Second line therapy of glioblastoma: chemotherapy

Salvatore Grisanti, Laura Deiana, Rebecca Pedersini and Alfredo Berruti

Department of Medical Oncology, Spedali Civili di Brescia
& University of Brescia

Disclosure of conflict of interest

None to disclose

Outline

Defining the problem

Options for second line chemotherapy

The metabolic puzzle: an emerging target

Defining the problem

GBM mortality rate: <5% survival at 5 years

George Gershwin, 1937
12 months survival

Ted Kennedy, 2009
13 months survival

Princess Marina,
Duchess of Kent, 1968
14 months survival

Second line chemo in GBM: why?

1. Epidemiological: >75% GBM patients will recur and die within 5 years from diagnosis **Warning! ECM question**

2. Methodological: second line chemotherapies offer unique models of activity that could be used in first line

Options for second line chemotherapy

No standard for second line chemo

ESMO clinical practice guidelines v.2010

Recurrent disease

For patients progressing after prior chemotherapy, there is no established chemotherapy regimen available …

Single-agent nitrosourea therapy may achieve tumour control in some patients, …
[II, C].

High imaging response rates and a steroid-sparing effect have been observed with administration of bevacizumab (*+/- irinotecan). However, the effect is frequently short lived and* may be largely due to changes in vascular permeability. The effect on life expectancy remains unknown [III, C].
On the basis of the available evidence bevacizumab is not currently approved by the European Medicines Agency for recurrent glioblastoma.

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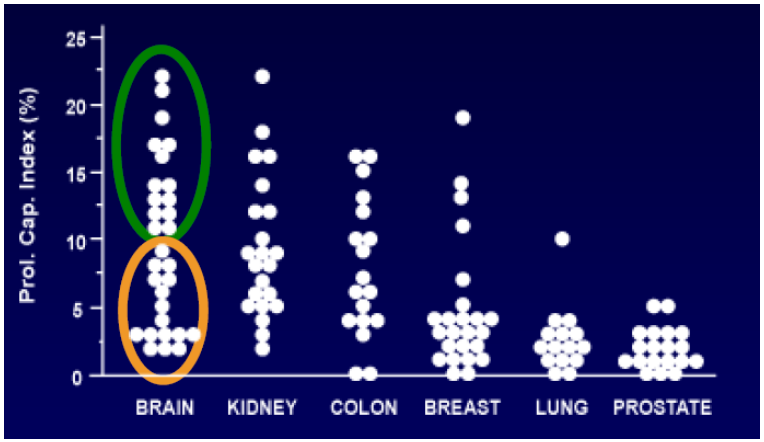
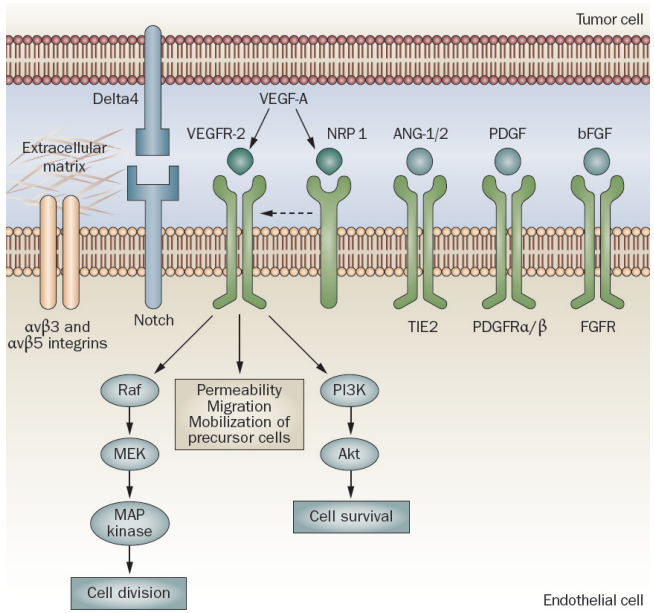
Activity of second line mono-chemotherapy of GBM

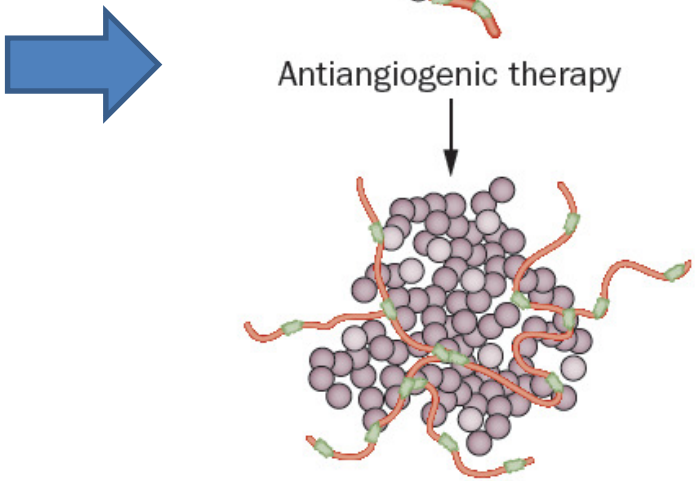
Drug/schedule	Author/year	ORR	6-PFS	Median OS
TMZ rechallenge 50 mg/sqm continuous dose	Perry, 2010	11%	24%	9.3 months
Lomustine 100-130 mg/sqm q 6 w	Wick, 2010	PR: 4% SD: 36%	19%	7.1 months
Carmustine 100 mg/sqm q 6w + Irinotecan 175 mg/sqm q 1w	Brandes, 2004	PR: 21% SD: 50%	30%	13 months
Fotemustine 100 mg/sqm (induction+mantainance)	Brandes, 2009	PR: 7% SD: 35%	21%	6 months
Irinotecan 400 mg/sqm q 3 w	Chamberlain, 2002	PD: 100%	nr	nr
Procarbazine 150 mg/sqm/d x 28d	Yung, 2000	PR: 5% SD: 27%	8%	6 months
PCV	Brada, 2010	nr	30%	6.7 months

