Giornate Formative Progetto Regione Veneto

Padova, 02 dicembre 2015

La clinica ed il valore delle terapie nel carcinoma colo-rettale

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Relazioni con soggetti portatori di interessi commerciali in campo sanitario

- Ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 18, 19 dell'Accordo Stato-Regione del 19 aprile 2012, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:
  - Roche
  - Amgen
  - Lilly
  - Bayer
  - Sanofi
  - Merck

Colorectal Cancer:
20 Years after meta-analysis 1992

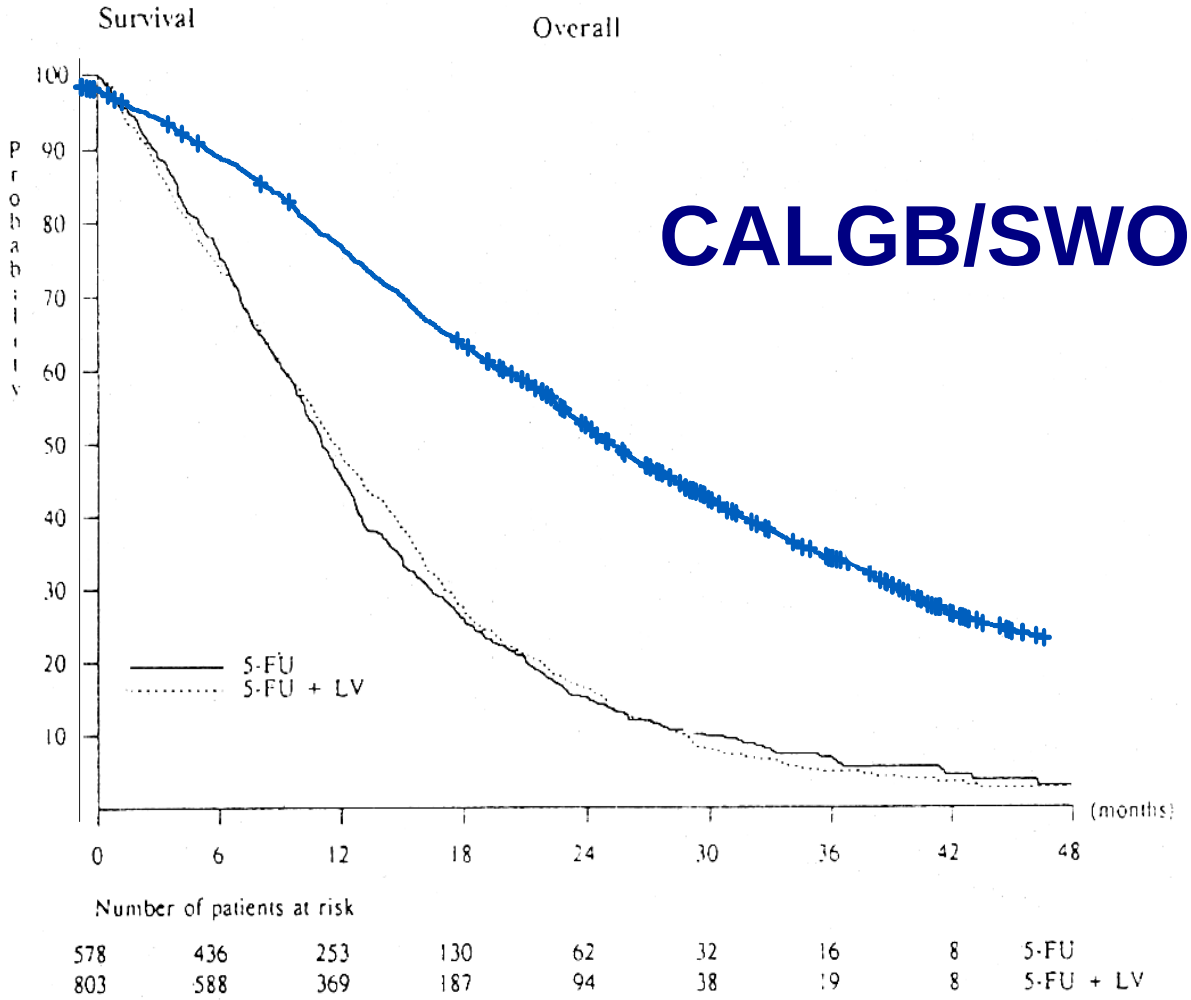
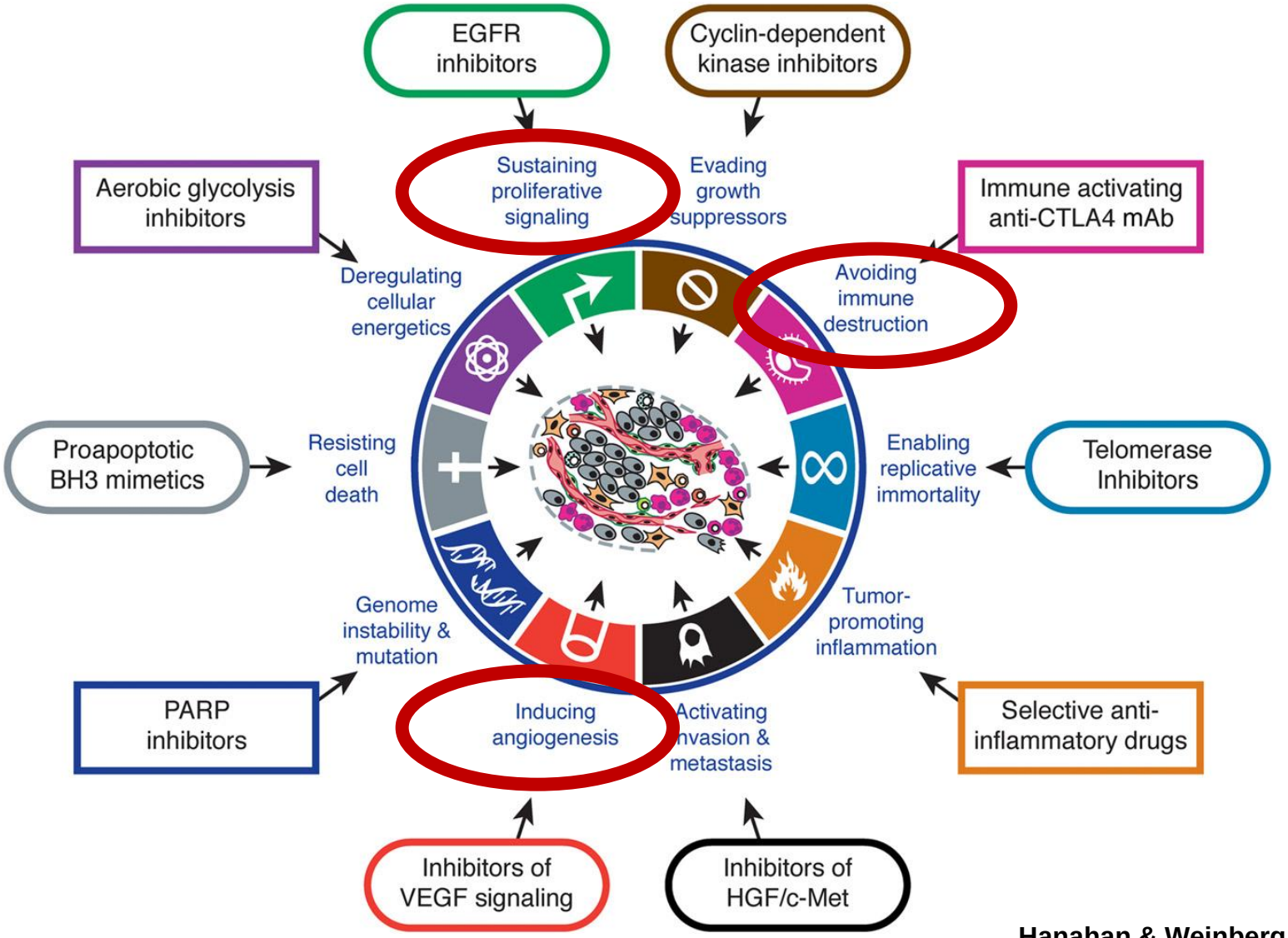


Fig 2. Overall survival.

