Terapia personalizată în tumorile cerebrale: promisiune eșuată sau promisiune amânată?

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Personalised medicine

1999, a short article entitled “New Era of Personalized Medicine: Targeting Drugs for Each Unique Genetic Profile,” appeared in *The Wall Street Journal* and here, the public was introduced to the term “personalized medicine” for the first time. A few months after publication of the article, it was reprinted in *The Oncologist*

(Langreth R, Waldholz M. New era of personalized medicine: Targeting drugs for each unique genetic profile. The Oncologist 1999;4:426–427)

Personalised medicine

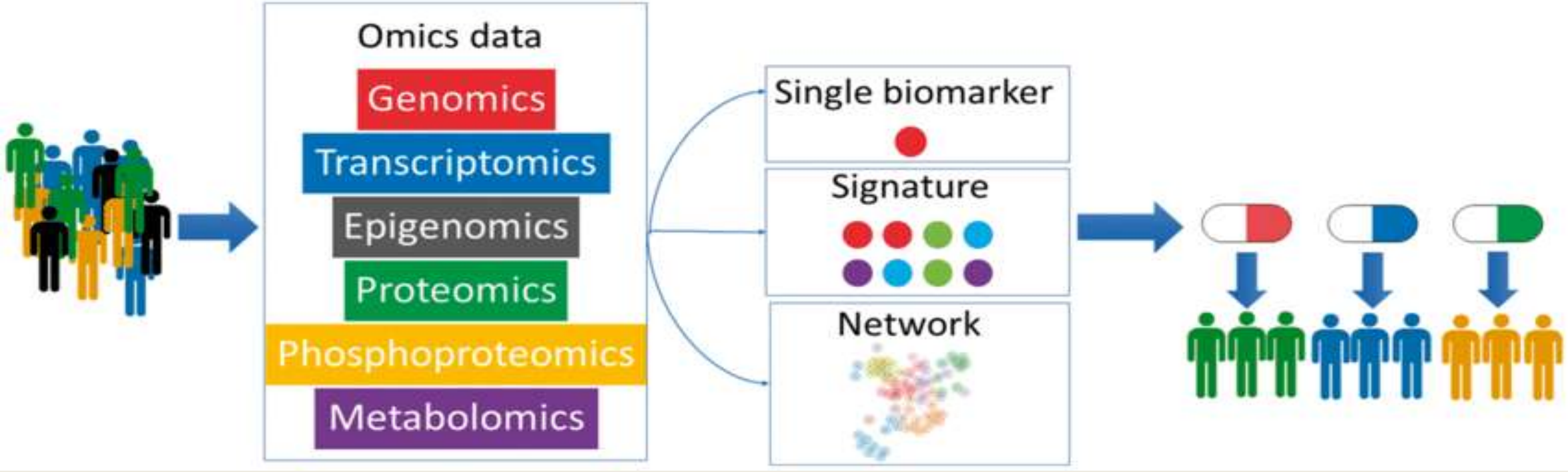
Personalised medicine aims at giving patients the best treatment according to their personal medical history, their physiological status and the molecular characteristics of their tumour.

(ESMO Patients Guide Series ESMO Personalised Medicine – Fact She)

Medicina Personalizată in bolile maligne

În cazul cancerului, pacienții oncologici sunt supusi unei testarări moleculare care ajută la identificarea biomarkerilor utilizati in stratificarea răspunsului la un anumit tip de tratament.

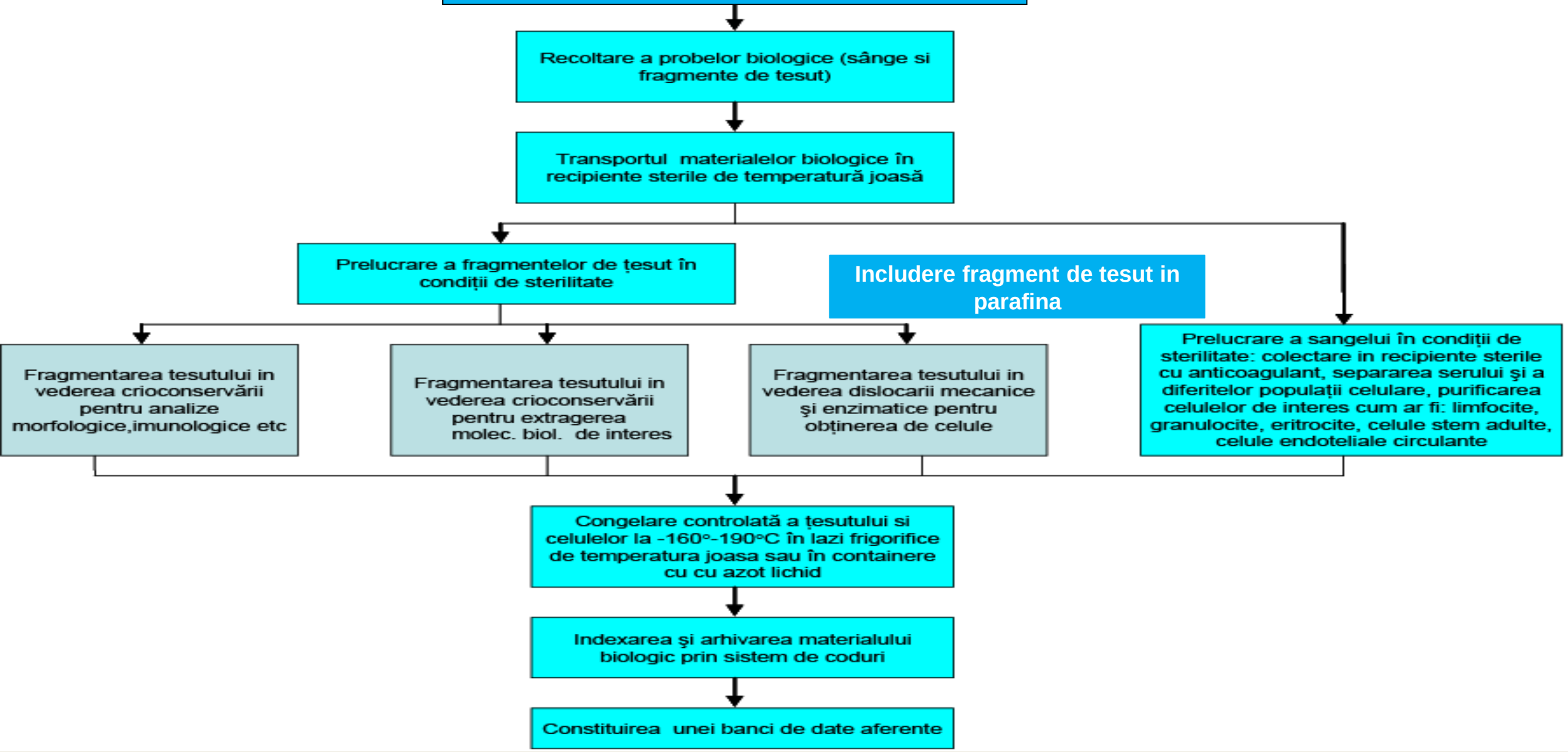
Aceste testarări moleculare au fost posibile datorită progreselor recente în tehnicile **Omics**.