Antiangiogenic therapy rationale in GBM

GBMs are hypervascular tumors







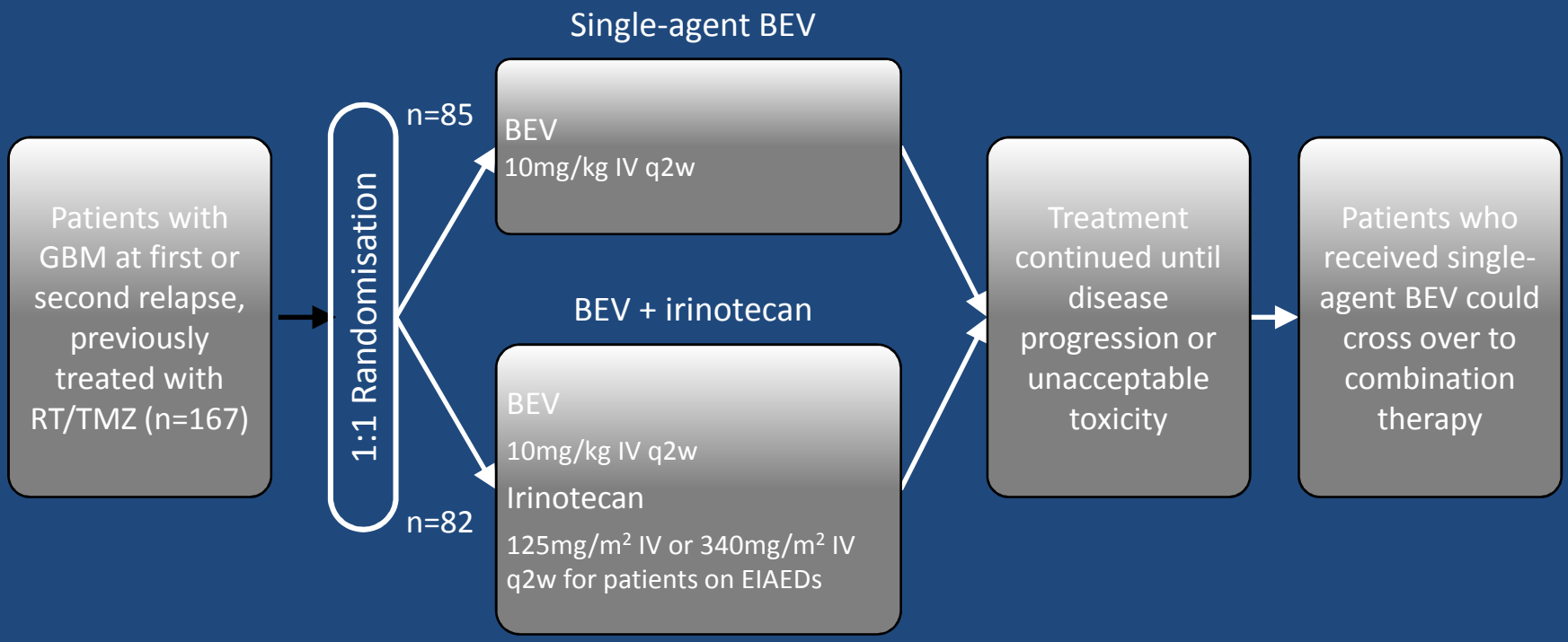
Antiangiogenic agents in phase II/III trials

Table 1 | Antiangiogenic agents in clinical trials for high-grade glioma

Primary target	Agent	Other targets	Mechanism of action
VEGF-A	Aflibercept (VEGF Trap)	VEGF-B, PlGF	Soluble decoy receptor
VEGF-A	Bevacizumab	None	Monoclonal antibody
VEGFR-2	Cediranib (AZD2171)	All VEGFR subtypes, PDGFRβ, c-Kit	Tyrosine kinase inhibitor
VEGFR-2	CT-322	All VEGFR subtypes	Adnectin
VEGFR-2	Pazopanib	All VEGFR subtypes, PDGFRα and β, c-Kit	Tyrosine kinase inhibitor
VEGFR-2	Sorafenib	VEGFR-3, B-Raf, PDGFRβ, c-Kit, Ras, p38α	Tyrosine kinase inhibitor
VEGFR-2	Sunitinib	PDGFRβ, FLT3, c-Kit	Tyrosine kinase inhibitor
VEGFR-2	Vandetanib (ZD6474)	EGFR	Tyrosine kinase inhibitor
VEGFR-2	XL-184	c-Met, RET, c-Kit, FLT3, TIE2	Tyrosine kinase inhibitor
CD36 receptor	ABT-510	None	Thrombospondin-1 mimetic peptide
FGFR	Brivanib	VEGFR-2	Tyrosine kinase inhibitor
HGF	AMG102	None	Monoclonal antibody
Integrins αvβ3 and αvβ5	Cilengitide (EMD121974)	None	Synthetic Arg–Gly–Asp peptide
PDGFRβ	Dasatinib	Src, BCR–ABL1, c-Kit, ephrin A2	Tyrosine kinase inhibitor
PDGFRβ	Imatinib	BCR–ABL1, c-Kit	Tyrosine kinase inhibitor
PDGFRβ	Tandutinib (MLN518)	FLT3, c-Kit	Tyrosine kinase inhibitor

Abbreviations: BCR, breakpoint cluster region protein; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; FLT3, FL cytokine receptor; HGF, hepatocyte growth factor; PDGFR, platelet-derived growth factor receptor; PlGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

BRAIN Study: Open-Label, Multicentre, Randomised, Non-Comparative Study of Bevacizumab in Recurrent GBM



- Primary endpoints: 6-month PFS, ORR as assessed by a blinded IRF
- Other endpoints: PFS, OS, DOR
- The study was not designed to compare efficacy and safety between the two treatment arms

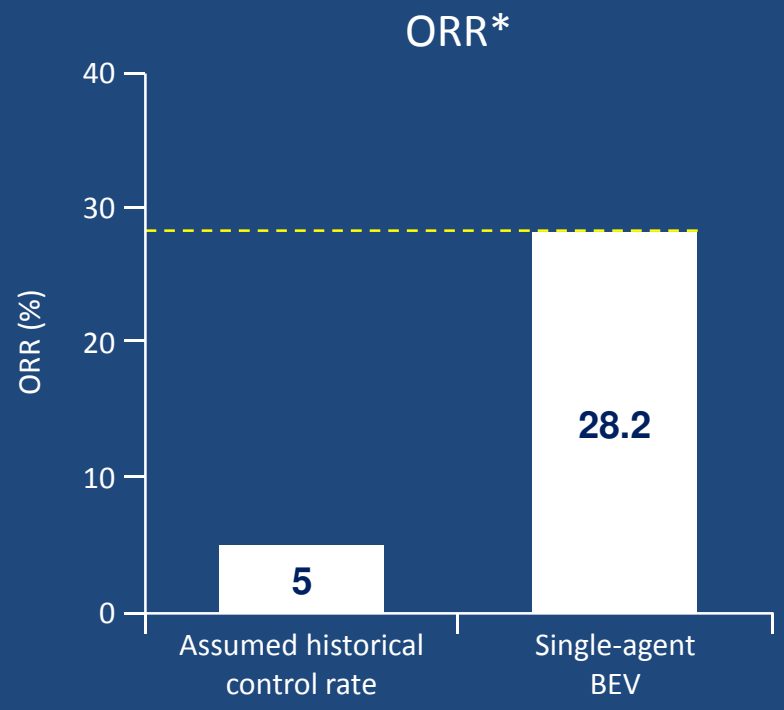
BEV = bevacizumab; DOR = duration of response; EIAED = enzyme-inducing anti-epileptic drug; GBM = glioblastoma; IV = intravenous; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; q2w = every 2 weeks