CALGB/SWOG 80405

J Clin Oncol, 1992

Molecular landscape of cancer



Hanahan & Weinberg Cell 2011

BRAF as druggable target

- **Encorafenib+Cetuximab+/-BYL 719 (PI3K inib.)**

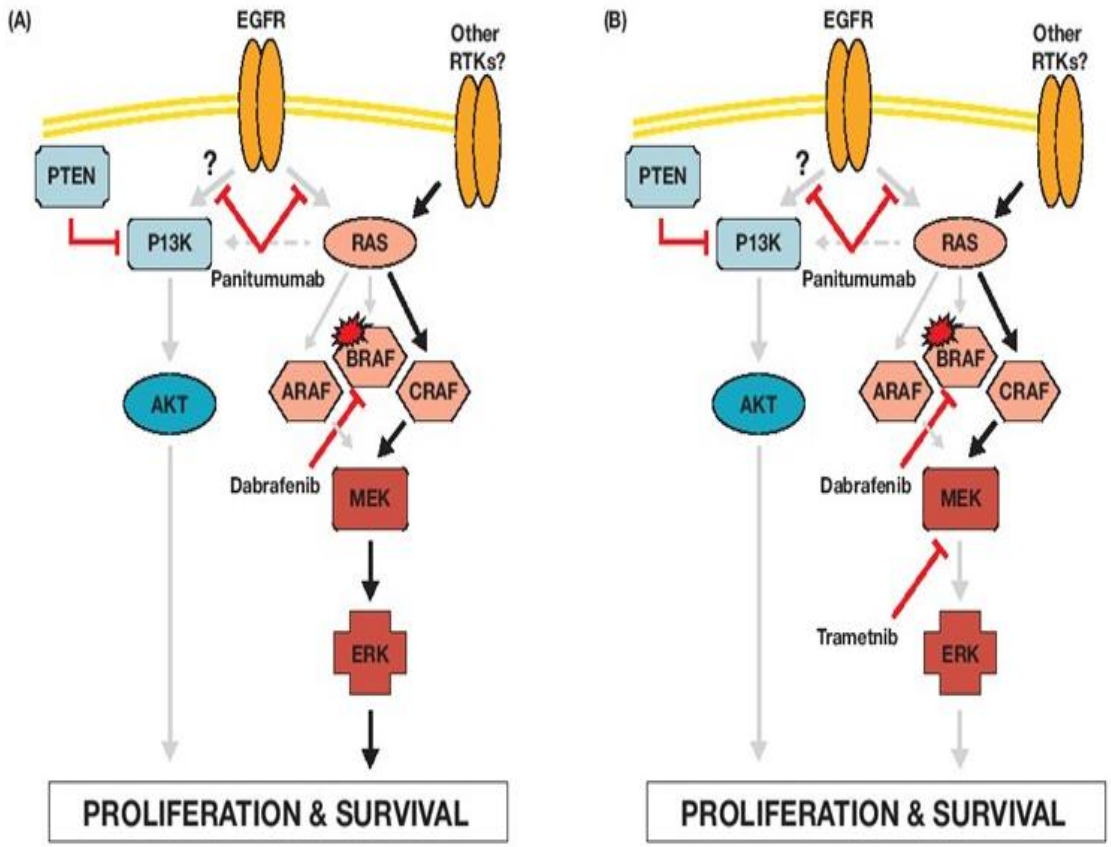
  (R. Van Geel et al. abst. 3514)
- **Dabrafenib+Panitumumab+/- Trametinib**

  (JC Bendell et al. abst. 3515)
- **Vemurafenib+Irinotecan+Cetuximab**

  (DS Hong et a. abst. 3516)
- **Dabrafenib+Trametinib**

  (RB Corcoran et al. abst. 3517)
- **Vemurafenib+/-Cetuximab**

  (J. Tabernero et al. abst. 3518)


(A)
EGFR
Other RTKs?
PTEN
?
P13K
RAS
Panitumumab
BRAF
ARAF
CRAF
AKT
Dabrafenib
MEK
ERK
PROLIFERATION & SURVIVAL
(B)
EGFR
Other RTKs?
PTEN
?
P13K
RAS
Panitumumab
BRAF
ARAF
CRAF
AKT
Dabrafenib
MEK
Trametnib
ERK
PROLIFERATION & SURVIVAL

Summary of preliminary activity in studies of BRAFi-based therapy in BRAFmut CRC

Regimen	N=	PR/CR	SD	DCR
D + T	43	12%	51%	63%
D + P	15	13.3%	73.3%	86.6%
V + C	11	-	36.3%	36.3%
E + C	**24**	**29.2%**	**50%**	**79.2%**
D + T + P	**15**	**40%**	**40%**	**80%**
V + C + Ir	**8**	**50%**	**50%**	**100%**
E + C + BYL	20	30%	60%	90%

D = dabrafenib, T = trametinib, P = panitumumab, V = vemurafenenib, C = cetuximab, E = encorafenib, Ir = irinotecan, BYL = BYL719

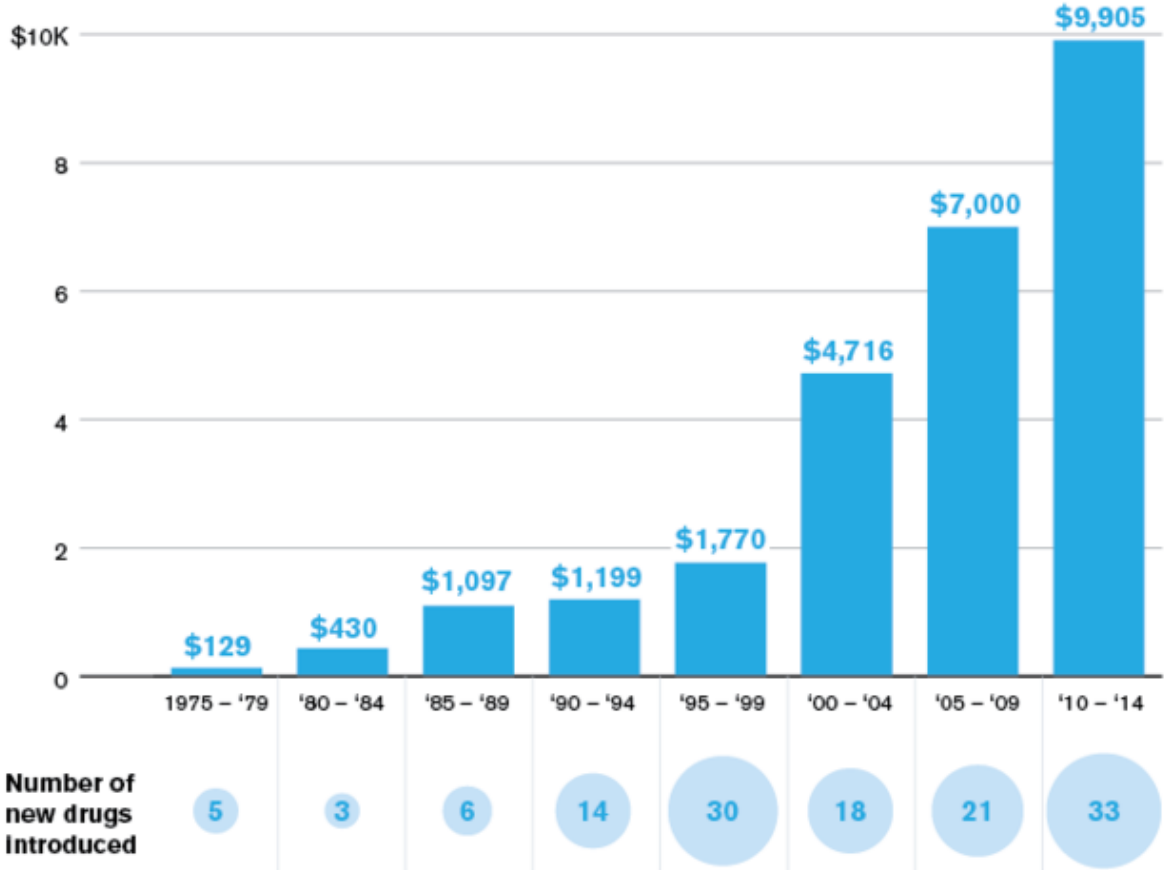
Very promising combinations but…

these drugs cost too much

Cancer Drugs Hit Market at Ever-Higher Prices

U.S. prices for new cancer drugs have soared since the 1970s despite an increasing number of available brands.

Median monthly cost for new cancer drugs during the five-year period



Note: Costs are monthly Medicare prices for each drug the year it was introduced, adjusted for inflation.

Source: Peter Bach and Geoffrey Schnorr at Memorial Sloan Kettering Cancer Center

Bloomberg Graphics

Robert Langreth Nov 25, 2014 1:05 PM **Bloomberg News**

Unsustainable

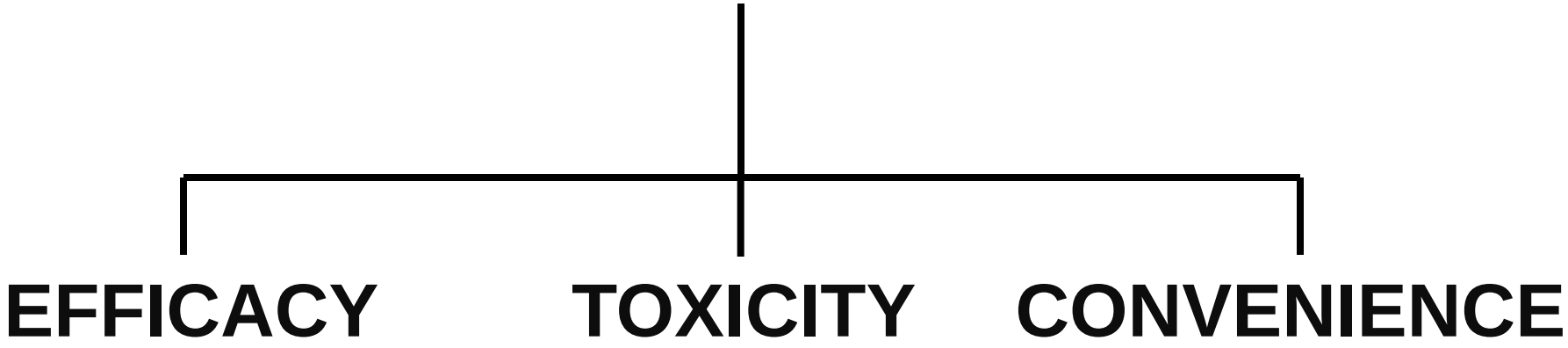
Unsustainable (adj): **not able to be maintained or supported in the future, esp. without causing damage or depletion of a resource.**

- Dictionary.com's 21st Century Lexicon

Value ≠ Benefit

$$\text{Value} \approx \frac{\text{Benefit}}{\text{Cost}}$$

Clinical benefit



Clinical benefit

EFFICACY **TOXICITY** **CONVENIENCE**

Setting
- **curative vs palliative**
- **prognosis within palliative**

Endpoint

Size

Increase in median OS for different HR as a function of prognosis

MST in control	Increase in median values as a function of HR					
	0.9	0.8	0.7	0.6	0.5	0.4
6	.6	1.5	2	4	6	9
24	2.6	6	10	16	24	36
	worthless		worthwhile		unrealistic	

