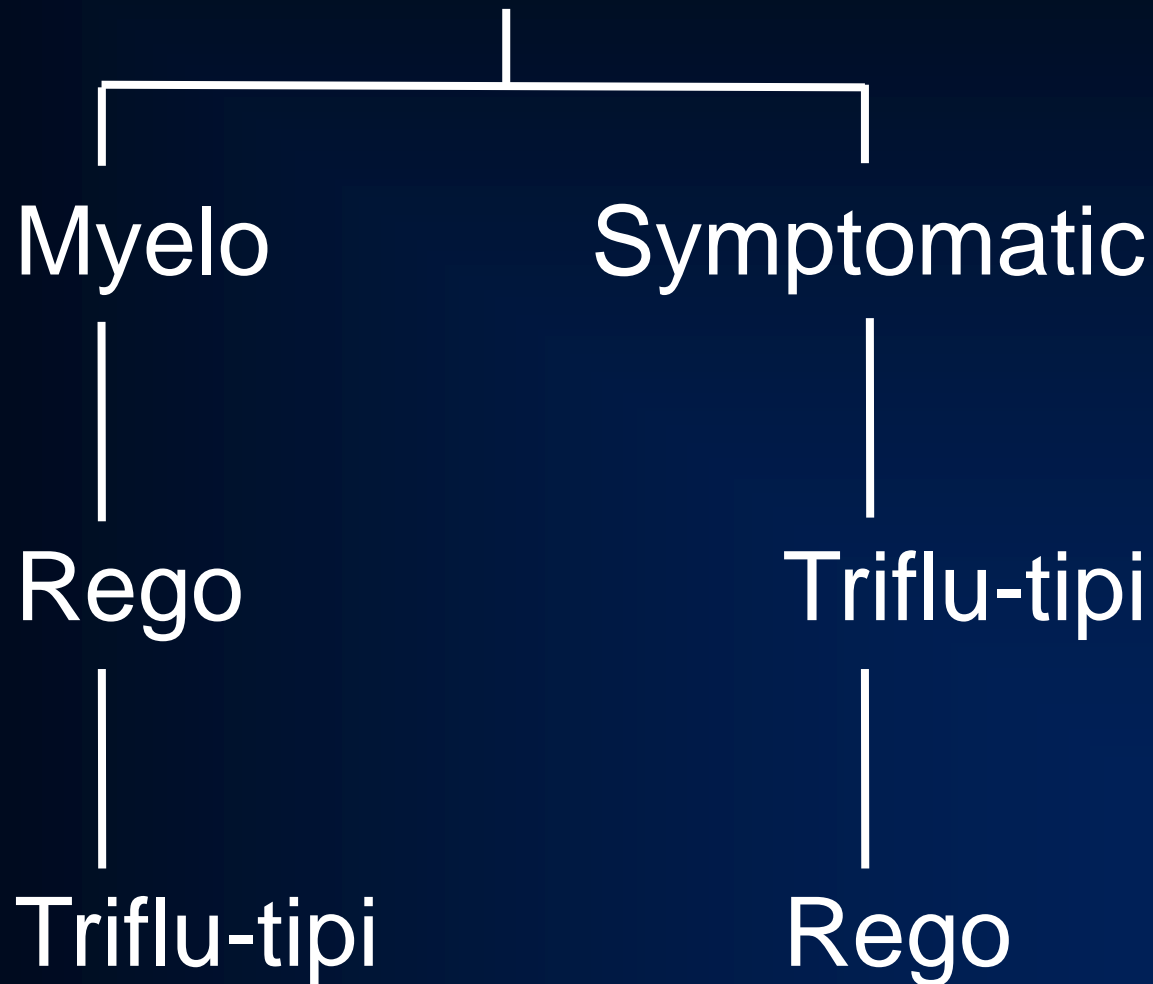
	REGO	TAS
1 One more theoretical chance	++++	+++
2 Possibility of outliers	++++	++++
3 OS	++	+++
4 25% prolonged PFS	++	++
5 Everybody benefits	+++	++
6 Tolerability	++	+++++
7 Tox-related determinant of efficacy	++	++++
8 'QOL'	+	+(+)

Lancet

New Eng. J. Med.