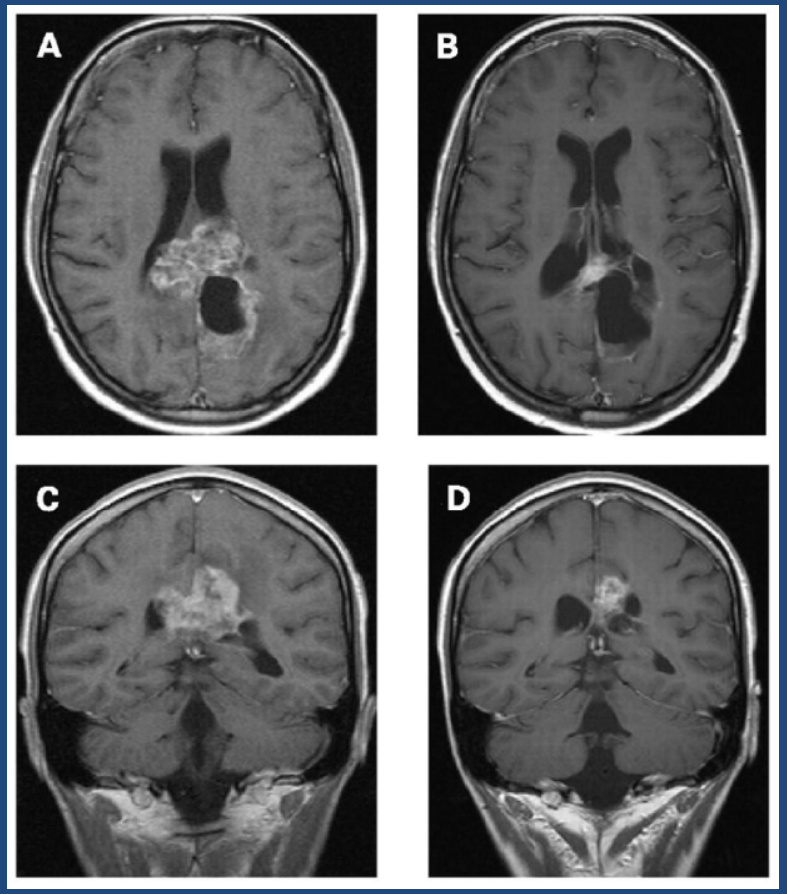
Friedman 2009

BRAIN Study: Response Rate

- 6-month PFS = 42.6%
- The ORR with single-agent bevacizumab was significantly better than that seen with historical controls (p<0.0001)

Warning! ECM question

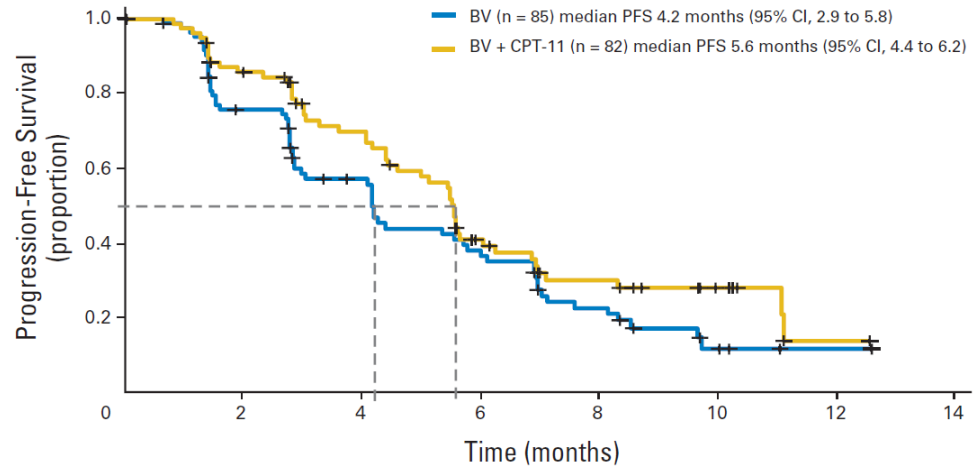


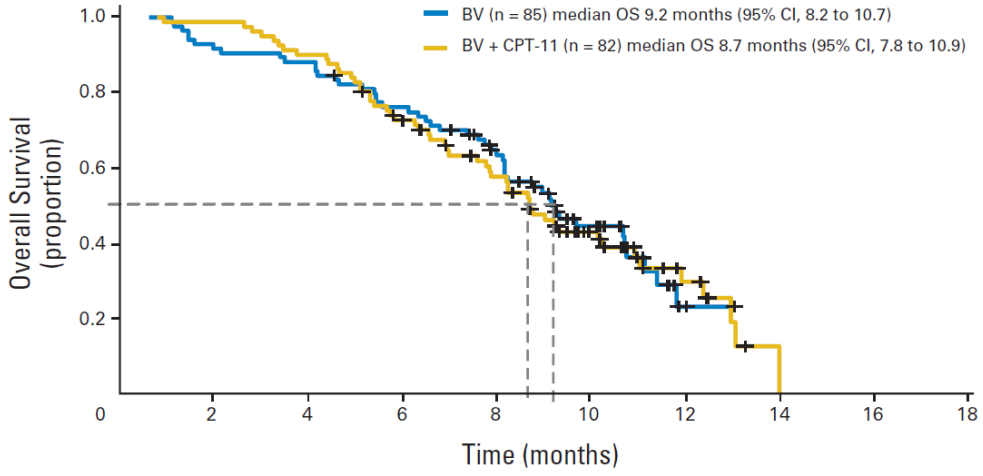


*Measured by a blinded IRF
BEV = bevacizumab; CI = confidence interval; DOR = duration of response; ORR = overall response rate; PFS = progression-free survival