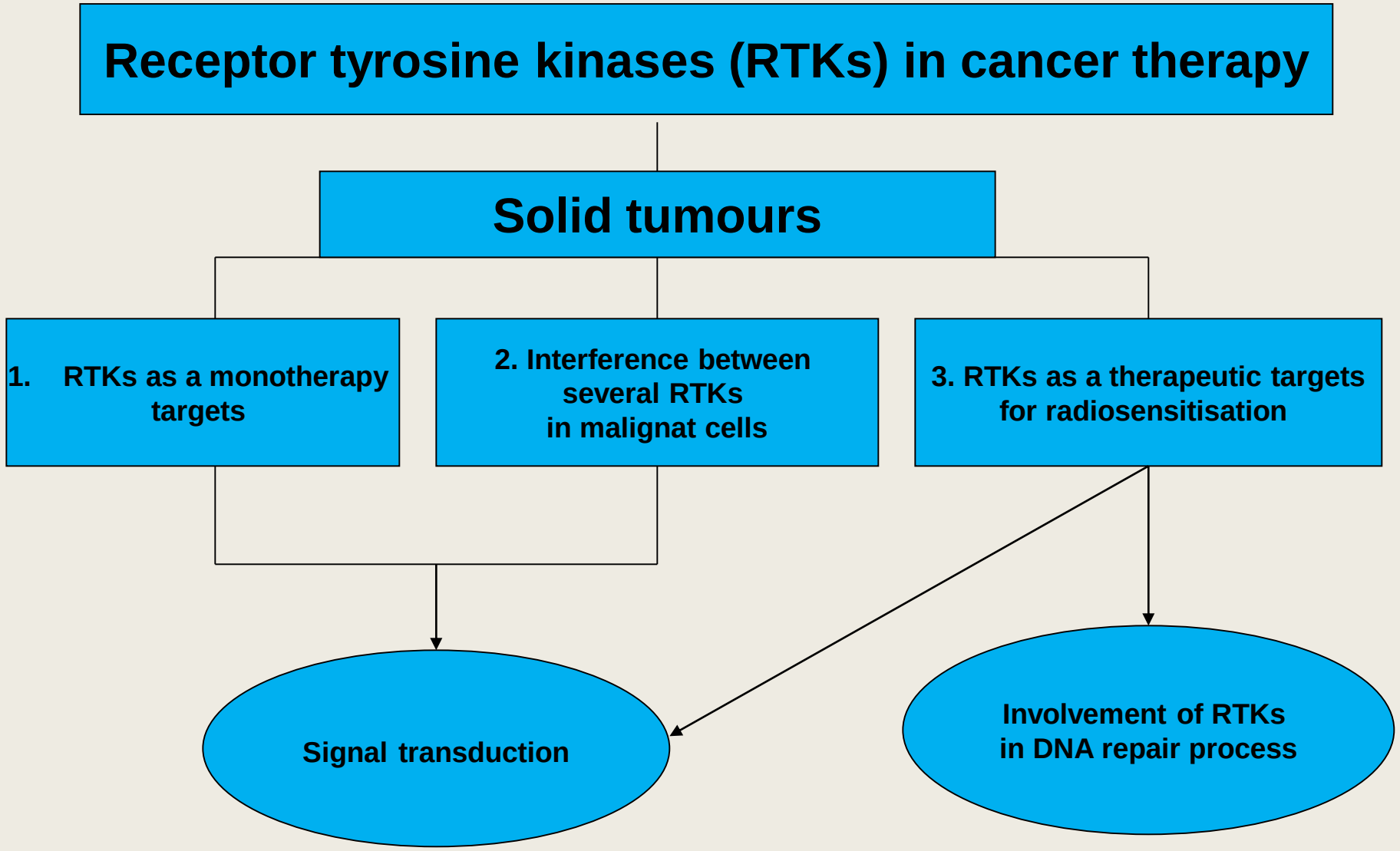


Medicina Personalizată se referă la o serie de resurse medicale integrate, stabilite pentru a răspunde nevoilor pacienților într-un mod **„holistic”.**

Tratament țintit pentru subgrupuri selectate de pacienți care prezintă acelasi tip de anomalii genetice/proteice/biochimice etc, considerate a fi cauza principală a bolii analizate.

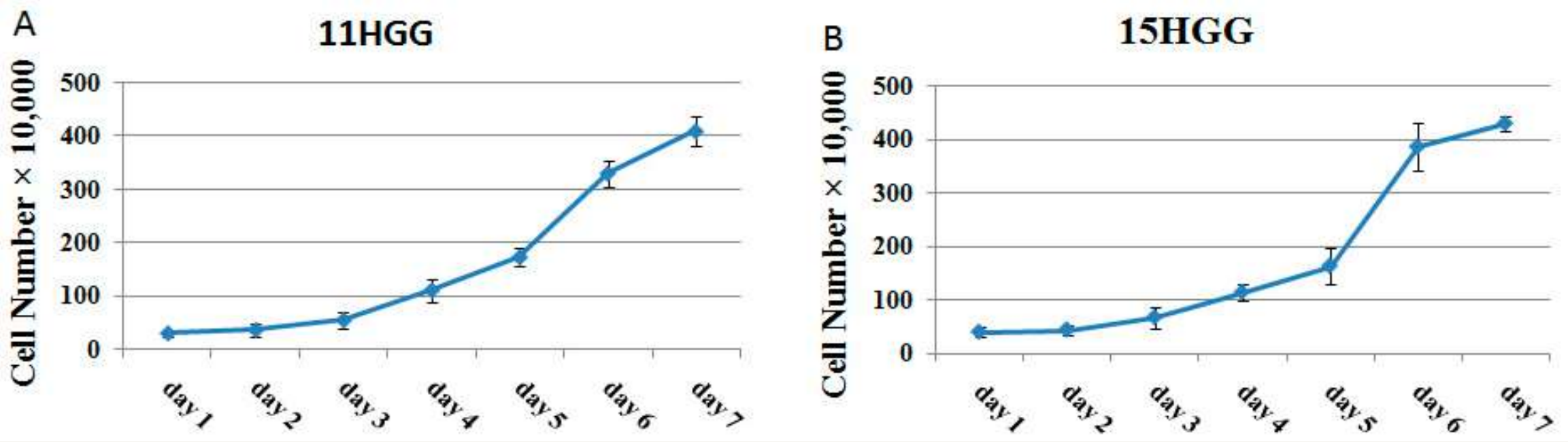
BANCA TUMORI CEREBRALE




Receptor tyrosine kinases (RTKs) in cancer therapy
Solid tumours
1. RTKs as a monotherapy targets
2. Interference between several RTKs in malignat cells
3. RTKs as a therapeutic targets for radiosensitisation
Signal transduction
Involvement of RTKs in DNA repair process

- **High Grade Glioma cell lines: 11HGG, 15 HGG,**
- **EGFR inhibitor: AG556;**
- **PDGFR inhibitor: AG1433,**
- **VEGFR inhibitor: SU1498**
- **Ionizing radiation, using a ^{137}Cs radiation source**

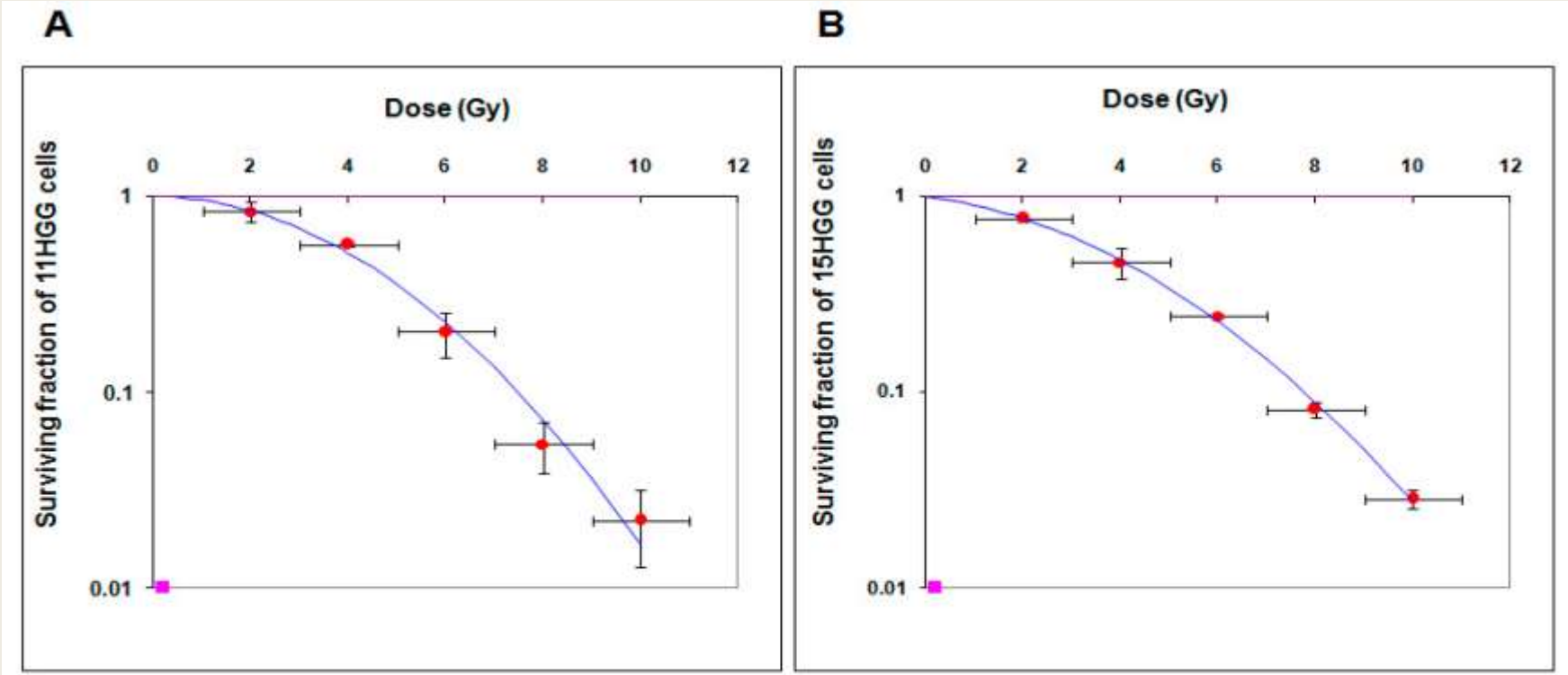
Growth curve of high grade glioma (HGG) cells