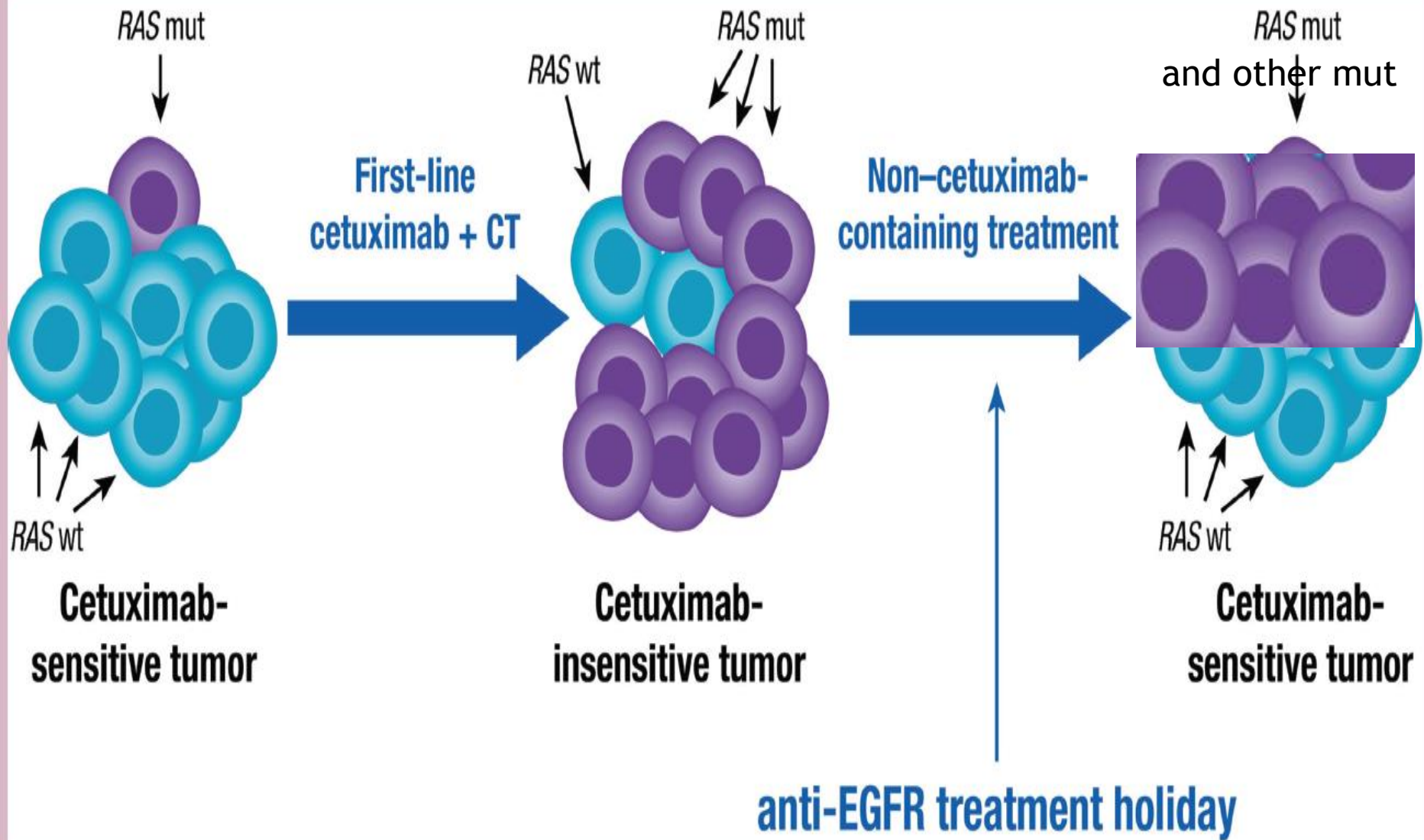
Place in therapy

Which toxicity so far ?