Increase in median OS for different HR as a function of prognosis

MST in control	Increase in median va[illegible] a function of HR				
	0.9	[illegible]	[illegible]	0.6	0.5 [illegible]
6	.6	[illegible]5	[illegible]	4	6	9
[illegible]	2.6	10	16	24	36
	worthless	worthwhile	unrealistic		

Clinically worthwhile relative delta is a function of prognosis

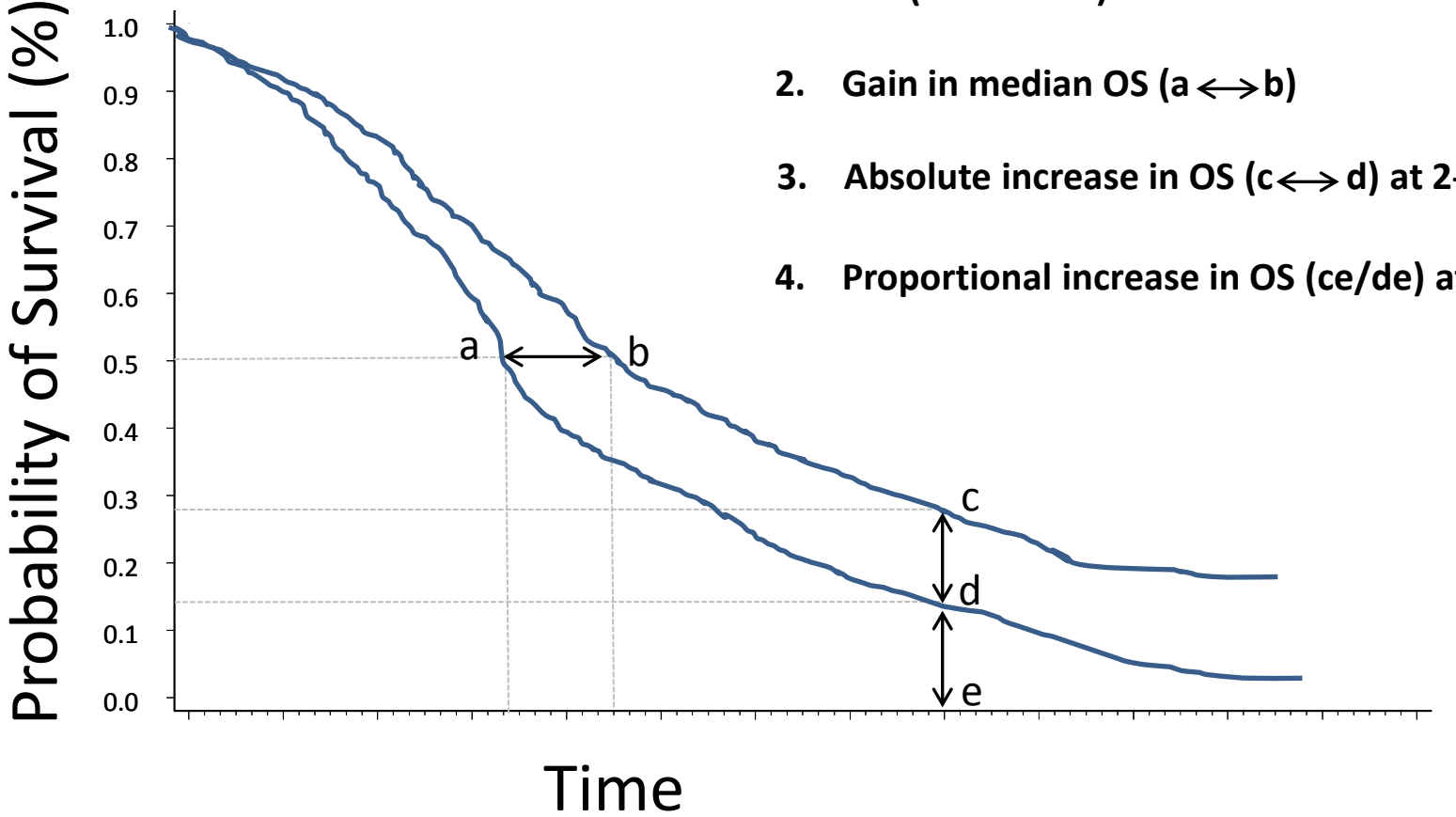
Both HR AND absolute gain must be considered

Clinical benefit

EFFICACY **TOXICITY** **CONVENIENCE**

Setting	**- curative vs palliative** **- prognosis within palliative**
Endpoint	**- type** **- ways to summarize the efficacy endpoint**
Size	

The 4 ways to interpret OS curves



1. **HR (Cox model)**
2. **Gain in median OS (a ⟷ b)**
3. **Absolute increase in OS (c ⟷ d) at 2-3 years**
4. **Proportional increase in OS (ce/de) at 2-3 years**

Clinical benefit

EFFICACY **TOXICITY** **CONVENIENCE**

Setting	**- curative vs palliative** **- prognosis within palliative**
Endpoint	**- type** **- ways to summarize the efficacy endpoint**
Size	**- extent of efficacy**

N. of trials meeting the low required benefit for MCBS out of 43 pivotal randomized studies analyzed.

		CRITERIA		NUMBER OF POSITIVE TRIALS			
Prognosis in control	N of trials	Hazard Ratio	gain in OS	Hazard Ratio	gain in OS	"either" parameter	"both" prameters
< 9 mo	9						
9-12 mo	8						
12-18 mo	9						
>18 mo	17						
TOT	43						

N. of trials meeting the low required benefit for MCBS out of 43 pivotal randomized studies analyzed.

		CRITERIA		NUMBER OF POSITIVE TRIALS			
Prognosis in control	N of trials	Hazard Ratio	gain in OS	Hazard Ratio	gain in OS	"either" parameter	"both" prameters
< 9 mo	9	0,70	2 mo				
9-12 mo	8	0,75	2,5 mo				
12-18 mo	9	0,75	3 mo				
>18 mo	17	0,80	3,5 mo				
TOT	43						

N. of trials meeting the low required benefit for MCBS out of 43 pivotal randomized studies analyzed.

		CRITERIA		NUMBER OF POSITIVE TRIALS			
Prognosis in control	N of trials	Hazard Ratio	gain in OS	Hazard Ratio	gain in OS	"either" parameter	"both" prameters
< 9 mo	9	0,70	2 mo	4	5	5	4
9-12 mo	8	0,75	2,5 mo	5	4	5	4
12-18 mo	9	0,75	3 mo	4	5	6	3
>18 mo	17	0,80	3,5 mo	4	7	7	4
TOT	43			17	21	23	15

N. of trials meeting the high required benefit for MCBS out of 43 pivotal randomized studies analyzed.

		CRITERIA		NUMBER OF POSITIVE TRIALS			
Prognosis in control	N of trials	Hazard Ratio	gain in OS	Hazard Ratio	gain in OS	"either" parameter	"both" prameters
< 9 mo	9	0,60	3 mo				
9-12 mo	8	0,65	4 mo				
12-18 mo	9	0,65	5 mo				
>18 mo	17	0,70	6 mo				
TOT	43						

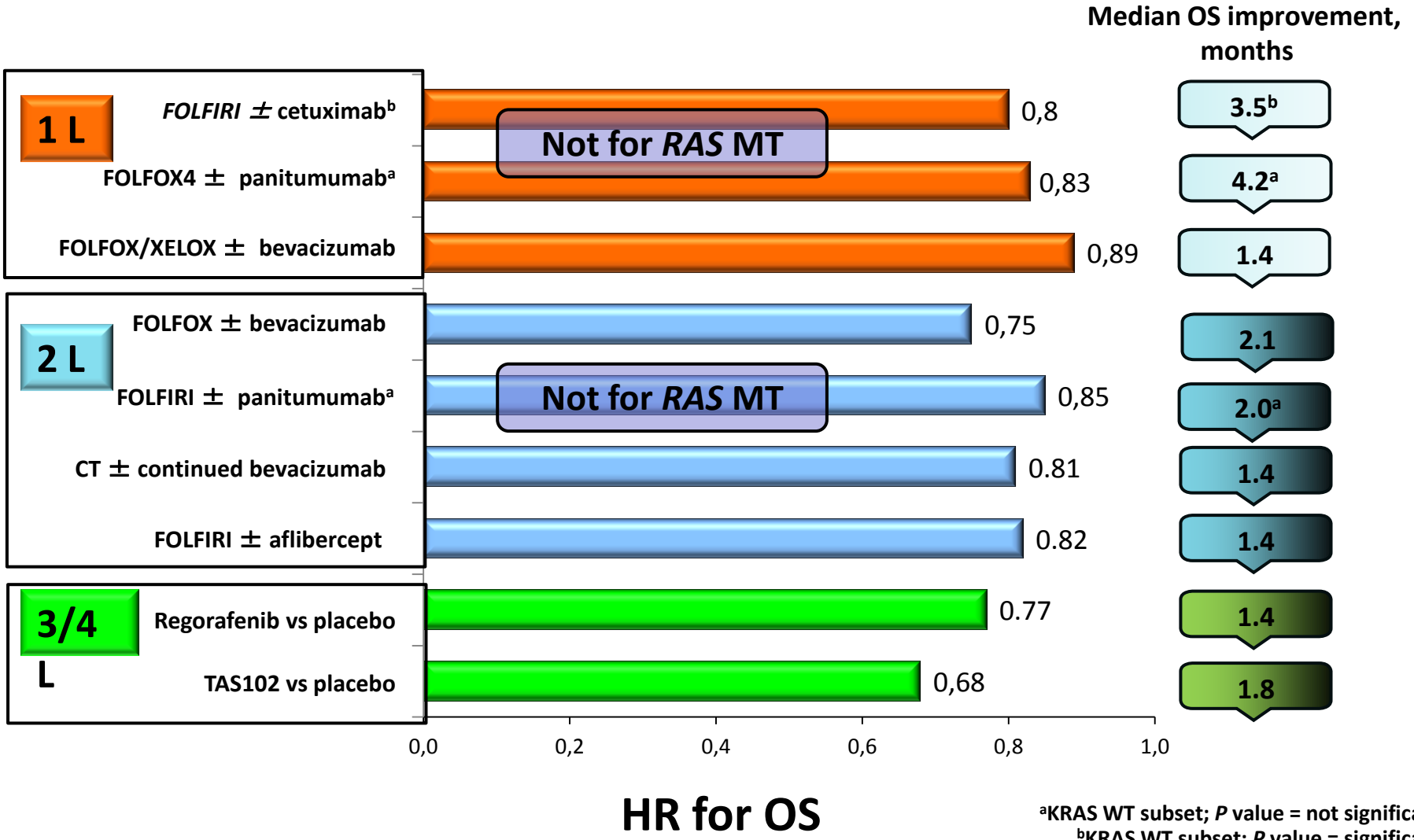
N. of trials meeting the high required benefit for MCBS out of 43 pivotal randomized studies analyzed.