The doubling time = 45.5 h

The doubling time = 48.8 h

Radiosensitivity determination of high grade glioma (HGG) cells



Cell line	PE	SF2
11HGG	0.82 ±0.036	0.84 ±0.057
15HGG	0.70±0,035	0.77 ±0.098

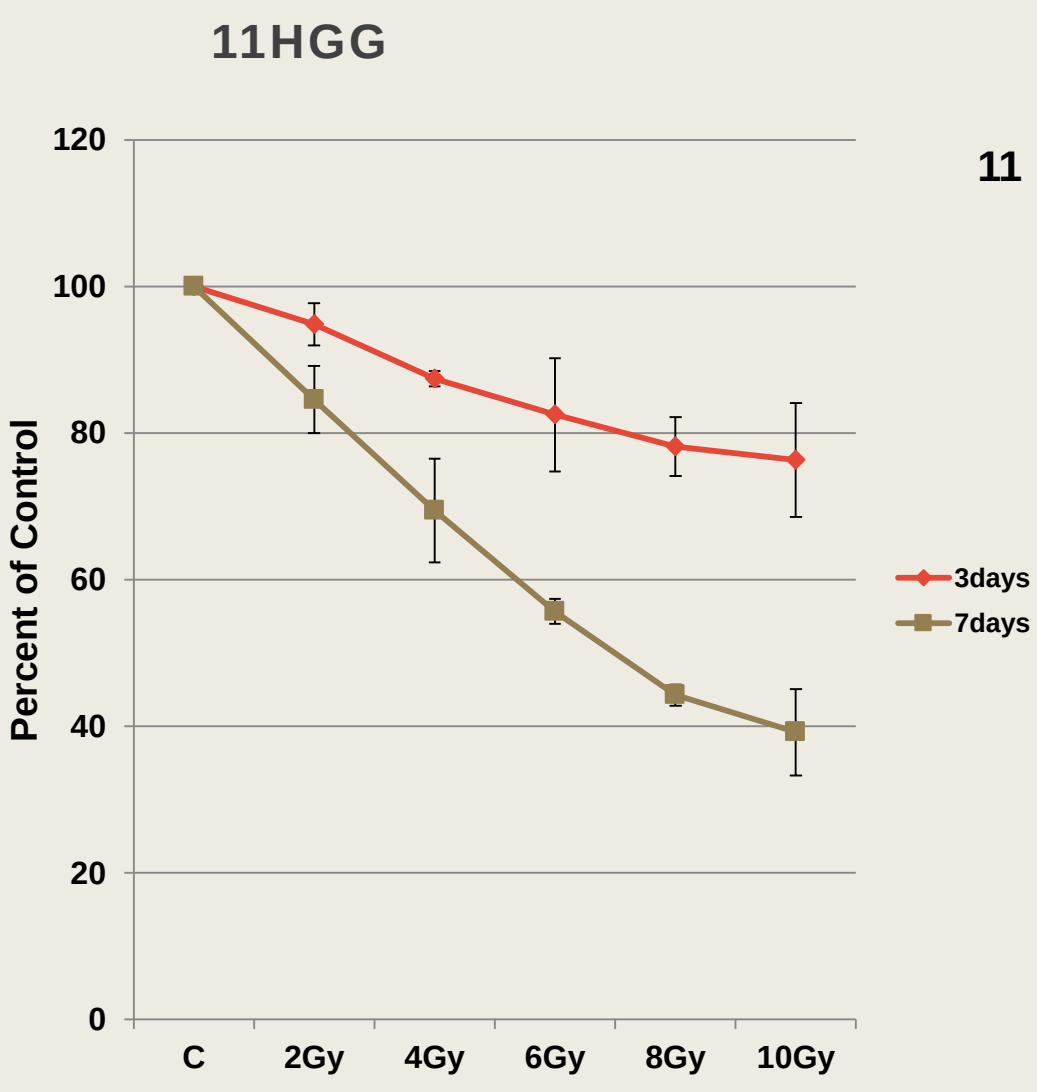
Experimental design

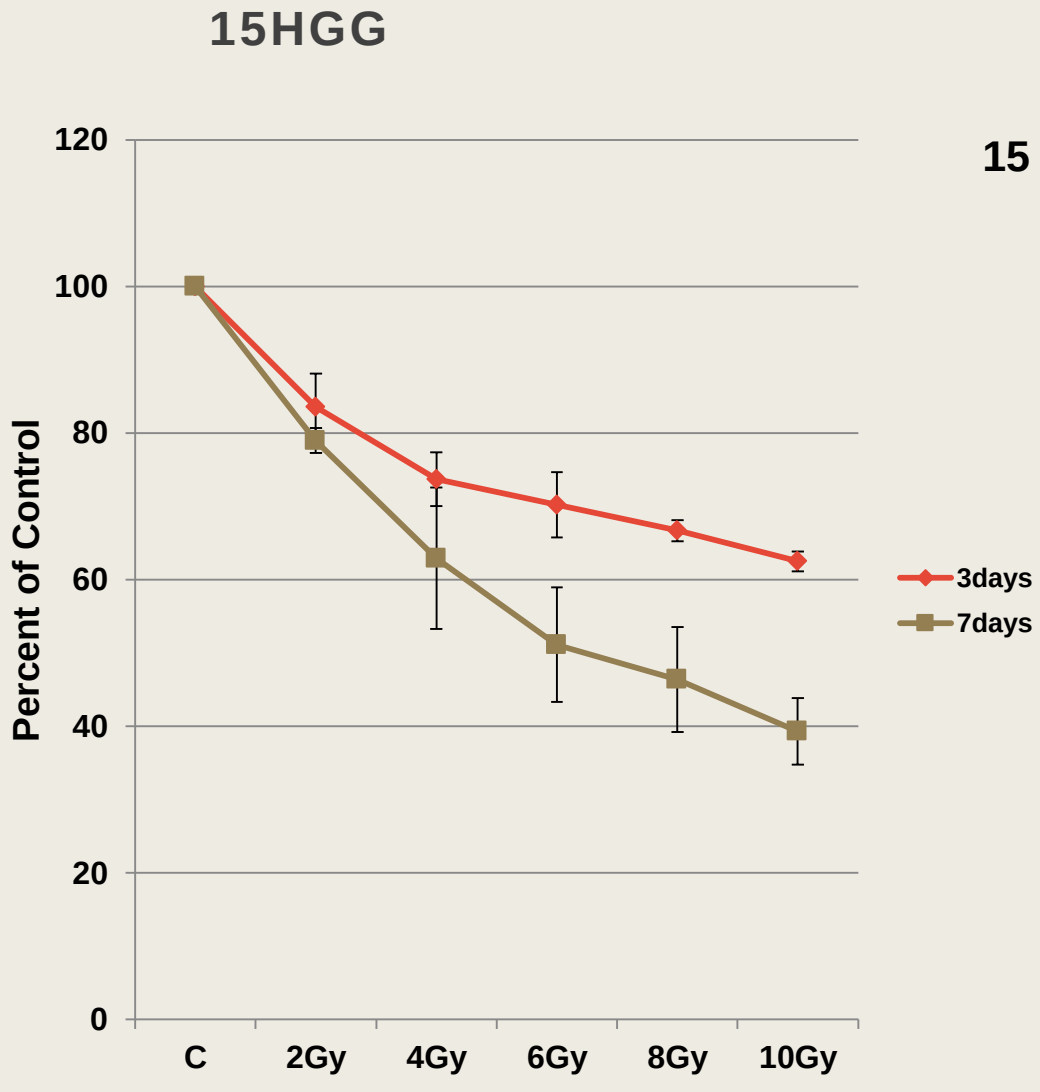
Cells were irradiated with a single-dose 2, 4, 6, 8 and 10 Gy. Cell proliferation was analysed after 3 and 7 days