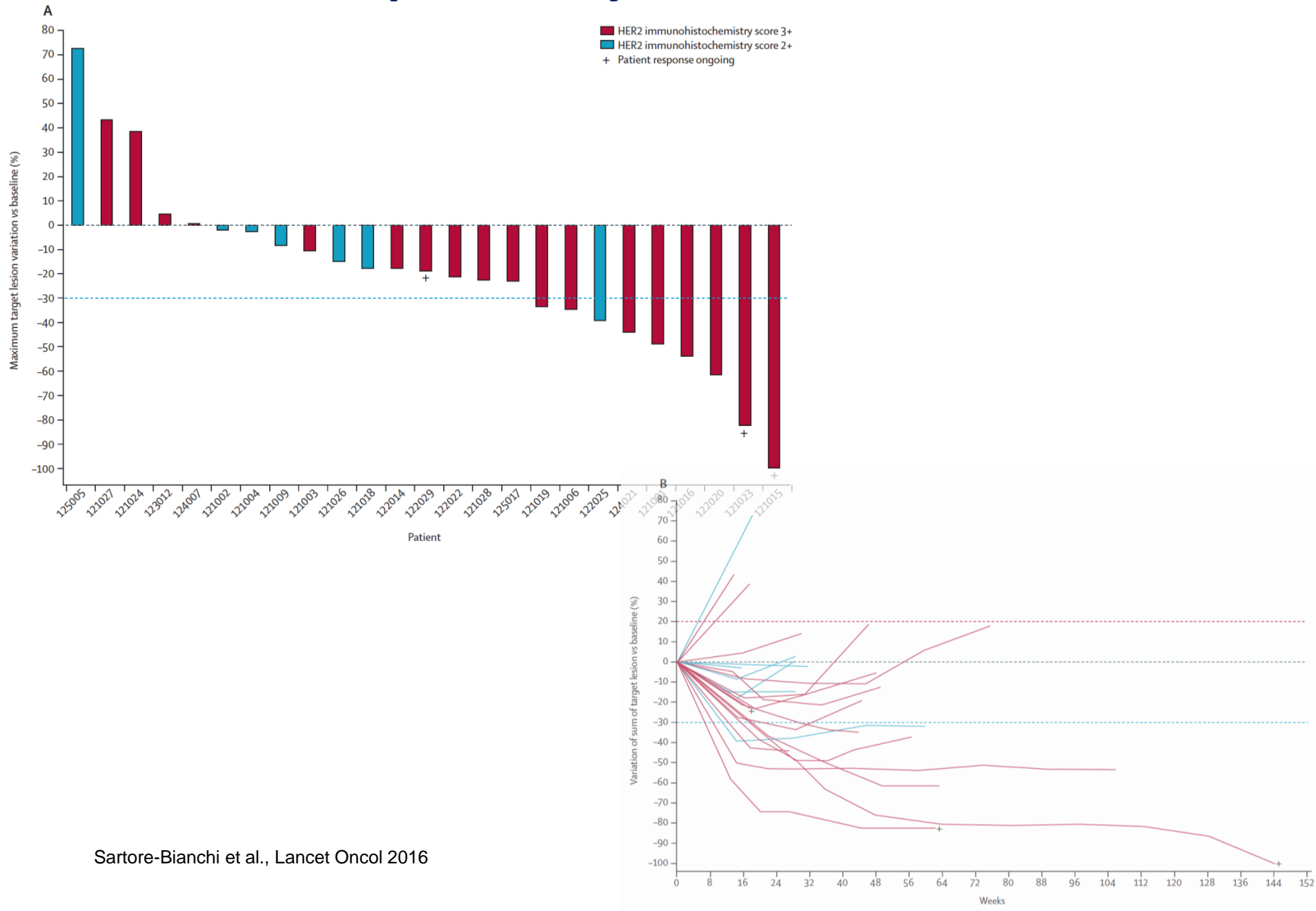
3511 Parseghian. Anti-EGFR resistant clones decay exponentially after progression: Implications for anti-EGFR rechallenge

- Discovery set from 135 MDA pts ; validation set from 267 /4000 pts
- Exponential decay with a t 1/2 of 4 to 5 months
- At progression, only 30% of the cells carry a mutation in RAS/EGFR/BRAF/MAP2K1. (Siena, Ann. Oncol 2017 36% on 39 pts)
- Rationale for re-challenge + timing (ctDNA monitoring).