		CRITERIA		NUMBER OF POSITIVE TRIALS			
Prognosis in control	N of trials	Hazard Ratio	gain in OS	Hazard Ratio	gain in OS	"either" parameter	"both" prameters
< 9 mo	9	0,60	3 mo	1	3	3	1
9-12 mo	8	0,65	4 mo	0	1	1	0
12-18 mo	9	0,65	5 mo	1	0	1	0
>18 mo	17	0,70	6 mo	2	2	3	1
TOT	43			4	6	8	2

Temsirolimus-kidney **vs IFN**
Ipilimumab-melanoma
Cetuximab-colon vs BSC
Abiraterone-prostate vs pred
Enzalutamide-prostate vs BSC
Tdm1-breast **vs cape lapatinib**
Cetuximab-head and neck **vs RT**
Bevacizumab-ovarian vs carbotaxol

Cetuximab-colon
Bevacizumab-ovarian

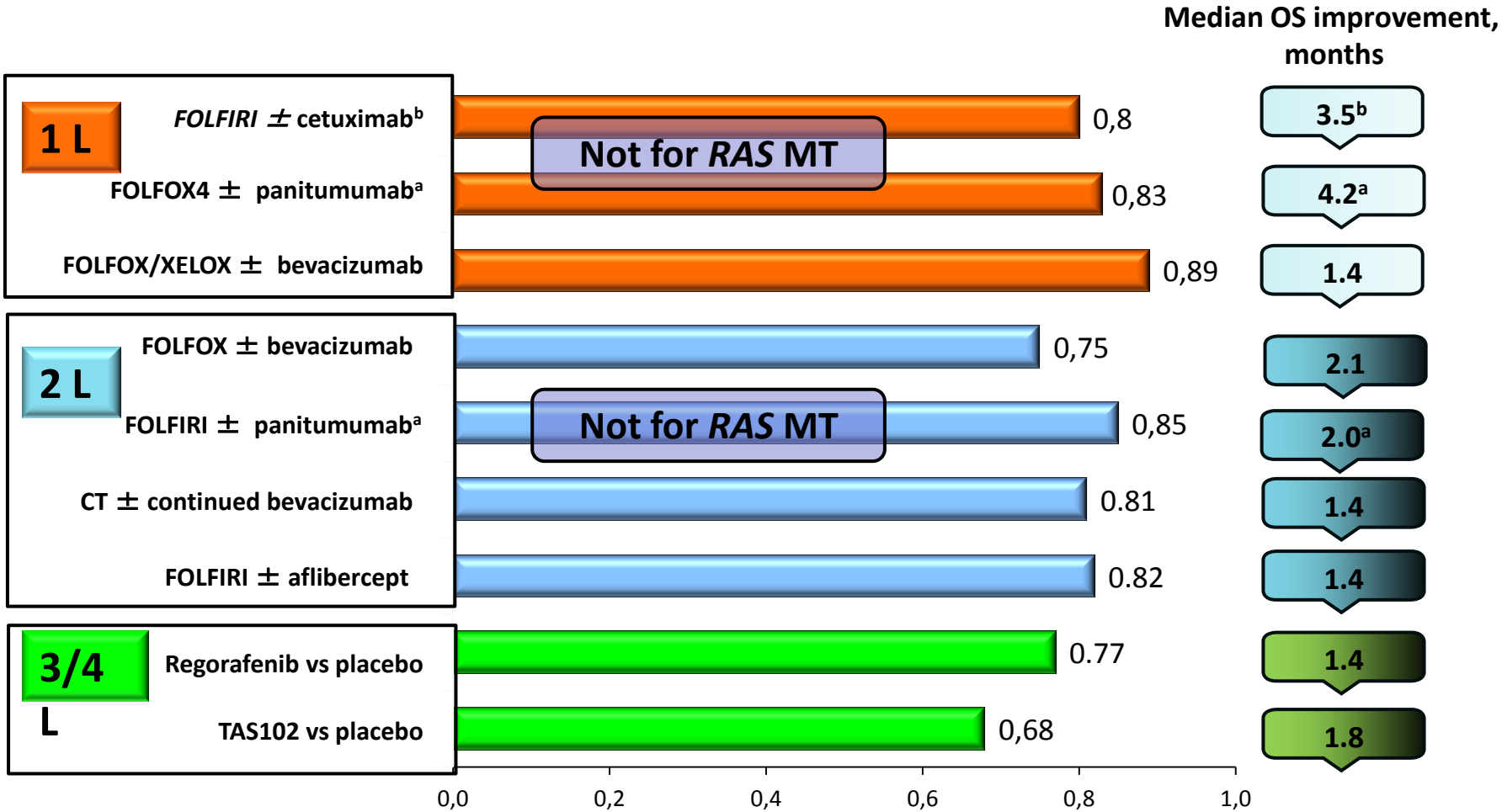
Proportional Impact on Magnitude of OS Benefit Achieved Across Lines of Therapy



[a]KRAS WT subset; *P* value = not significant.
[b]KRAS WT subset; *P* value = significant.

1. Saltz LB, et al. *J Clin Oncol.* 2008;26(12):2013-2019; 2. Douillard, J-Y, et al. *J Clin Oncol.* 2010;28(31):4697-4705; 3. Van Cutsem E, et al. *J Clin Oncol.* 2011;29(15): 2011 -2019; 4. Van Cutsem E, et al. *J Clin Oncol.* 2012;30(28):3499-3506; 5. Bennouna J, et al. *Lancet Oncol*. 2013;14(1):29-37; 6. Giantonio BJ, et al. *J Clin Oncol.* 2007;25(12)1539-1544; 7. Peeters M, et al. *J Clin Oncol* . 2010;28:4706-4713; 8. Grothey A, et al. *Lancet*. 2013;381:303-312. Van Cutsem E, et al. *ESMO 2014*

Proportional Impact on Magnitude of OS Benefit Achieved Across Lines of Therapy



Sobrero et al. Clin Cancer Res 2014:
Medium threshold for minimal clinically meaningful outcome
OS HR: 0.75, mOS +4 months

Table 2. Maximal preliminary scores

Treatments with curative intent (form 1)

>5% improvement of survival at ≥3-year follow-up

Improvements in DFS alone HR <0.60 (primary end point) in studies without mature survival data

Treatments with non-curative intent (form 2)

Primary outcome OS (form 2a)

Control ≤12 months

HR ≤0.65 *AND* gain ≥3 months *OR*

Increase *in* 2-year survival alone ≥10%

Control >12 months

HR ≤0.70 *AND* gain ≥5 months *OR*

Increase *in* 3-year survival alone ≥10%

Primary outcome PFS (form 2b)