The cells were treated with 10, 20 and 30 μM, TKIs and cell proliferation was analysed after 3 and 7 days

The cells were treated with combined RTKIs and gamma-radiation and Cell proliferation was analyzed after 3 and 7 days

Response of HGG cells to radiation treatment





The Influence of EGFR Inactivation on the Radiation Response in High Grade Glioma.Alexandru O, Purcaru SO, Tataranu LG, Lucan L, Castro J, Folcuţi C, Artene SA, Tuţă C, Dricu A.Int J Mol Sci. 2018 Jan 12;19(1):229. doi: 10.3390/ijms19010229.PMID

EGFR expression in HGG

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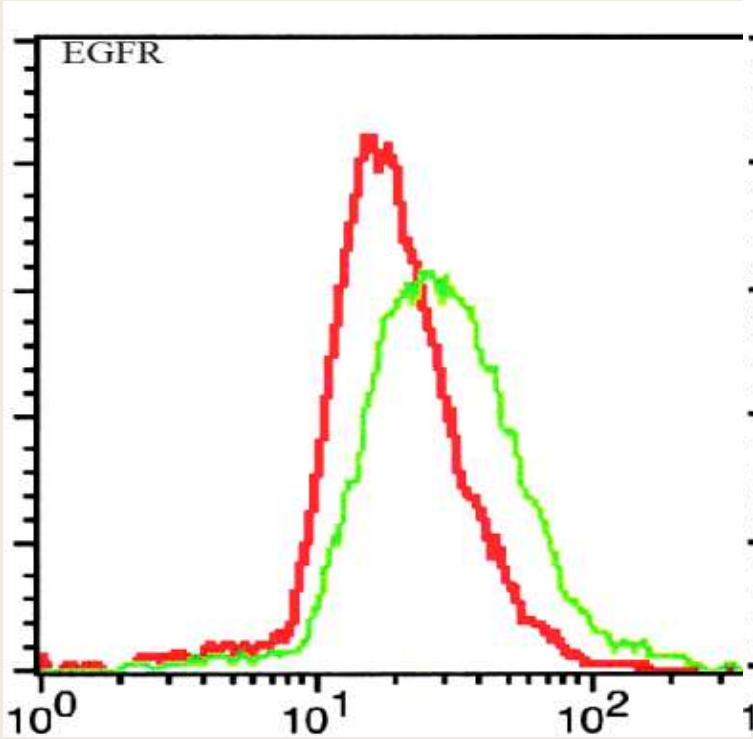

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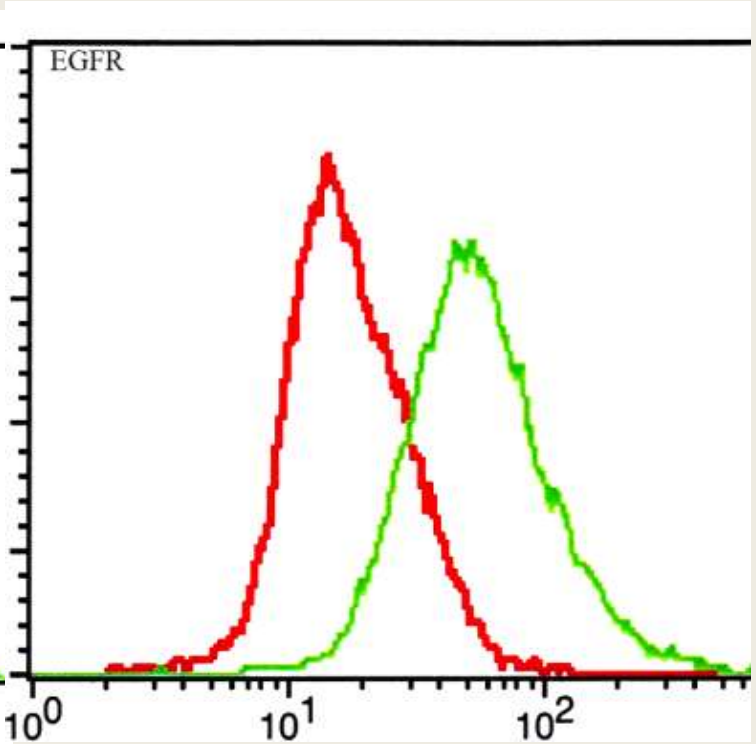
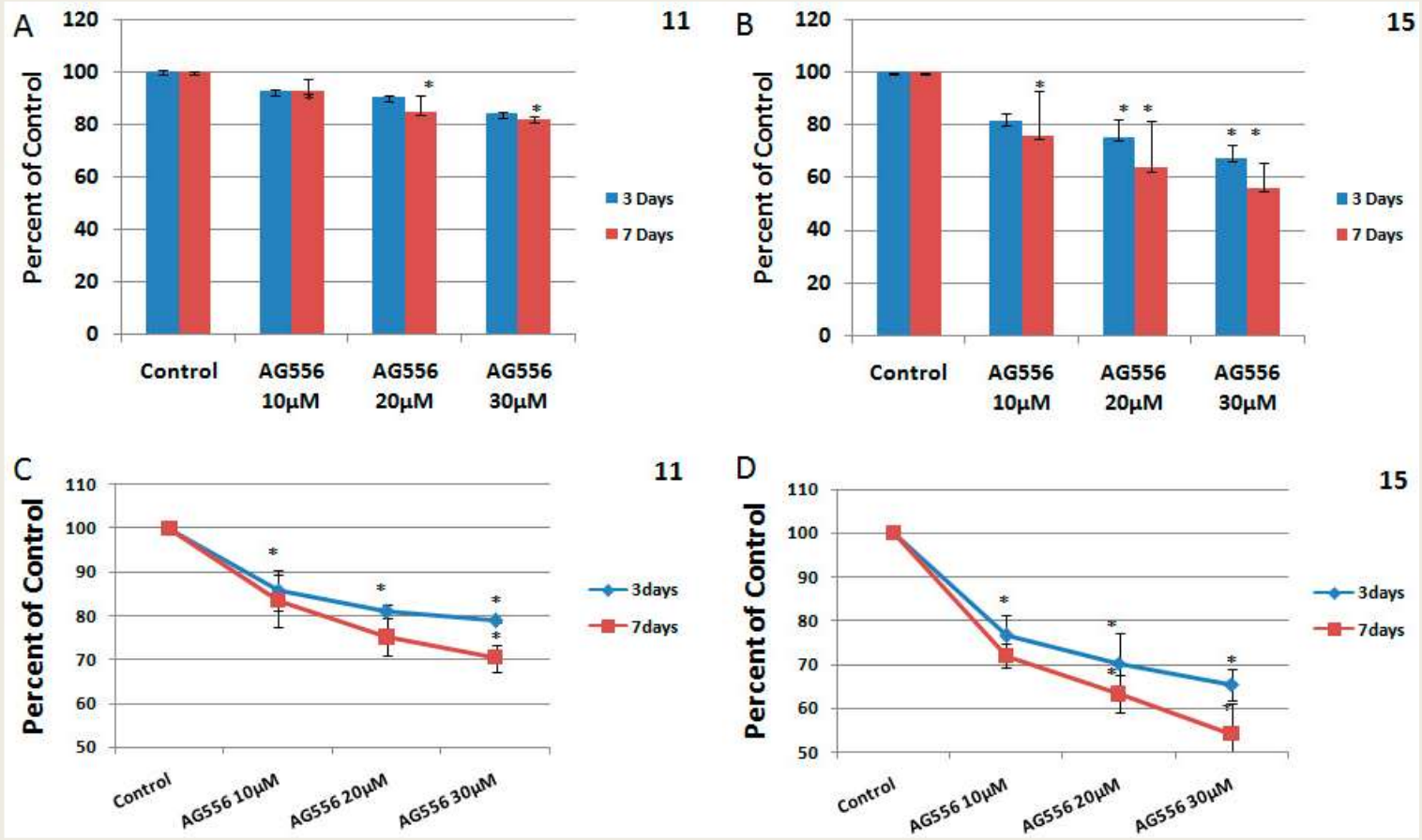