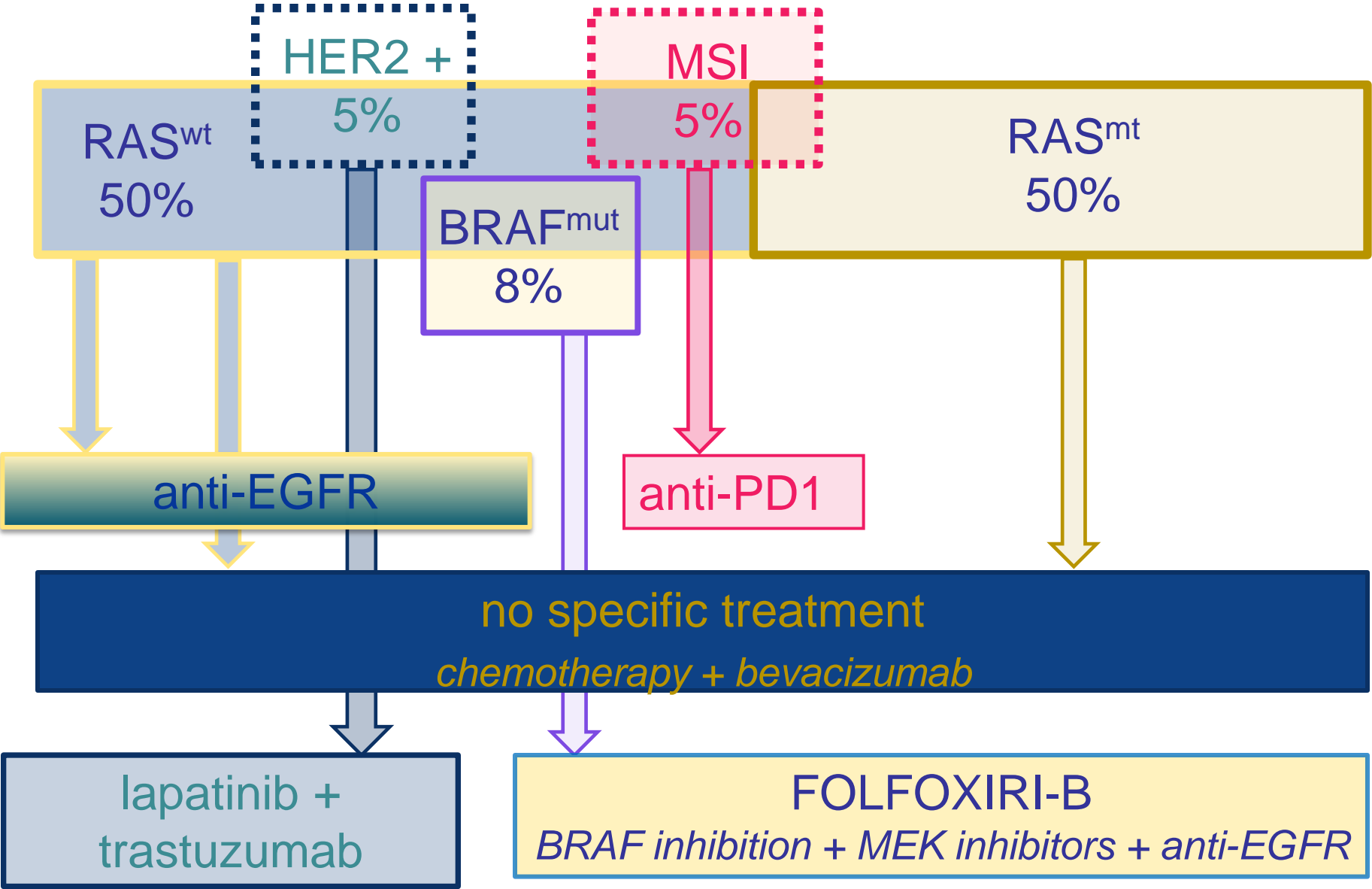


From Goldberg R et al. 2018

Responses by HER2 IHC Score



Heterogeneity of mCRC: treatment options