Control ≤6 months

HR ≤0.65 *AND* gain ≥1.5 months

Control >6 months

HR ≤0.65 *AND* gain ≥3 months

Cherny et al, Ann oncol 2015

Table 6. Field testing ESMO-MCBS v1.0: colorectal cancer

Colorectal cancer												
Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESMO-MCBS
FOLFOX4 ± panitumumab	PRIME	First-line metastatic (*post hoc* KRAS, NRAS BRAF WT)	PFS	7.9 months	2.3 months	0.72 (0.58–0.90)	20.2 months	5.8 months	0.78 (0.62–0.99)			4
Panitumumab + mFOLFOX6 versus bevacizumab + mFOLFOX6	PEAK	First-line metastatic (KRAS-WT)	PFS			NS	24.3 months	9.9 months	0.62 (0.44–0.89)			4[a]
FOLFIRI ± cetuximab	CRYSTAL	First-line metastatic stratified for KRAS-WT (*post hoc* KRAS, NRAS WT)	PFS	8.4 months	3.0 months	0.56 (0.41–0.76)	20.2 months	8.2 months	0.69 (0.54–0.88)			4
Cetuximab versus best supportive care		Refractory metastatic KRAS-WT	OS	1.9 months	1.8 months	0.4 (0.30–0.54)	4.8 months	4.7 months	0.55 (0.41–0.740			4
FOLFOX4 ± panitumumab	PRIME	First-line metastatic KRAS-WT	PFS	8 months	1.6 months	0.80 (0.66–0.97)	19.4 months	4.4 months	0.83 (0.70–0.98)			3
FOLFIRI ± cetuximab	CRYSTAL	First-line metastatic stratified for KRAS-WT	PFS	8.4 months	1.5 months	0.70 (0.56–0.87)	20 months	3.5 months	0.80 (0.67–0.95)			3
ILF ± bevacizumab		First-line metastatic	OS				15.6 months	4.7 months	0.66 (0.54–0.81)			3
FOLFIRI ± panitumumab		Second-line metastatic KRAS-WT	PFS	3.9 months	2 months	0.73 (0.59–0.90)						3
FOLFOX ± bevacizumab versus bevacizumab alone	E3200	Second-line metastatic after FOLFIRI	OS				10.8 months	2.1 months	0.75 (0.63–0.89)			2
Panitumumab, versus best supportive care		Third-line metastatic stratified for KRAS	PFS	7.3 weeks	5 weeks	0.45 (0.34–0.59)						2
FOLFIRI bevacizumab versus FOLFOXIRI bevacizumab		First-line metastatic	PFS	9.7 months	2.4 months	0.75 (0.62–0.90)			NS			2
TAS-102 versus placebo	CONCOURSE	Third-line or beyond metastatic	OS				5.3 months	1.8 months	0.68 (0.058–0.81)			2
Regorafenib versus placebo	CORRECT	Third-line metastatic	OS				5 months	1.4 months	077 (0.64–0.94)			1
Second-line chemotherapy ± bevacizumab	ML18147	Second line beyond progression on bevacizumab	OS				9.6 months	1.5 months	0.81 (0.69–0.94)			1
FOLFIRI ± aflibercept	VELOUR	Second line after oxaliplatin-based treatment	OS	4.7 months	2.2 months	0.76 (0.66–0.87)	12.1 months	1.5 months	0.82 (0.71–0.94)			1
FOLFIRI ± Ramucirumab	RAISE	Second-line metastatic after bevacizumab, oxaliplatin, fluoropyrimidine	OS				11.7 months	1.6 months	0.84 (0.73–0.97)			1

[a]Unbalanced crossover.

Cherny et al, Ann oncol 2015

Clinical benefit

EFFICACY **TOXICITY** **CONVENIENCE**

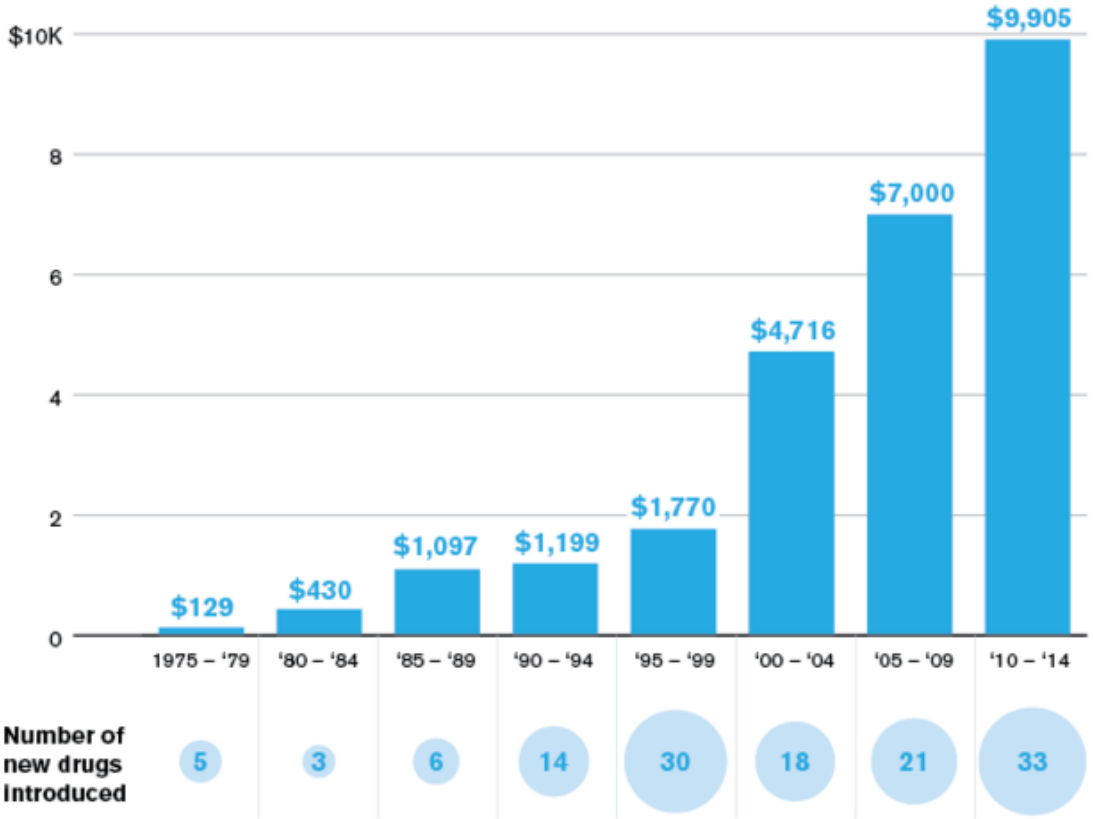
- Toxic deaths
- Hospitalization rate
- Impact on QOL
- % grade 3-4 of symptomatic toxicity
- Need for growth factors

$$\text{Value} \approx \frac{\text{Benefit}}{\text{Cost}}$$

Cancer Drugs Hit Market at Ever-Higher Prices

U.S. prices for new cancer drugs have soared since the 1970s despite an increasing number of available brands.

Median monthly cost for new cancer drugs during the five-year period



Note: Costs are monthly Medicare prices for each drug the year it was introduced, adjusted for inflation.

Source: Peter Bach and Geoffrey Schnorr at Memorial Sloan Kettering Cancer Center

Bloomberg Graphics

Courtesy L. Saltz, ASCO Annual Meeting Plenary Session 2015

Cancer Drugs Hit Market at Ever-Higher Prices

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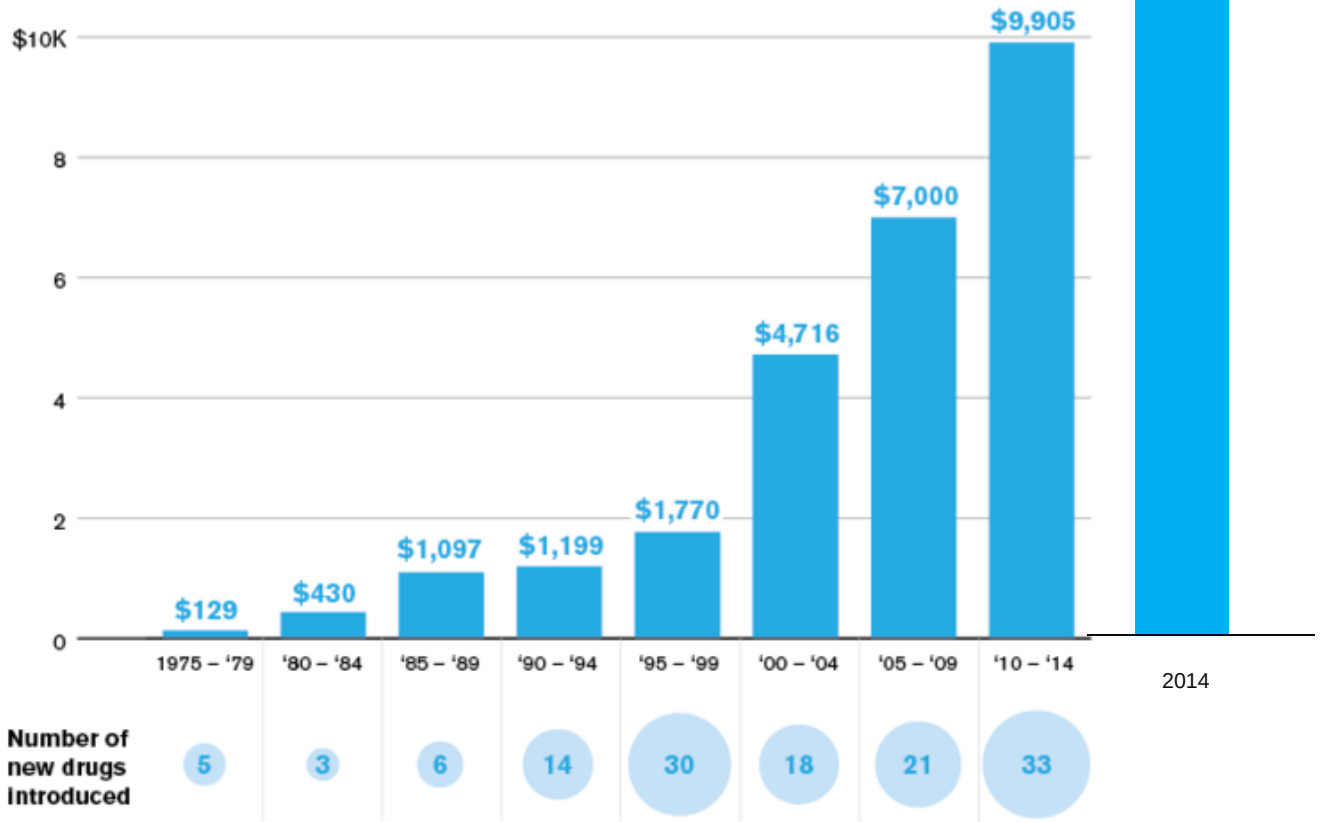


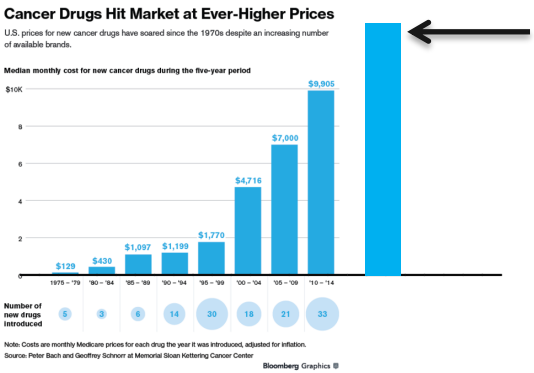
Pembrolizumab 2 mg/kg

← $14,500

Note: Costs are monthly Medicare prices for each drug the year it was introduced, adjusted for inflation.