EGFR inhibition



11 HGG , 3 days

Rad (Gy)	AG556 (μM)	Predicted Survival	Observed Survival	Effect
2	10	0.9	0.8	SYN
	20	0.8	0.8	ADD
	30	0.8	0.8	ADD
4	10	0.9	0.8	SYN
	20	0.9	0.8	SYN
	30	0.8	0.8	ADD
6	10	0.9	0.8	SYN
	20	0.8	0.8	ADD
	30	0.8	0.7	SYN
8	10	0.8	0.8	ADD
	20	0.8	0.7	SYN
	30	0.8	0.6	SYN
10	10	0.8	0.9	SUB
	20	0.8	0.8	ADD
	30	0.8	0.6	SYN

11 HGG , 7 days

Rad (Gy)	AG556 (μM)	Predicted Survival	Observed Survival	Effect
2	10	0.6	0.6	ADD
	20	0.6	0.7	SUB
	30	0.6	0.7	SUB
4	10	0.6	0.6	ADD
	20	0.6	0.6	ADD
	30	0.6	0.6	ADD
6	10	0.5	0.5	ADD
	20	0.5	0.5	ADD
	30	0.5	0.5	ADD
8	10	0.5	0.5	ADD
	20	0.5	0.5	ADD
	30	0.5	0.40	SYN
10	10	0.4	0.5	SUB
	20	0.4	0.5	SUB
	30	0.4	0.5	SUB

30% of the combinations were synergic
50% were additive and
20% were subadditive

15 HGG , 3 days

Rad (Gy)	AG556 (μM)	Predicted Survival	Observed Survival	Effect
2	10	0.7	0.7	ADD
	20	0.6	0.7	SUB
	30	0.6	0.6	ADD
4	10	0.6	0.7	SUB
	20	0.5	0.7	SUB
	30	0.5	0.7	SUB
6	10	0.5	0.7	SUB
	20	0.5	0.6	SUB
	30	0.5	0.6	SUB
8	10	0.5	0.7	SUB
	20	0.5	0.6	SUB
	30	0.5	0.6	SUB
10	10	0.6	0.7	SUB
	20	0.5	0.6	SUB
	30	0.5	0.6	SUB

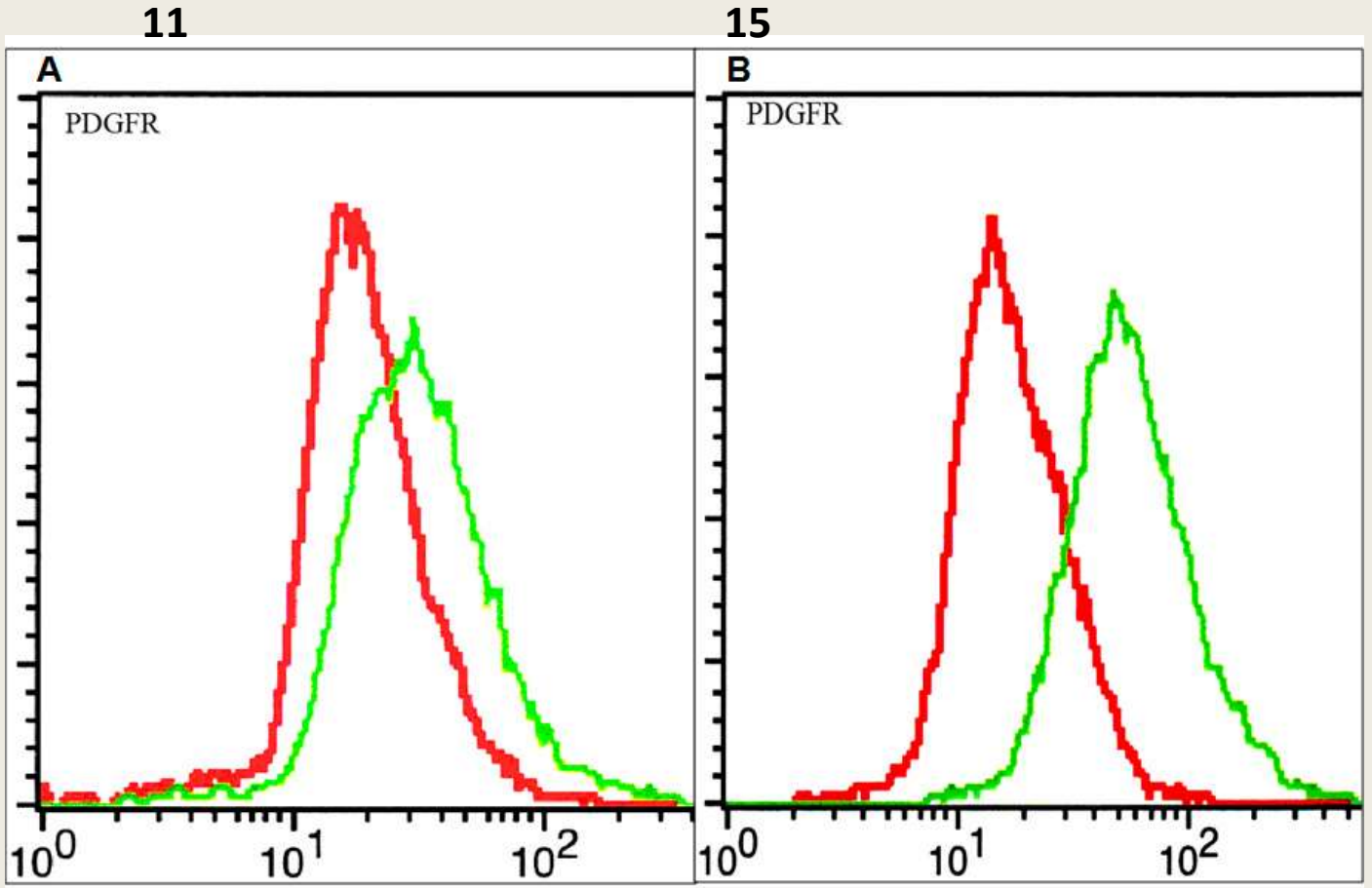
15 HGG , 7 days

Rad (Gy)	AG556 (μM)	Predicted Survival	Observed Survival	Effect
2	10	0.6	0.7	SUB
	20	0.5	0.6	SUB
	30	0.5	0.5	ADD
4	10	0.4	0.5	SUB
	20	0.4	0.5	SUB
	30	0.3	0.4	SUB
6	10	0.4	0.5	SUB
	20	0.4	0.5	SUB
	30	0.3	0.4	SUB
8	10	0.4	0.4	ADD
	20	0.3	0.4	SUB
	30	0.3	0.4	SUB
10	10	0.3	0.4	SUB
	20	0.3	0.4	SUB
	30	0.3	0.4	SUB