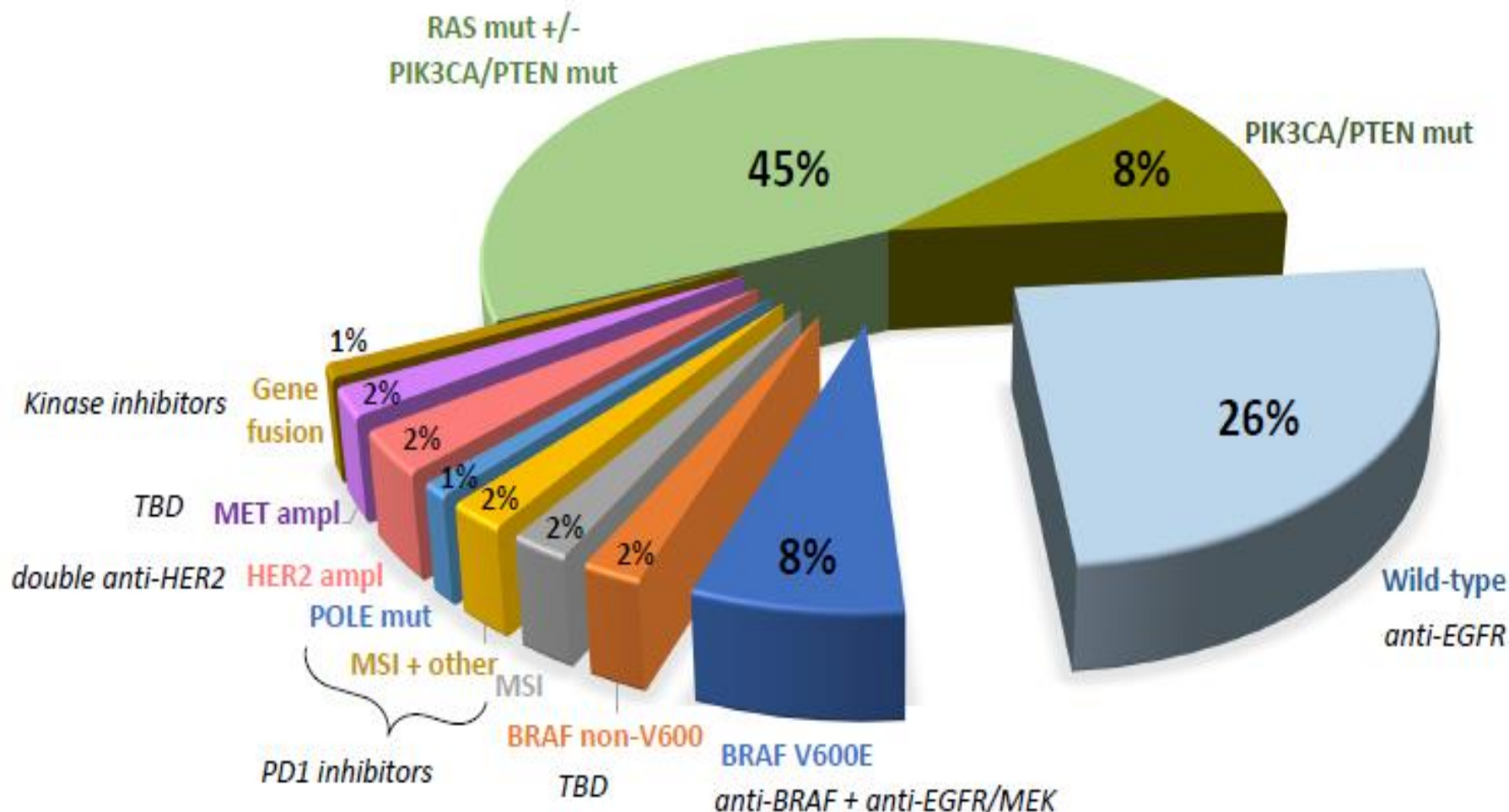


Pembro- nivo-ipi in MSI CRC

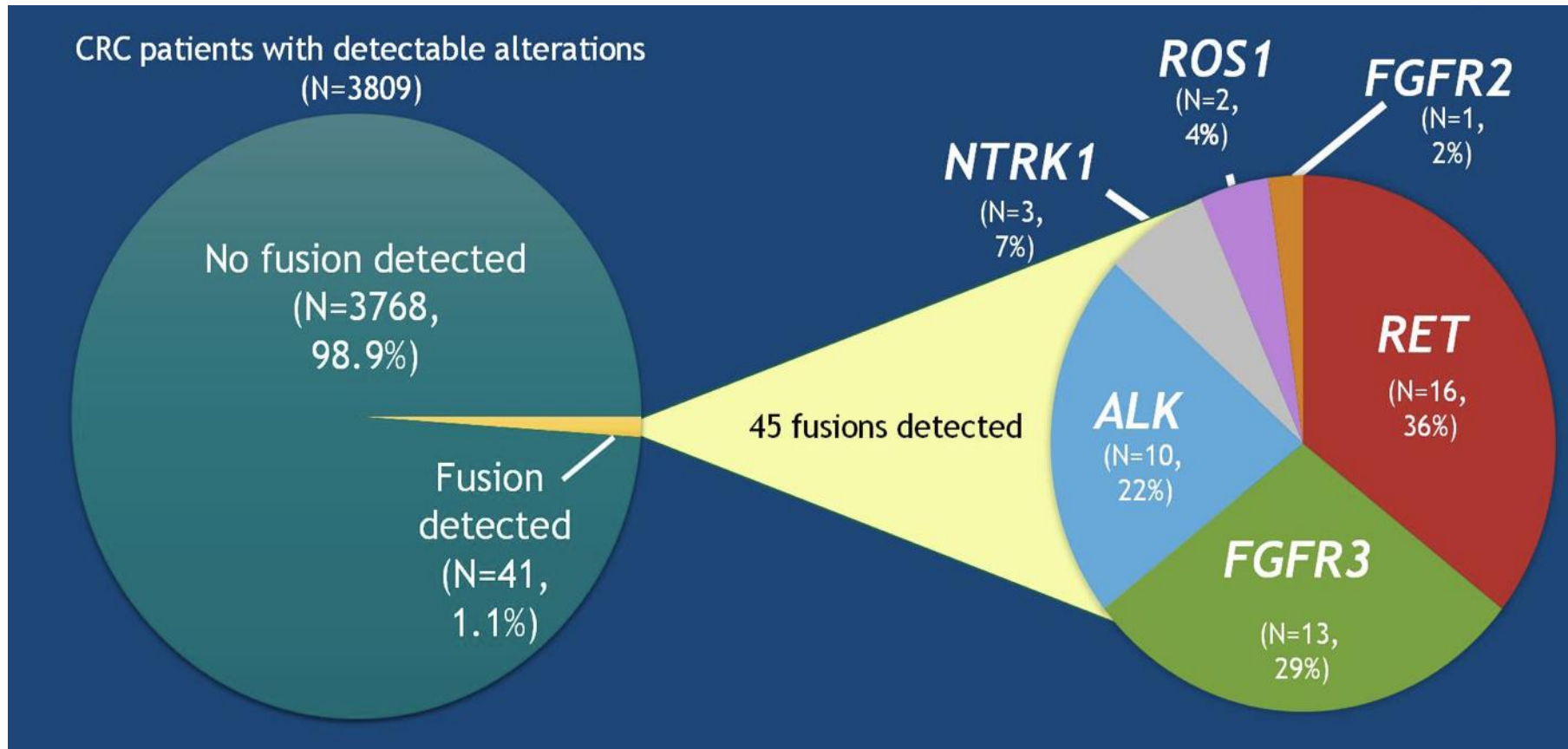
- 3 studies
- RR 31%-55%
- PFS at 1 yr 50%-77%
- Pembro stopped at 2 yrs and 18 pts non P
- B-RAF, PDL-1 , Lynch → non predictive



Genomic classification



Guardant360 for fusions!



It Adds Up.....