Friedman 2009

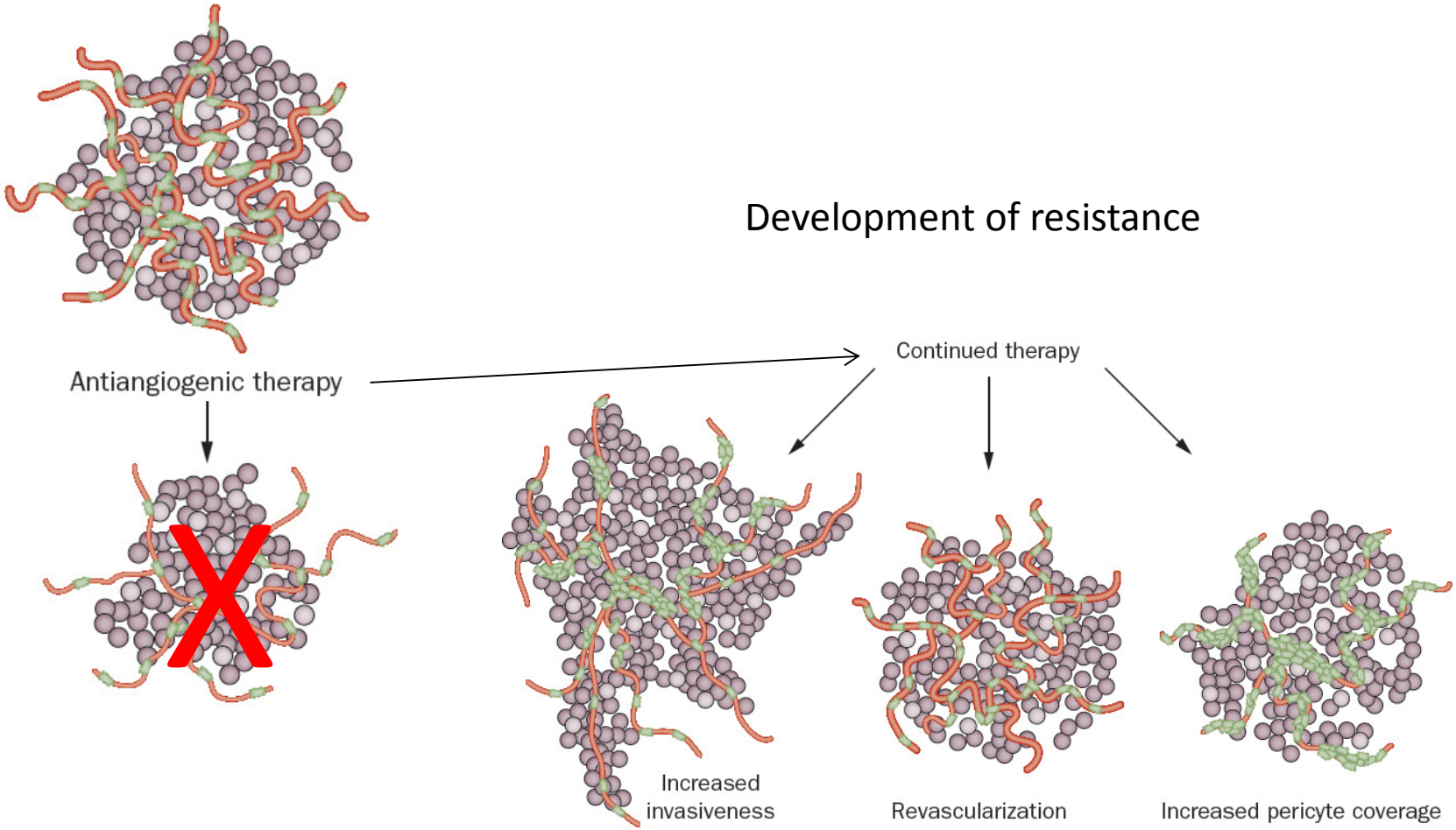
BRAIN Study: Survival





J Clin Oncol 27:4733-4740. © 2009 by American Society of Clinical Oncology

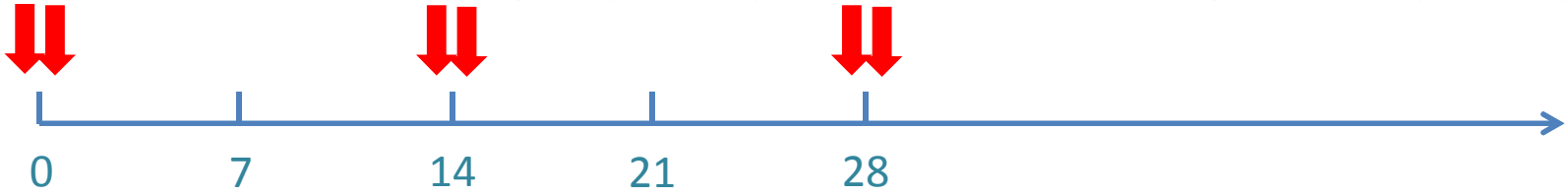
Resistance to antiangiogenic therapy



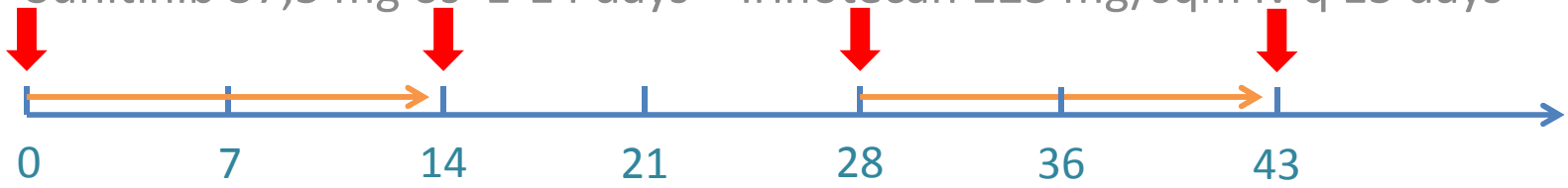
No comparison exists between conventional chemo vs BSC vs antiangiogenic therapy

A non-randomized phase II trial of two different anti-angiogenic strategies vs conventional chemotherapy vs BSC: a study from the Gruppo Neuro-Oncologico Bresciano

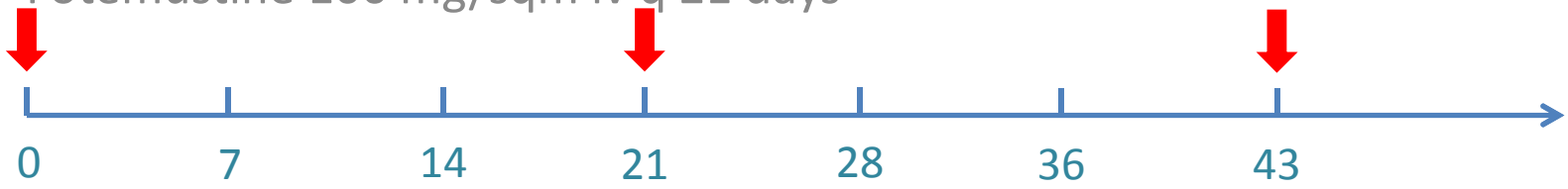
- Bevacizumab 10 mg/kg iv q 14 days + Irinotecan 125 mg/sqm iv q 14 days



- Sunitinib 37,5 mg os 1-14 days + Irinotecan 125 mg/sqm iv q 15 days



- Fotemustine 100 mg/sqm iv q 21 days



Results (1): demographics and pts allocation

- From April 2008 to June 2011: 30 patients sequentially observed

- Sunitinib/Irinotecan (n = 6)
- Bevacizumab/Irinotecan (n = 5)
- Fotemustine (n = 10)
- Best supportive care (n = 9)

• Median age at recurrence:	55 years (21-71)
• RPA score at diagnosis:	III: 1 (3%) IV: 20 (67%) V: 9 (30%)
• ECOG PS at recurrence:	1: 18 (60%) 2: 10 (33%) 3: 2 (7%)

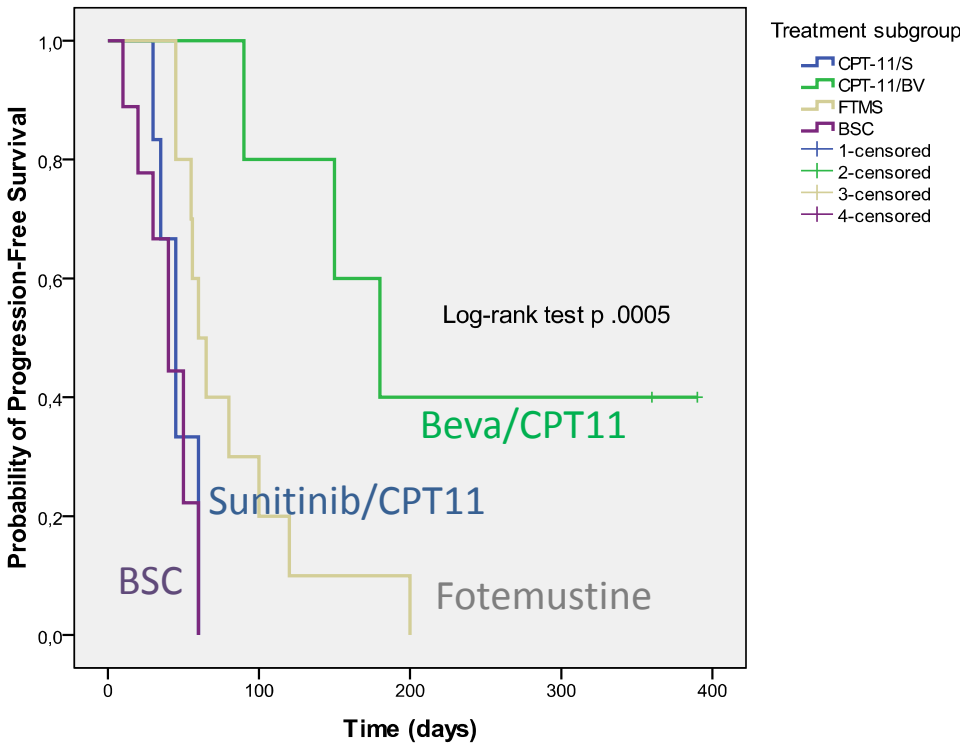
Results (2): evaluation of best radiological response