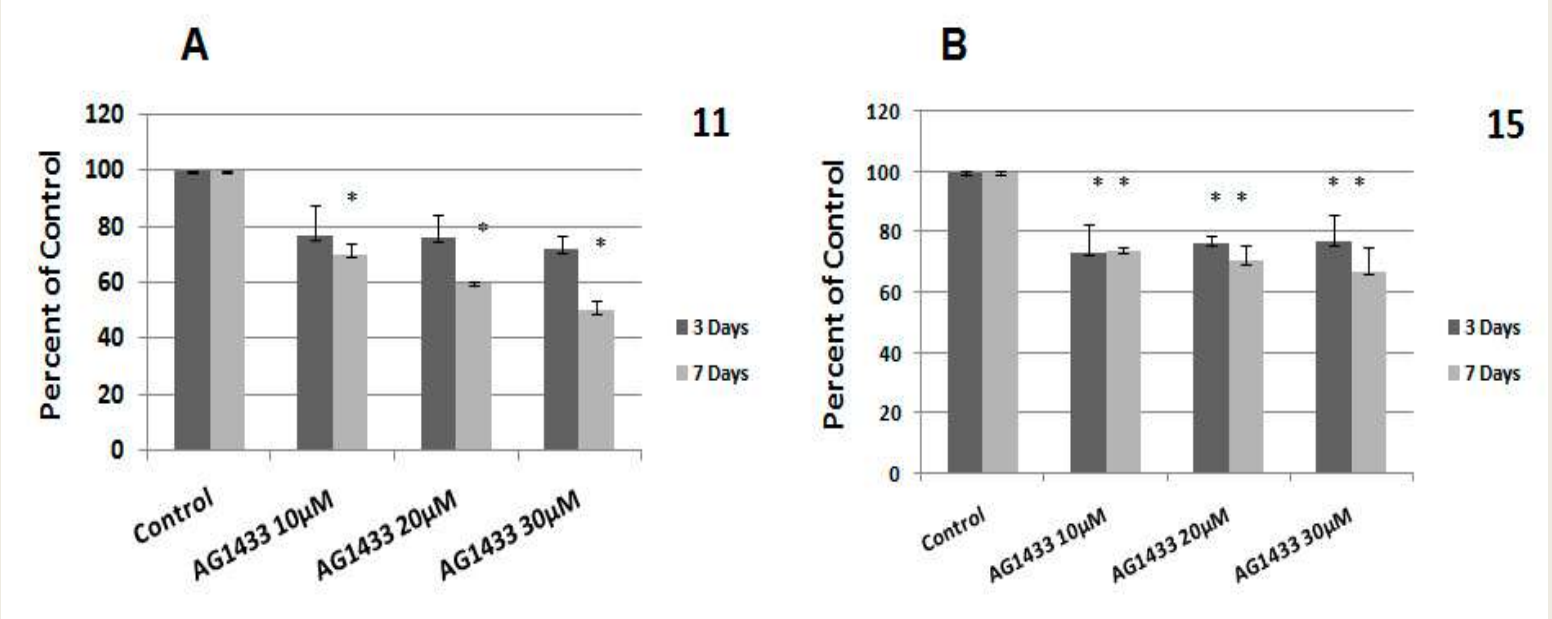
0% of the combinations were synergic
13% were additive and
87% were subadditive

Platelet-Derived Growth Factor Receptor and Ionizing Radiation in High Grade Glioma Cell Lines. Alexandru O, Sevastre AS, Castro J, Artene SA, Tache DE, Purcaru OS, Sfredel V, Tataranu LG, Dricu A. Int J Mol Sci. 2019 Sep 20;20(19):4663. doi: 10.3390/ijms20194663

PDGFR expression in HGG cells



PDGFR inhibition



The interaction between combined treatment in 11 HGG cells

50% of the combinations had an additive effect and a synergistic effect was not achieved in any of the attempted combinations.

Rad (Gy)	AG1433 (μM)	Days after the Treatment	Predicted Survival	Observed Survival	Effect
2	10	3	0.7	0.7	ADD
		7	0.4	0.5	SUB
	20	3	0.7	0.7	ADD
		7	0.3	0.4	SUB
	30	3	0.7	0.7	ADD
		7	0.3	0.4	SUB
4	10	3	0.7	0.7	ADD
		7	0.4	0.4	ADD
	20	3	0.7	0.7	ADD
		7	0.3	0.4	SUB
	30	3	0.7	0.7	ADD
		7	0.3	0.4	SUB
6	10	3	0.7	0.7	ADD
		7	0.3	0.4	SUB
	20	3	0.7	0.8	SUB
		7	0.3	0.4	SUB
	30	3	0.7	0.8	SUB
		7	0.2	0.4	SUB
8	10	3	0.7	0.7	ADD
		7	0.3	0.3	ADD
	20	3	0.7	0.7	ADD
		7	0.3	0.3	ADD
	30	3	0.6	0.8	SUB
		7	0.2	0.4	SUB
10	10	3	0.7	0.7	ADD
		7	0.3	0.3	ADD
	20	3	0.7	0.7	ADD
		7	0.2	0.3	SUB
	30	3	0.6	0.8	SUB
		7	0.2	0.4	SUB

93% of the combinations resulted in a sub-additive effect and only 7% had an additive effect . We did not obtain a synergistic effect in any of the attempted combinations.

The interaction between combined treatment in 15 HGG cells

Rad (Gy)	AG1433 (μM)	Days after the Treatment	Predicted Survival	Observed Survival	Effect
2	10	3	0.6	0.7	SUB
		7	0.5	0.6	SUB
	20	3	0.6	0.7	SUB
		7	0.5	0.6	SUB
	30	3	0.6	0.7	SUB
		7	0.5	0.6	SUB
4	10	3	0.5	0.6	SUB
		7	0.4	0.4	ADD
	20	3	0,5	0.7	SUB
		7	0.4	0.5	SUB
	30	3	0.5	0.8	SUB
		7	0.4	0.5	SUB
6	10	3	0.5	0.7	SUB
		7	0.4	0.4	ADD
	20	3	0.6	0.7	SUB
		7	0.4	0.5	SUB
	30	3	0.6	0.8	SUB
		7	0.4	0.6	SUB
8	10	3	0.5	0.6	SUB
		7	0.3	0.4	SUB
	20	3	0.5	0.7	SUB
		7	0.3	0.7	SUB
	30	3	0.5	0.6	SUB
		7	0.3	0.5	SUB
10	10	3	0.5	0.6	SUB
		7	0.3	0.4	SUB
	20	3	0.5	0.8	SUB
		7	0.3	0.5	SUB
	30	3	0.5	0.7	SUB
		7	0.3	0.5	SUB

Targeting VEGFR for high grade glioma radiosensitization

VEGFR expression in HGG cells

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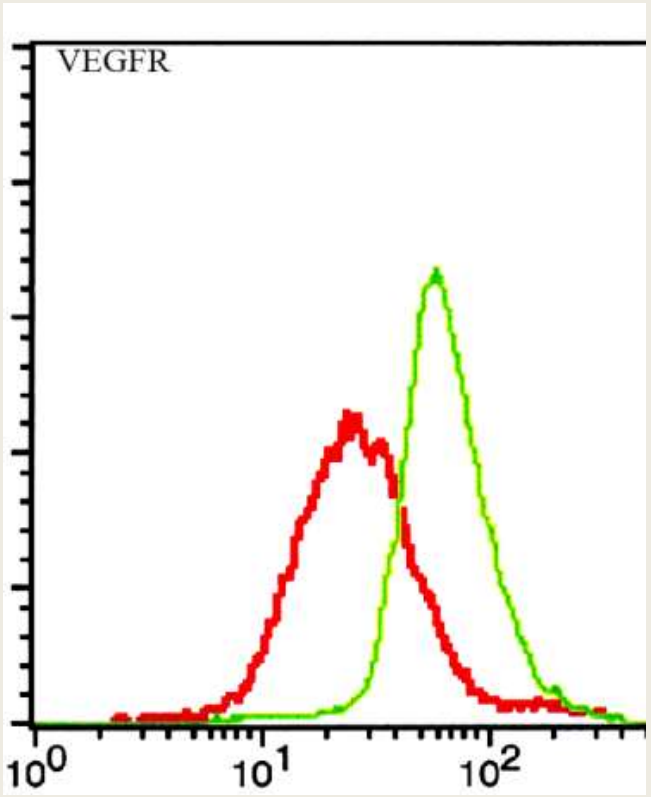