Dabrafenib + Tremetinib + Panitumumab for BRAF V600E mutant CRC

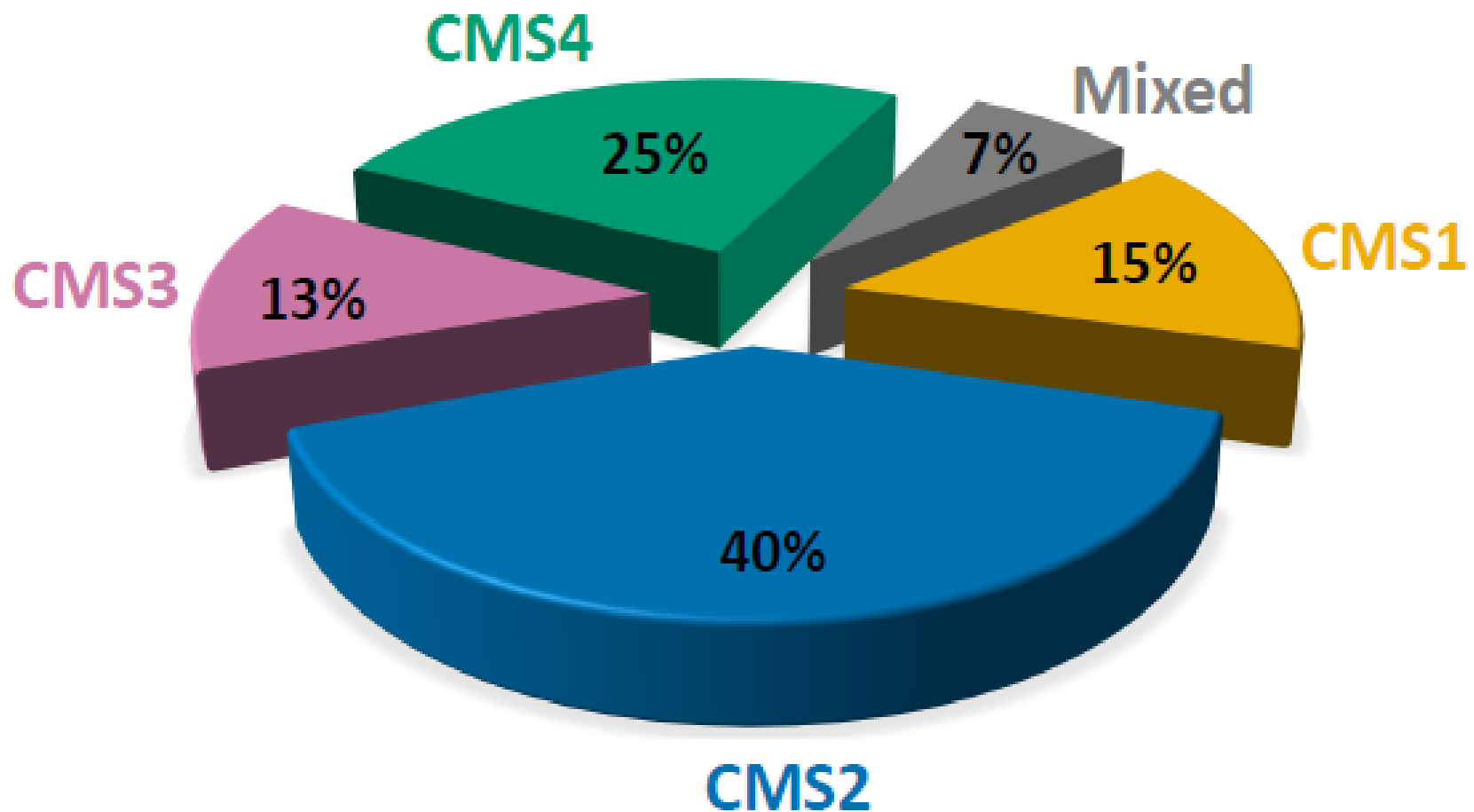
- Cost of four weeks of therapy:

• Dabrafenib	150 mg bid	\$11,586.09
• Tremetinib	2 mg qd	\$12,573.88
• Panitumumab	6 mg/kg	<u>\$13,457.50</u>
		\$37,617.47

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Transcriptomic classification



The ICER system... and its 'hypocrisy'

1. Simplification : reduces advances to 1 dimension: \$
2. Links cost to benefit \$/benefit
3. Imposes a limit for reimbursement (40K)
4. BUTit tries to be flexible
 - End of life conditions
 - Hidden discounts
 - Cancer drug fund
 - Ultra orphan drugs
5. Example ipi for melanoma (ICER 96 K →60K → 42K)

Effects of cetuximab re-challenge in pts progressing on CET-based therapy and a second non anti-EGFR therapy: phase II studies

Author	N	interval	RR
Santini 2012	39	6 months	58%
Liu 2015	89	4.6 months	54%
Rossini 2017	22	-	25%