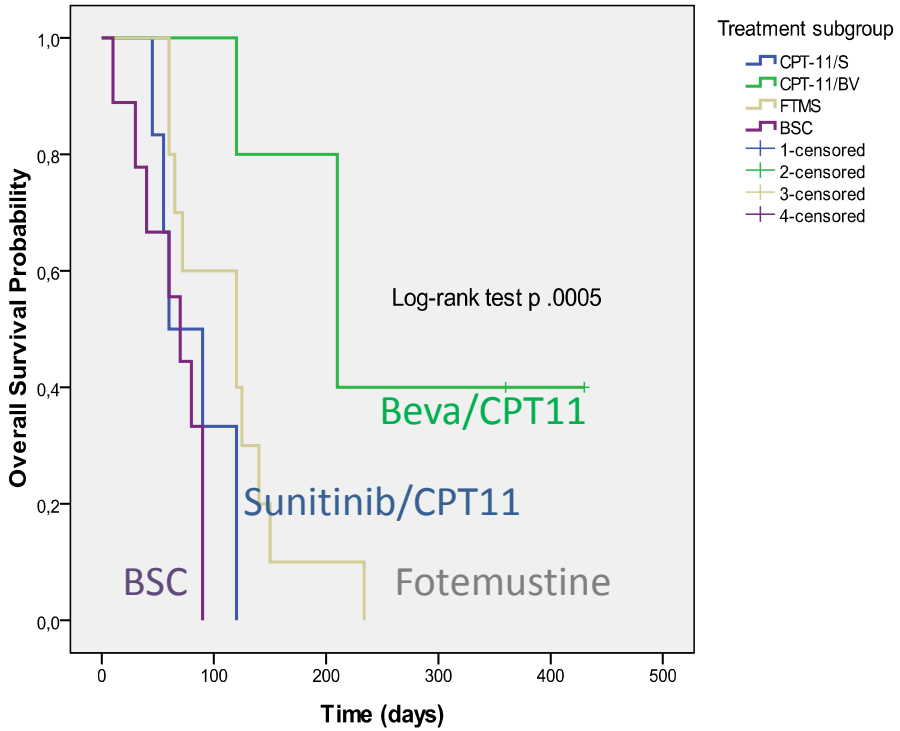
- Sunitinib/Irinotecan (n = 6)
  - CR: 0
  - PR: 0
  - SD: 1
  - PD: 5
- Bevacizumab/Irinotecan (n = 5)
  - CR: 1
  - PR: 2
  - SD: 1
  - PD: 1
- Fotemustine (n = 10)
  - CR: 0
  - PR: 1
  - SD: 4
  - PD: 5

Table 1. Current Response Criteria for Malignant Gliomas (Macdonald Criteria)[5]

Response	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; no corticosteroids; and stable or improved clinically
Partial response	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no new lesions; stable or reduced corticosteroid dose; and stable or improved clinically
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; and stable clinically
Progression	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions; any new lesion; or clinical deterioration

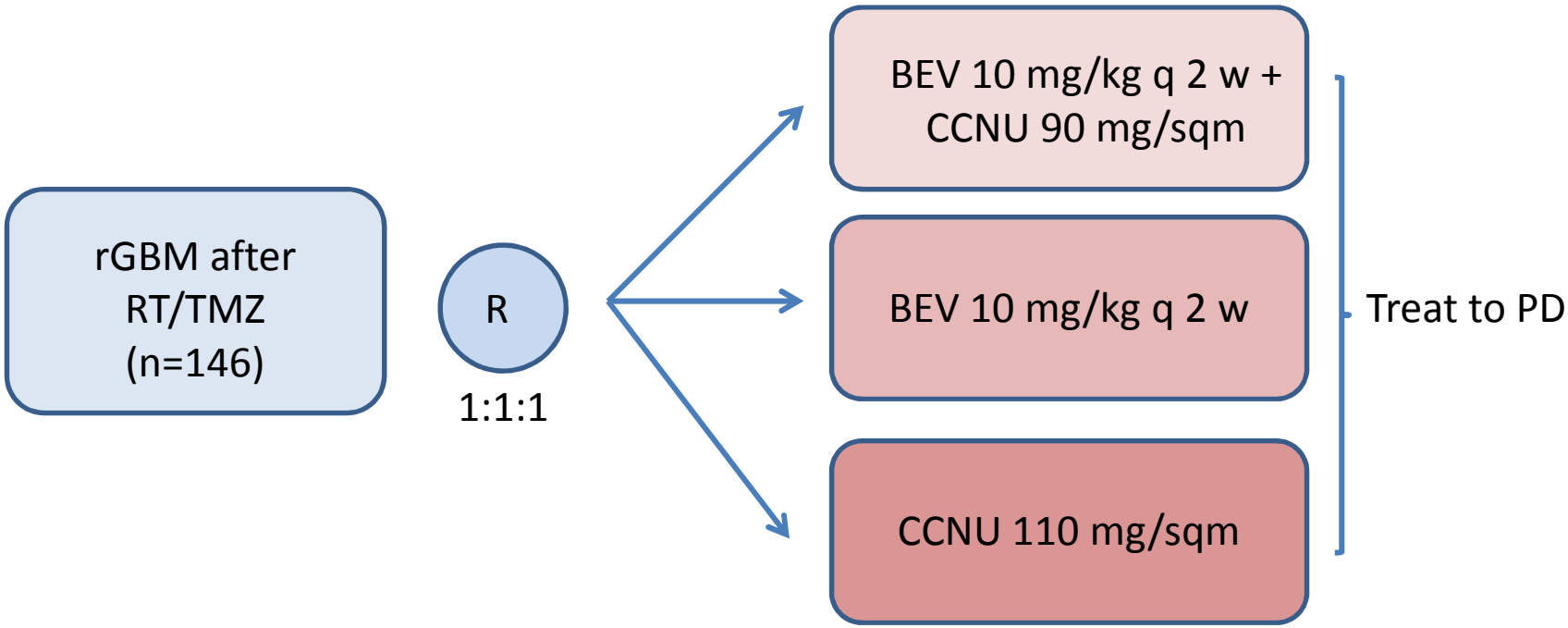
Results (3): survival





The future of antiangiogenic therapy: combination therapy with Nitrosourea-based chemotherapy ?

A randomized phase II study of bevacizumab versus bevacizumab plus lomustine versus lomustine single agent in recurrent glioblastoma: the Dutch BELOB study.



Taal et al, ASCO 2013

A randomized phase II study of bevacizumab versus bevacizumab plus lomustine versus lomustine single agent in recurrent glioblastoma: the Dutch BELOB study.