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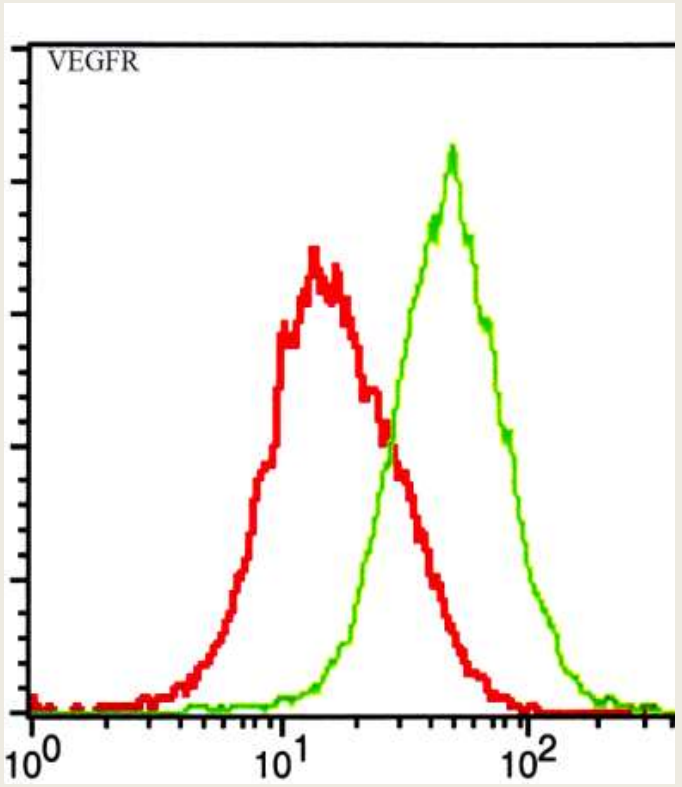
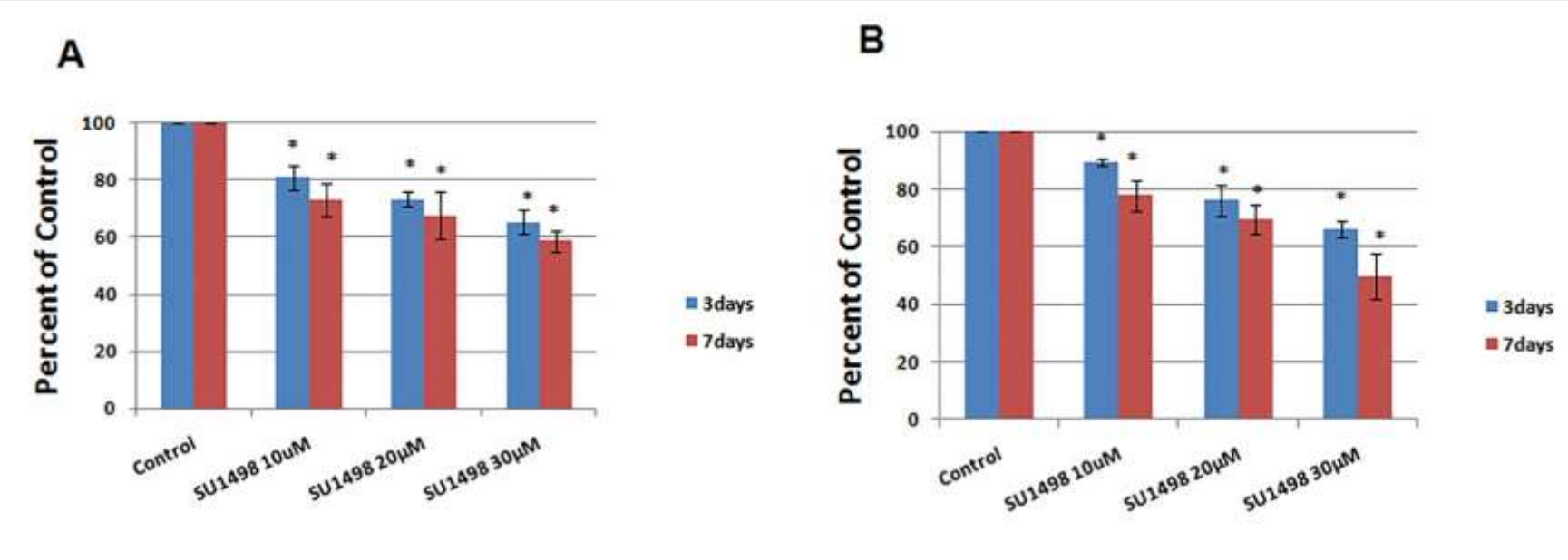


VEGFR inhibition



11 HGG , 3 days

Rad (Gy)	SU1498 (μM)	Predicted survival	Observed survival	Effect
2	10	0.78	0.8	SUB
	20	0.86	0.81	SYN
	30	0.71	0.77	SUB
4	10	0.8	0.78	SYN
	20	0.89	0.76	SYN
	30	0.74	0.71	SYN
6	10	0.77	0.78	SUB
	20	0.85	0.76	SYN
	30	0.7	0.71	SUB
8	10	0.76	0.8	SUB
	20	0.84	0.77	SYN
	30	0.7	0.71	SUB
10	10	0.74	0.78	SUB
	20	0.82	0.82	ADD
	30	0.68	0.69	SUB

11 HGG , 7 days

Rad (Gy)	SU1498 (μM)	Predicted survival	Observed survival	Effect
2	10	0.48	0.57	SUB
	20	0.46	0.58	SUB
	30	0.48	0.62	SUB
4	10	0.43	0.44	SUB
	20	0.41	0.47	SUB
	30	0.43	0.46	SUB
6	10	0.36	0.38	SUB
	20	0.35	0.41	SUB
	30	0.36	0.37	SUB
8	10	0.39	0.33	SYN
	20	0.38	0.31	SYN
	30	0.39	0.25	SYN
10	10	0.3	0.28	SYN
	20	0.29	0.28	SYN
	30	0.3	0.25	SYN

40% of the combinations were synergic
3% were additive and
57% were subadditive

15 HGG , 3 days

Rad (Gy)	SU1498 (μM)	Predicted survival	Observed survival	Effect
2	10	0.54	0.69	SUB
	20	0.49	0.66	SUB
	30	0.48	0.65	SUB
4	10	0.5	0.69	SUB
	20	0.46	0.65	SUB
	30	0.45	0.64	SUB
6	10	0.51	0.6	SUB
	20	0.46	0.62	SUB
	30	0.46	0.61	SUB
8	10	0.5	0.61	SUB
	20	0.46	0.61	SUB
	30	0.45	0.67	SUB
10	10	0.48	0.7	SUB
	20	0.44	0.61	SUB
	30	0.43	0.58	SUB

15 HGG , 7 days

Rad (Gy)	SU1498 (μM)	Predicted survival	Observed survival	Effect
2	10	0.54	0.55	SUB
	20	0.52	0.56	SUB
	30	0.59	0.58	SUB
4	10	0.42	0.37	SYN
	20	0.41	0.39	SYN
	30	0.47	0.39	SYN
6	10	0.38	0.37	SYN
	20	0.37	0.37	ADD
	30	0.42	0.31	SYN
8	10	0.33	0.32	SYN
	20	0.32	0.31	SYN
	30	0.36	0.31	SYN
10	10	0.31	0.29	SYN
	20	0.3	0.35	SUB
	30	0.34	0.28	SYN