Source: Peter Bach and Geoffrey Schnorr at Memorial Sloan Kettering Cancer Center

Bloomberg Graphics



Pembrolizumab 2 mg/kg
q 2 weeks

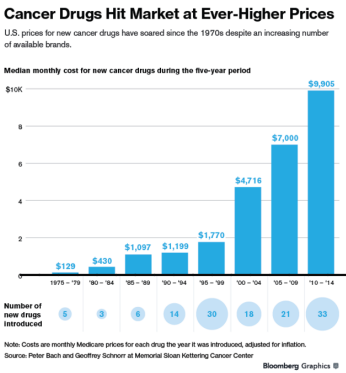
$16,700/month

Pembrolizumab 10 mg/kg q 2 weeks

$83,500/month

Pembrolizumab 2 mg/kg q 2 weeks

$16,700/month



Pembrolizumab AWP
(Redbook online): $51.792 / mg

$51.792 x 10 mg/kg x 75 kg x 26 doses/year =

Pembrolizumab 10 mg/kg
q 2 weeks

$83,500/month

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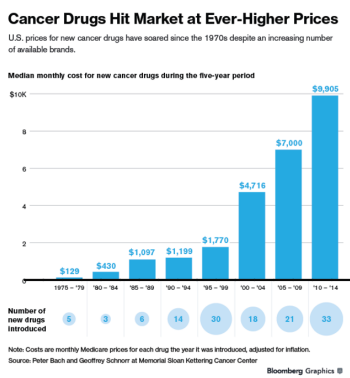

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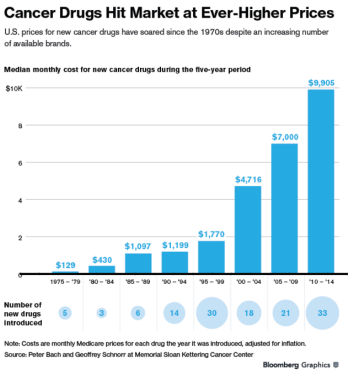

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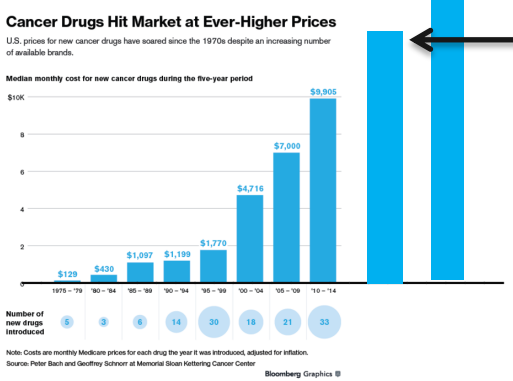
$83,500/month

Selection of 2015 ASCO abstracts using Pem 10 mg/kg q 2 wks:

abstract # 4010 (esophageal ca)
abstract # 5510 (ovarian ca)
abstract # 7502 (Small cell Lung ca)
abstract # 8035 (non-small cell lung ca)
abstract # 9040 (melanoma)



Pembrolizumab 2 mg/kg q 2 weeks

$16,700/month

So why are these prices so high?

Do we need prices *this high* to drive innovation?

- Consider sofosbuvir (Sovaldi®) for Hep C:
  - Invented by a university faculty member, much of whose initial work was federally funded
  - Inventor founded company which forecast charging $36,000 per course.
  - A second company bought the drug for $11 billion, then marketed it at $84,000 per course

    (Recouped full investment in first year of sales)

Avron J. N Eng J Med 2015:372 (20): 1877-9.
Bach P: Forbes.com http://www.forbes.com/sites/matthewherper/2014/10/23/could-high-drug-prices-be-bad-for-innovation/

New Drug or "Me Too" Drug…
…Is Cost related to Innovation?

- 51 drugs approved for 63 indications in 2009-2013

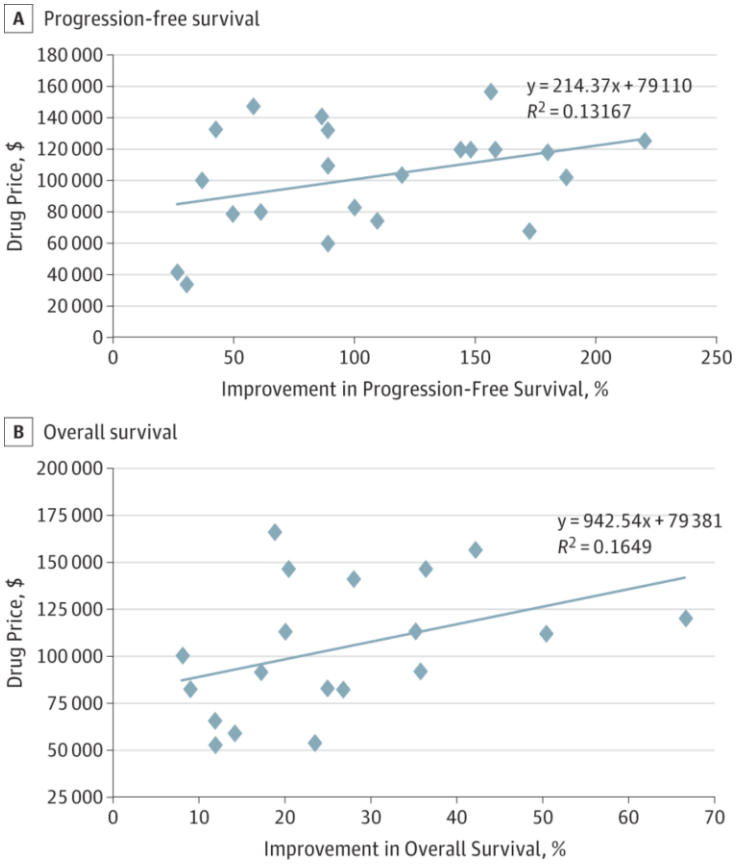
  21 (41%) novel mechanisms of action
  30 (59%) next in class

  Median price per year:
  - Novel mechanism: $116,100
  - Next in class: $119, 765

  (P=.42)

Mailankody, Prasad: JAMA Oncol. Published online April 02, 2015. doi:10.1001/jamaoncol.2015.0373

Is Cost related to efficacy?



Drug Price vs % Improvement in Survival

No significant relationship between cost and the % improvement in PFS or OS

PFS $R^2 = 0.132$
OS $R^2 = 0.165$

"Our results suggest that current pricing models are not rational but simply reflect what the market will bear."

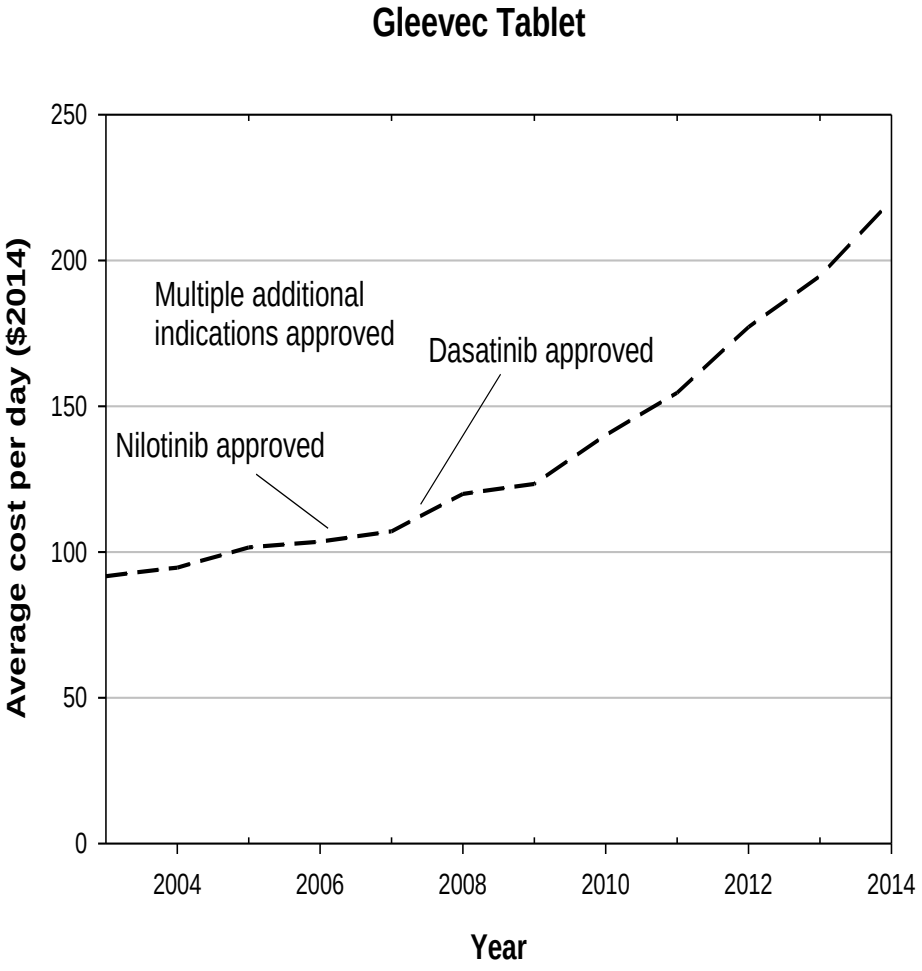
Mailankody S, Prasad V: JAMA Oncol.
Published online April 02, 2015

Do prices reflect development costs? Does competition bring down those prices?