Treatment	n	% 9 mo OS [95% CI]	Median PFS (mo)	% 6 mo PFS [95% CI]
BEV	50	38% [25, 51]	3	18 [9, 30]
Lomustine	46	43% [29, 57]	2	11 [4, 22]
BEV/lomustine 90 mg/m²	44	59% [43, 72]	4	41 [26, 55]
BEV/lomustine 110 mg/m²	8	88% [39, 98]	11	50 [15, 77]

Taal et al, ASCO 2013

The metabolic puzzle: an emerging target

Clinical background

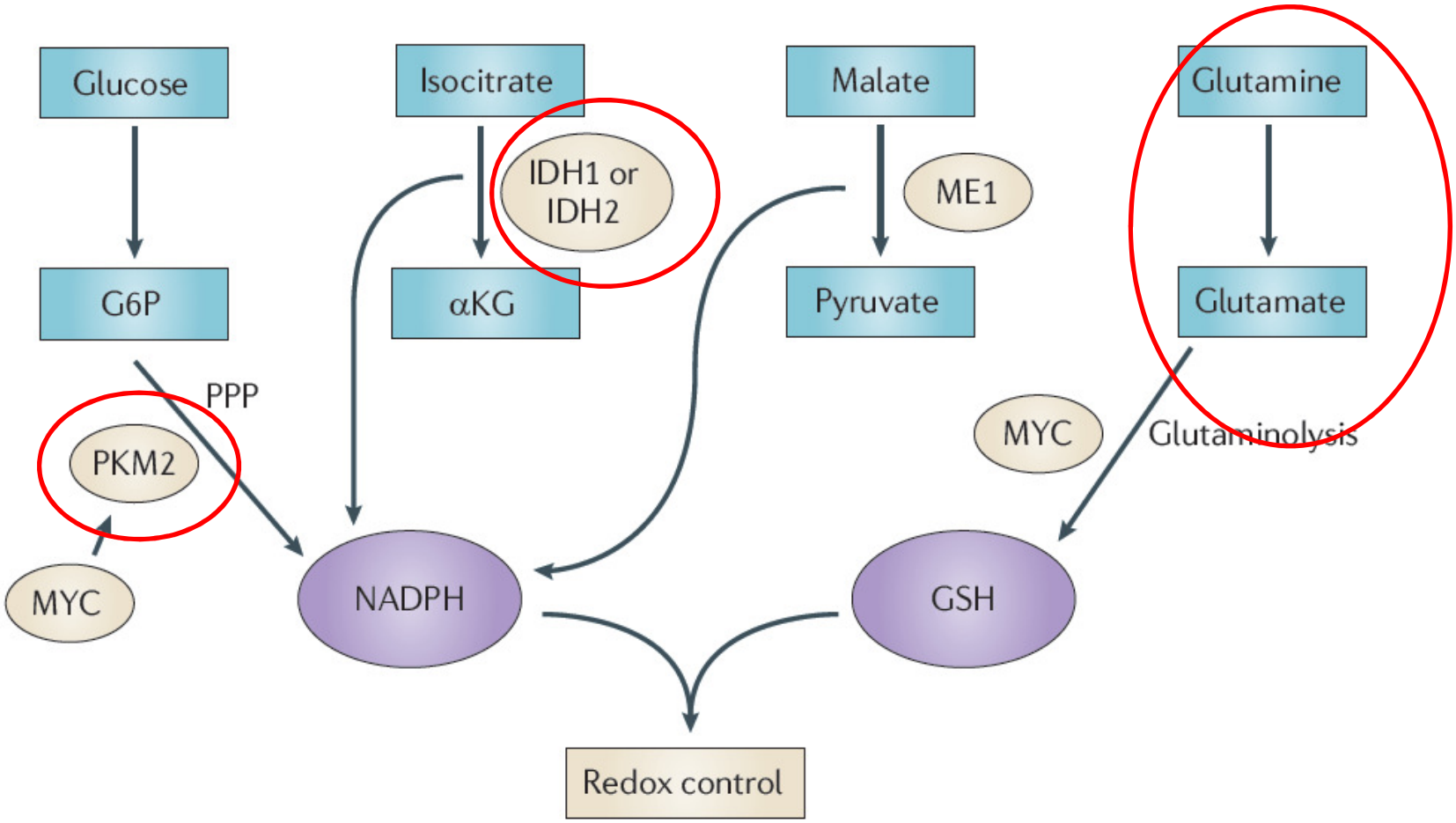
- Diabetes mellitus and hyperlipidaemia are associated with decreased survival in GBM

- Metformin has anticancer properties and potentiates TMZ activity in GBM

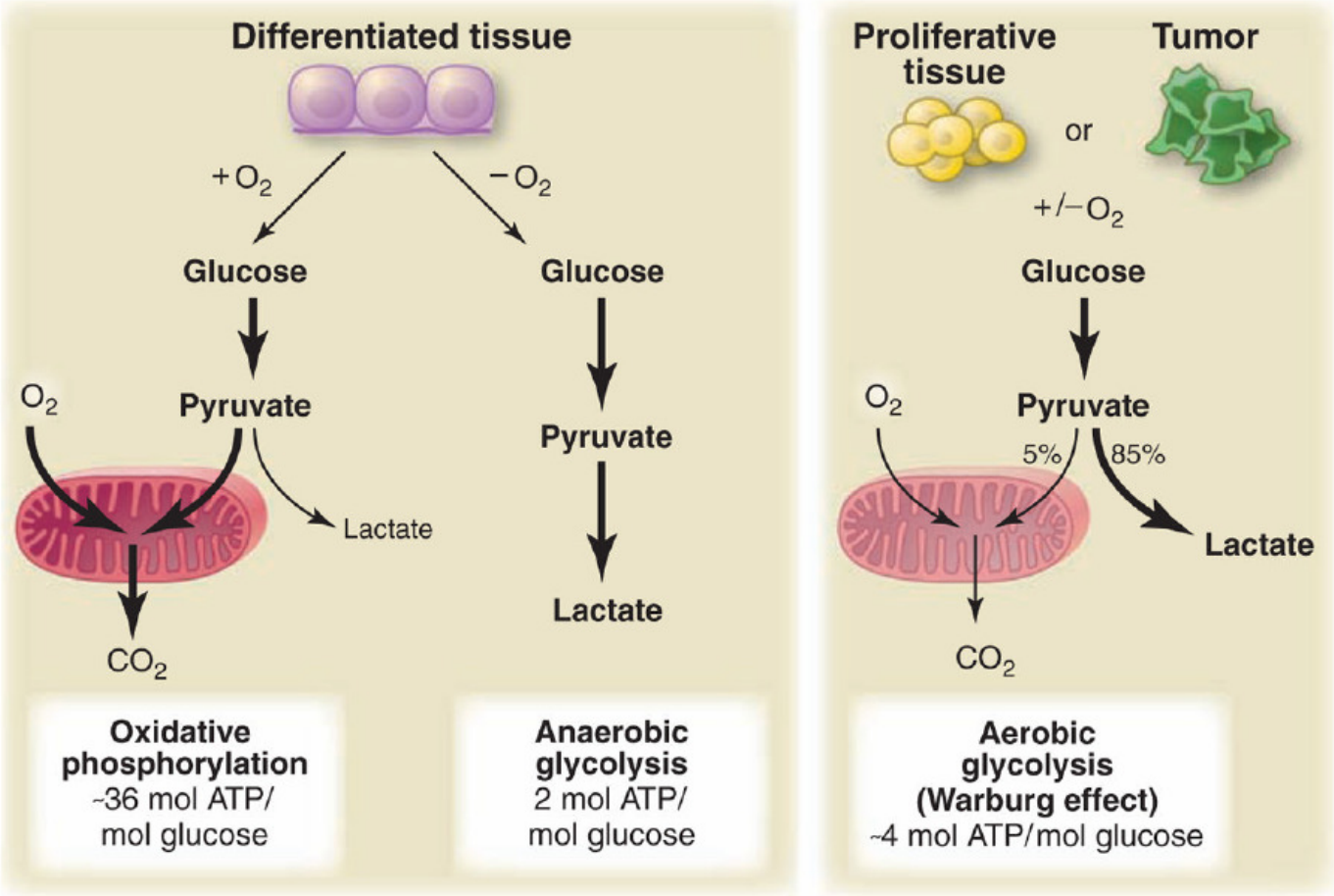
- Statins at low dose are thought to have anticancer properties by inhibiting tumor angiogenesis