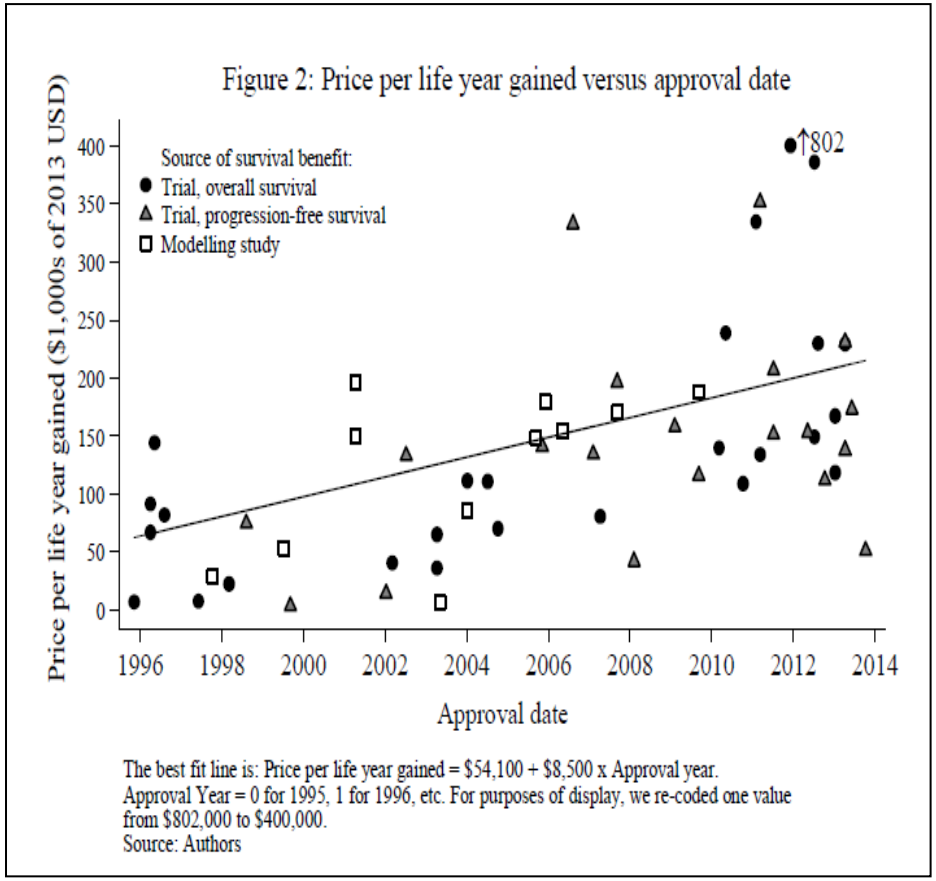
Not for Gleevec:

Since entering the market, U.S. price has steadily risen and nearly tripled….

…… despite entry of new drugs and an expanding market with new indications.



Is a year of life priceless?
The market has already set a price tag on an additional year of life….



…..and it goes up each year (inflation-adjusted) by $8500
Approximate cost to gain one year of life in 2014: $224,000

Howard DH, Bach PB, Berndt ER, Conti RM:
J Economic Perspectives 2015; 29 (1):139-62.

Conclusions:

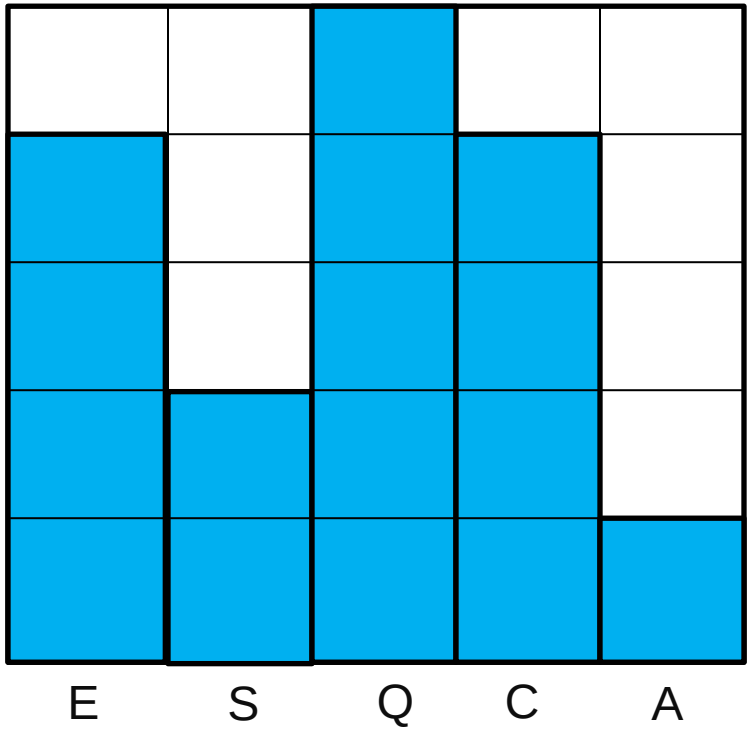
- Cancer drug prices are not related to the *value* of the drug,
- Rather, prices are based on what has come before, and what the seller believes the market will bear.
- The unsustainably high prices of cancer drugs is a big problem, and it's our problem.
- *All* of us (physicians, pharma/biotech, insurers, government, patients) need to urgently engage in active, open, constructive discussions to find fair, practical, sustainable solutions.

“Players” of the challenge:

- Scientific Societies
- Governments
- Pharma/biotech
- Researchers
- Physicians
- Patients

Example of NCCN Evidence Block

- Retain Categories of Evidence but supplement them
- Dimensions
  - Efficacy
  - Safety
  - Quality of Evidence
  - Consistency of Evidence
  - Affordability
- More shading is better
- Patents filed



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“We cannot have precision medicine without precision genomics”

Medscape MULTISPECIALTY

News & Perspective | Drugs & Diseases | CME & Education

Medscape Medical News > Oncology

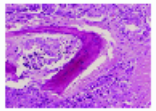
Precision Medicine Needs 'Precision Genomics'

Pam Harrison

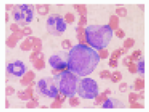
April 15, 2015

6 comments | Print | Email

EDITORS' RECOMMENDATIONS



Study Provides 'Better Picture' of Lethal Prostate Cancer



Order of Mutation Acquisition Predicts Progression in MPNs

One Biopsy Not Enough to Reveal Genetic Landscape of a Tumor

Landscape of a Tumor

When tumor-only gene sequencing is used to identify potential genetic alterations, nearly half of all patients are at risk of receiving treatment that is inappropriate for their tumor type, new research shows.

"Our analyses have highlighted the limitations of current tumor-only sequencing approaches and the benefit of tumor-normal analyses," said principal investigator Victor Velculescu, MD, PhD, professor of oncology and pathology at Johns Hopkins University School of Medicine in Baltimore, who is a cofounder of Personal Genome Diagnostics.

"We all want precision medicine, but one conclusion from these

"We all want precision medicine, but one conclusion from these

Concordare tutte le scelte di trattamento con il referente di patologia, considerando ove presenti alternative di pari efficacia anche l'impegno economico delle stesse

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. et al: Proc ASCO 2015)

Valutare la durata della terapia e l'opportunità di pause terapeutiche, ove indicato

Maintenance with beva

STUDY	AGENTS	DESIGN	OUTCOME
MACRO	XELOX-bev vs bev	non-inf, PFS	slightly inferior to contin CT + bev
CAIRO-3	obs vs cape-bev	sup, PFS2	PFS and (minor) OS gain vs nothing
SAKK	obs vs bev	non-inf, TTP	minor PFS and OS gain vs nothing
AIO0207	cape-bev vs bev vs obs	non-inf, TSF	bev not-inferior to cape-bev obs not not-inferior to cape-bev

1. **Bev plus FP OK as maintenance**
2. **Bev alone as maintenance slightly inferior**
3. **Consider personalized approach (chemo vacations if not aggressive disease)**

Considerare in pazienti oligometastatici approcci chirurgici/locoregionali, ove indicati, anche al fine di procrastinare l'inizio della terapia sistemica

Trattamenti locoregionali

Phase II and II randomized trials in chemorefractory mCRC pts with liver-limited/dominant disease