Stevens et al, Neurology 2012

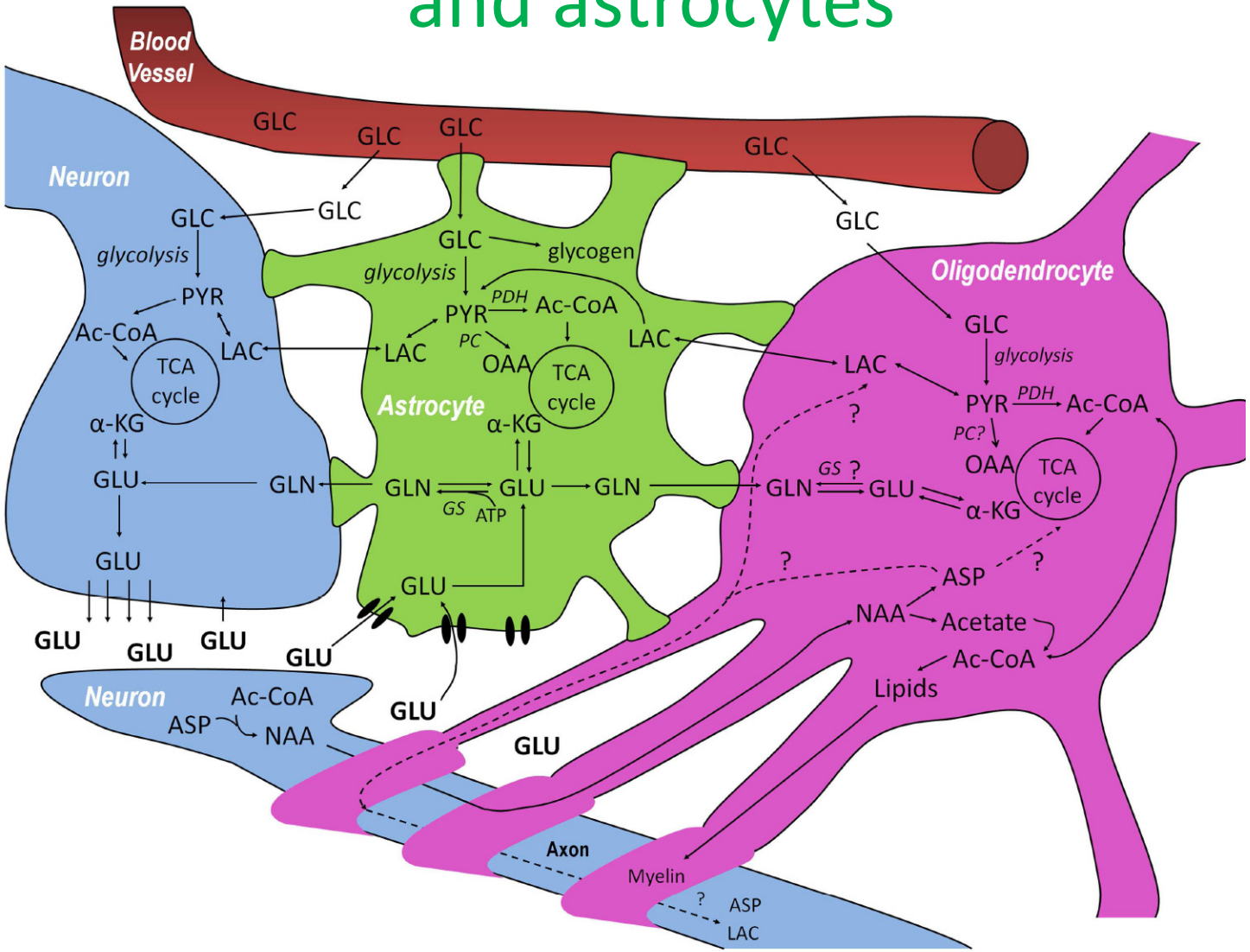
Components of the puzzle



Energetic sources in normal and malignant cells: the Warburg effect



Metabolic interactions between neurons and astrocytes



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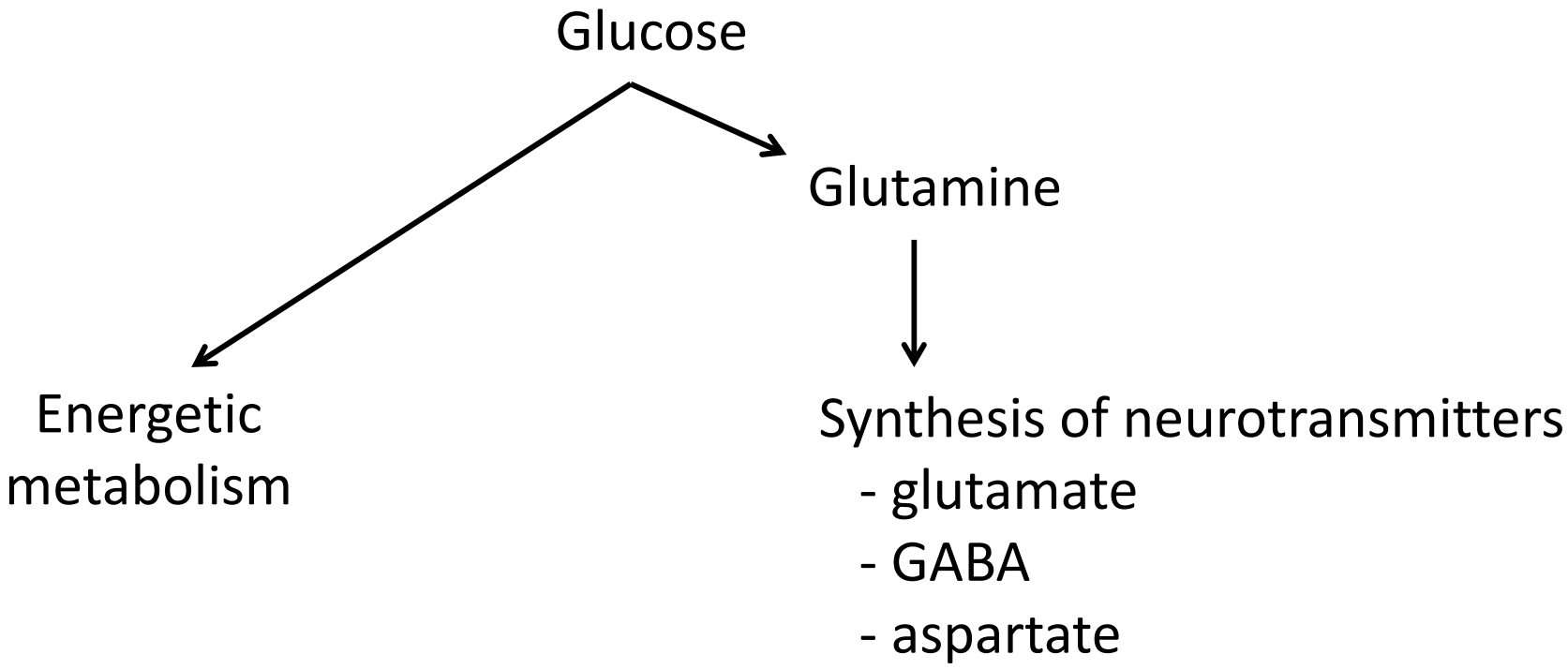
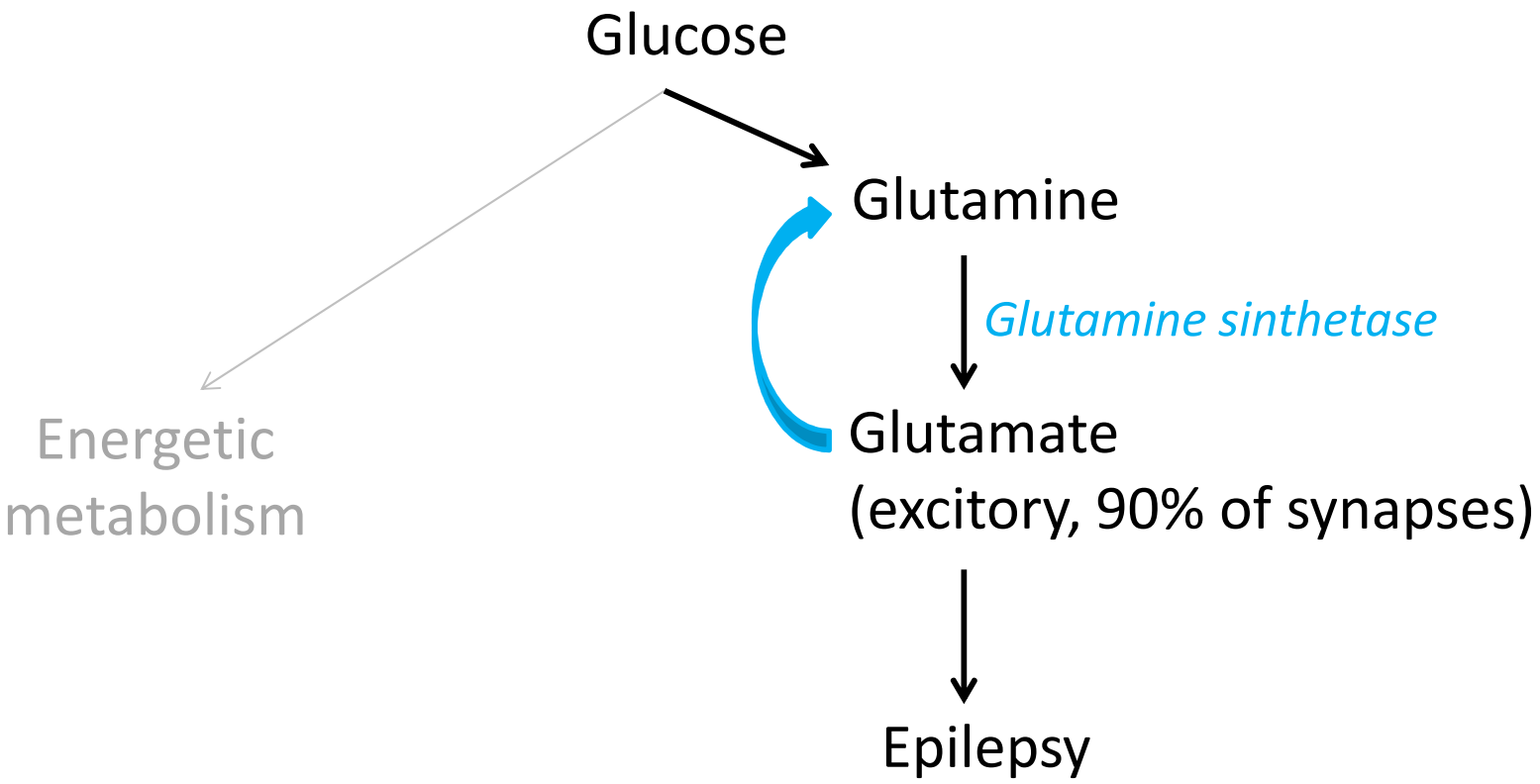


Glutamine, glutamate and epilepsy



Glutamine, glutamate and epilepsy

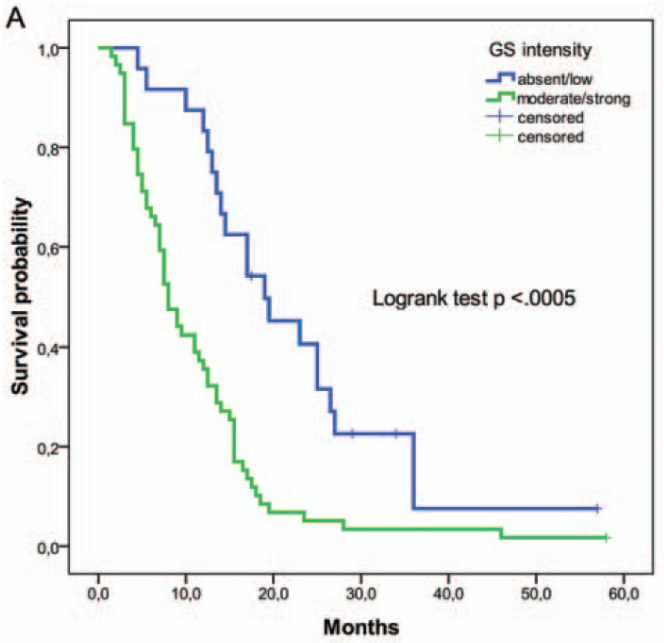
Glutamine synthetase expression as a valuable marker of epilepsy and longer survival in newly diagnosed glioblastoma multiforme

Anna Rosati, Pietro Luigi Poliani, Alice Todeschini, Manuela Cominelli, Daniela Medicina, Marco Cenzato, Edda Lucia Simoncini, Stefano Maria Magrini, Michela Buglione, Salvatore Grisanti, and Alessandro Padovani

Rosati et al, Neuro-Oncol 2013

Glutamine sinthetase in GBM

Immunostaining	No. (%) of Patients		
	Pts with epilepsy (n = 34)	Pts without epilepsy (n = 49)	*P*
GS expression			
Absent	7 (20.6)	4 (8.2)	
Present	27 (79.4)	45 (91.8)	.180
Intensity of staining			
Absent/low	17 (50)	7 (14)	<.0001
Moderate/strong	17 (50)	42 (86)	



Rosati et al, Neuro-Oncol 2013

Conclusions (1)

- There is no a standard second line chemotherapy for recurrent GBM;

- Nitrosourea-based chemotherapy is active (ORR, PFS);

- Bevacizumab is standard treatment in rGBM in USA but not in Europe; it increases PFS and radiological response; continued therapy offers prolonged response but resistance ultimately develops;

Conclusions (2)

- Combination therapy of Bevacizumab + Nitrosourea chemotherapy is promising

- There is a strong rationale to exploit the pathways of energetic metabolism as possible therapeutic targets