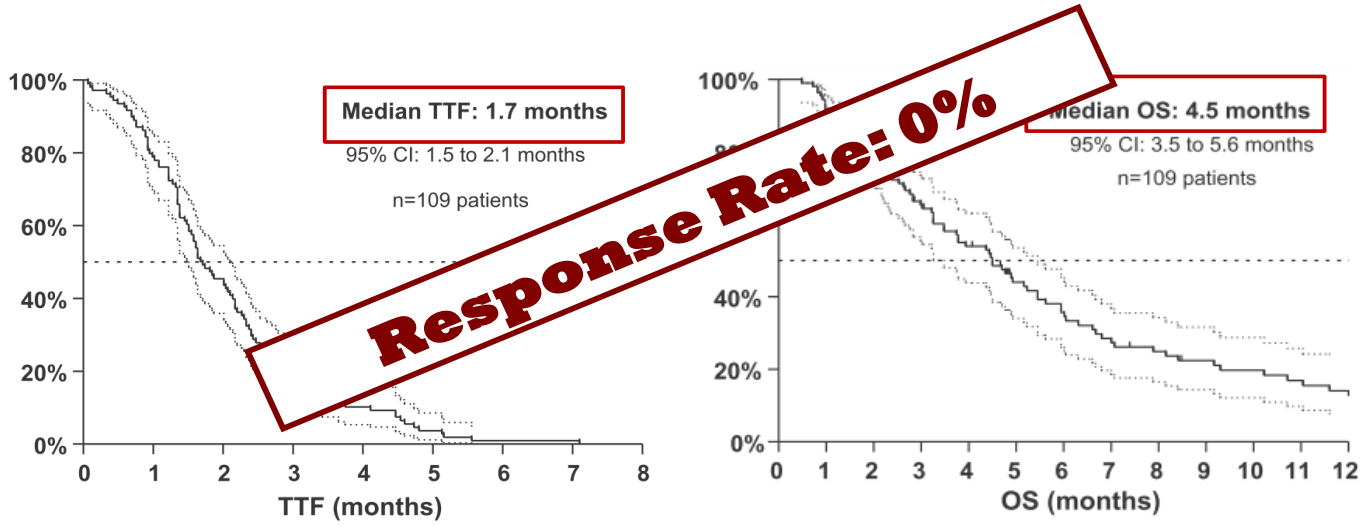
Treatment	Phase	N	Setting	ORR (%)	mPFS (mos)	mOS (mos)
Oxa+Irino+5FU [HAI] +Cet	II	35	≥3rd line	38	7.3	15.2
DEBIRI	II	55	≥3rd line	50	11.0	19.0
DEBIRI	II ran	74	≥3rd line	69	7.0	22.0
FOLFIRI				20	4.0	15.0
^{90}Yttrium SIRT	II	50	≥4th line	24	3.7	12.6
5FU	II ran	44	≥3rd line	0	2.1	7.3
^{90}Yttrium SIRT +5FU				10	4.5	10.0

Ducreux et al, ASCO 2013
Martin et al, Ann Surg Oncol 2011
Fiorentini et al, Anticancer Res 2013
Cosimelli et al, Br J Cancer 2010
Hendlisz et al, J Clin Oncol 2010

Evitare chemioterapie, in particolare dopo la seconda linea, senza solida evidenza scientifica

Real life experience : MD Anderson e centri brasiliani

Mitomycin C +/- fluoropirimidine in 109 refractory mCRC pts



Ferrarotto et al, Eur J Cancer 2012

Implementare le attività di cure simultanee e palliative, anche al fine di evitare i trattamenti oncologici attivi a fine vita fornendo al paziente un punto di riferimento maggiormente appropriato alla fase pre-terminale.

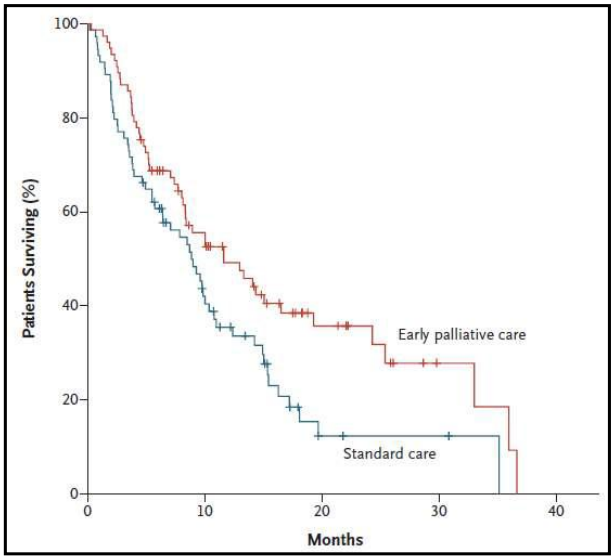
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

Patients assigned to early palliative care had

- *Better quality of life (p= 0.03)*
- *Fewer depressive symptoms (p=0.01)*
- *Fewer aggressive end-of-life care (p=0.05)*
- *Longer median survival (p=0.02)*



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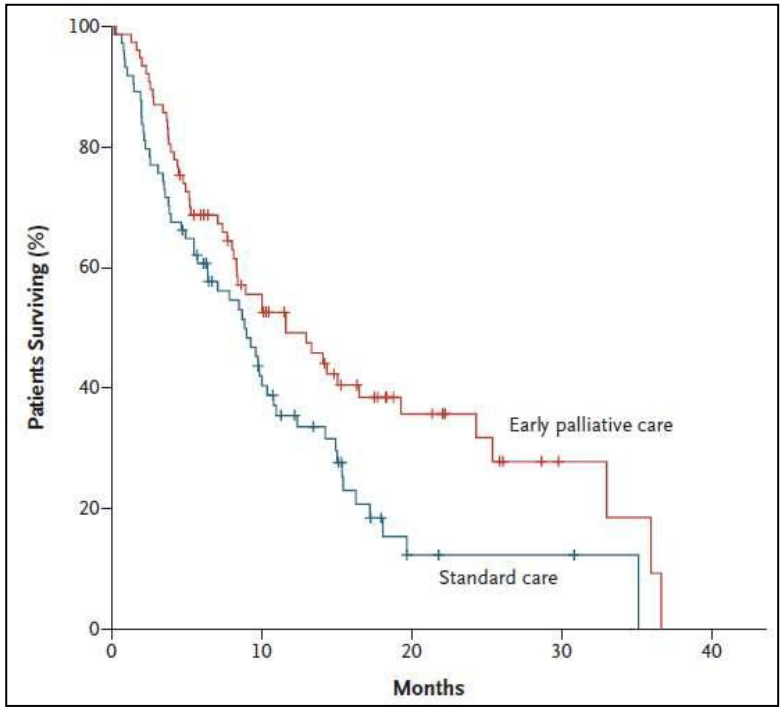
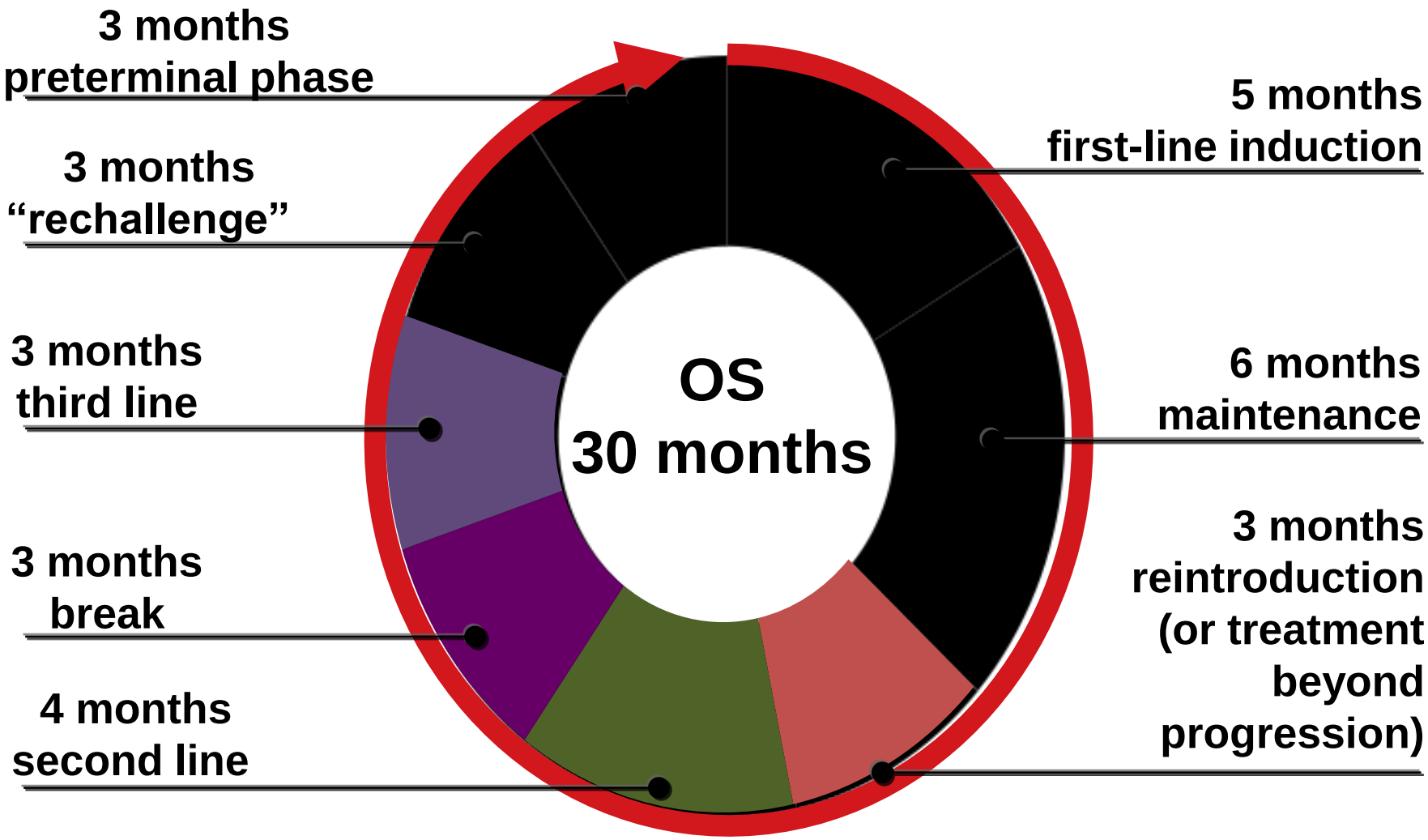


Implementare l’attivazione di trials clinici con farmaci forniti dallo Sponsor

Verificare l’esito dei trattamenti mediante studi “real practice” per patologia

2015: A classical case of mCRC



Courtesy: Eric Van Cutsem

“Non è vero che abbiamo poco tempo…

…la verità è che ne perdiamo molto.”

Lucio Anneo Seneca

sara.lonardi@ioveneto.it