33% of the combinations were synergic
3% were additive and
64% were subadditive

Conclusions

11 HGG	15 HGG
23% SYN	11% SYN
34% ADD	8% ADD
42 % SUBADD	81 % SUBADD

11HGG more sensitive to combined treatment than 15HGG cell line

11HGG more radioresistant than 15HGG

15HGG express more RTKs on the cell surface compared to11HGG

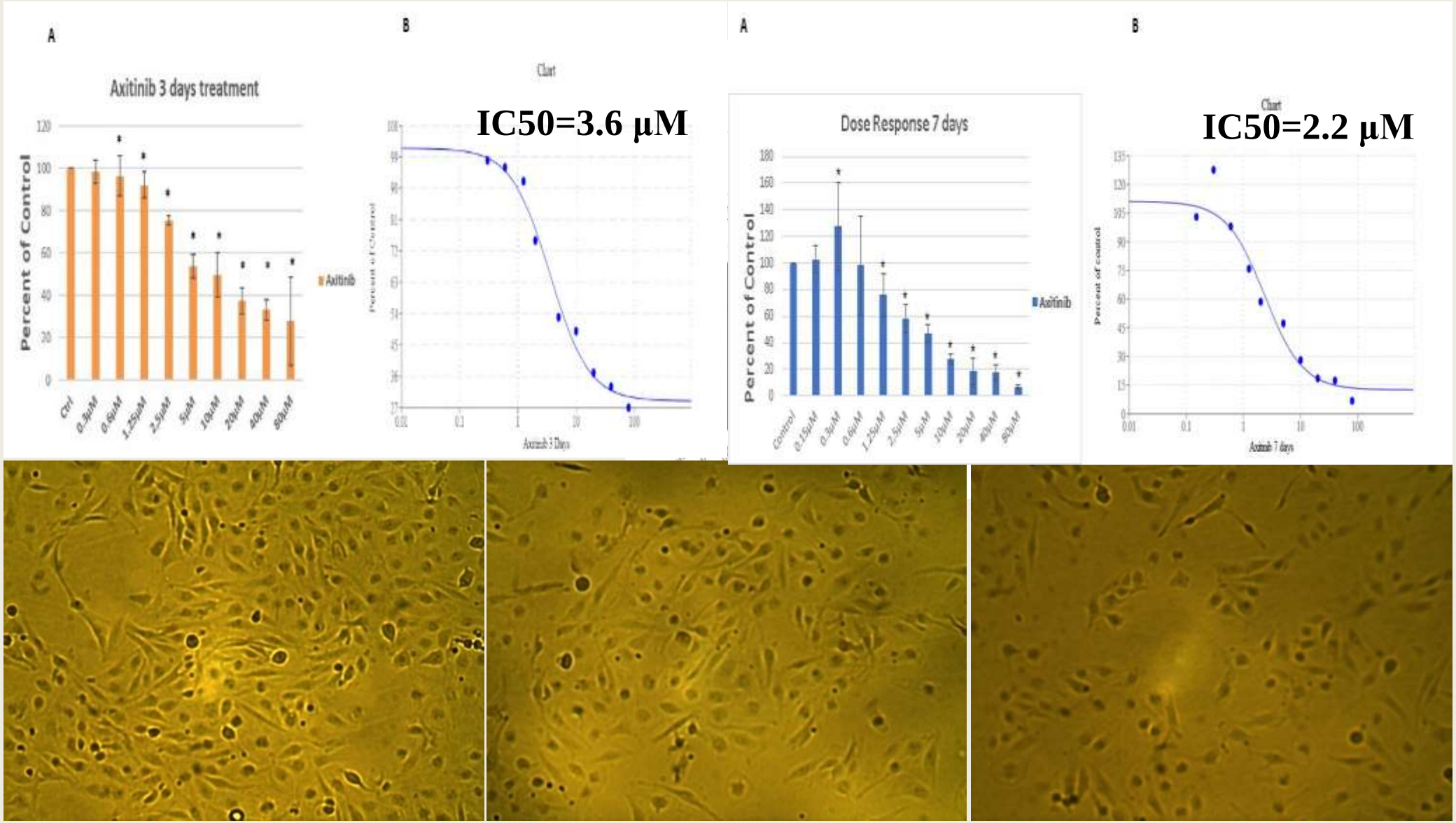
Two HGG cell lines can behave completely different when exposed to similar combinations of treatment, underscoring the importance of just how important PERSONALIZED TREATMENTS might prove to be in the near future, for unpredictable cancers such as malignant gliomas.

AXITINIB, SORAFENIB Treartment

AXITINIB - brand name **Inlyta,** developed by Pfizer
-It is a small molecule tyrosine kinase inhibitor for VEGFR 1–3, c-KIT and PDGFR
-Approval: 2012 for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.
-This has been described clinically for patients with a wide variety of advanced solid malignancies, including lung, and thyroid etc.

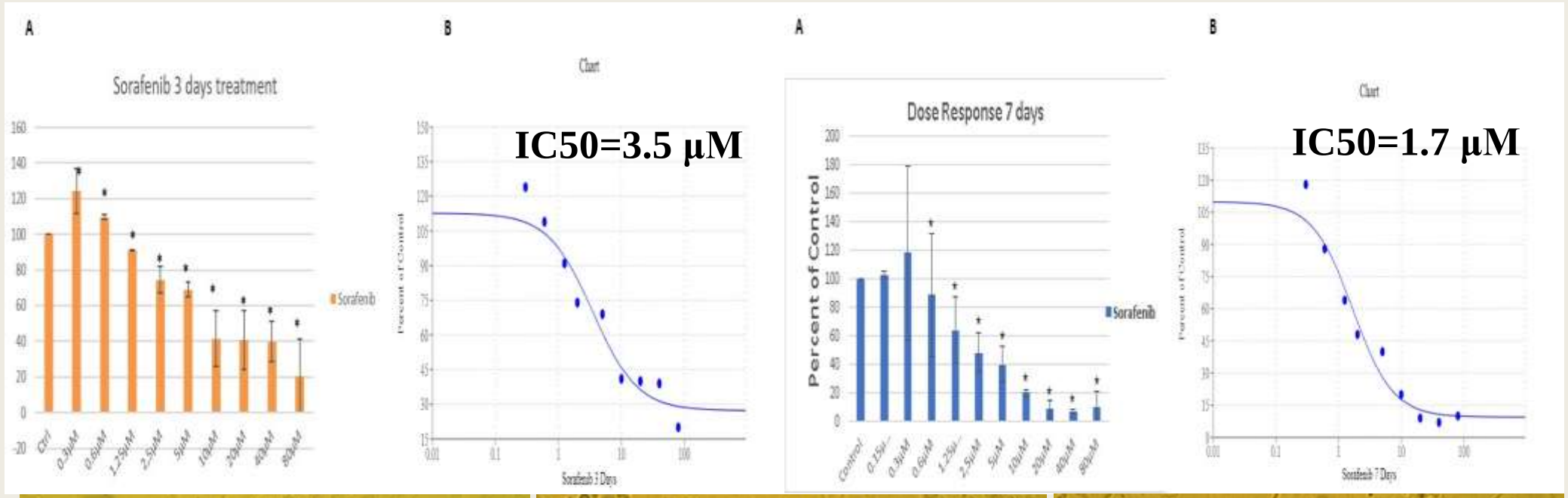
SORAFENIB - brand name **Nexavar-** developed by Bayer Pharma AG
-It is a protein kinase inhibitor with activity against VEGFR, PDGFR and RAF kinases.
-Approved for the treatment of primary kidney cancer (advanced renal cell carcinoma),
-Is also indicated as a treatment for advanced primary liver cancer (hepatocellular carcinoma), FLT3-ITD positive Acute myeloid leukemia (AML) and radioactive iodine resistant advanced thyroid carcinoma.

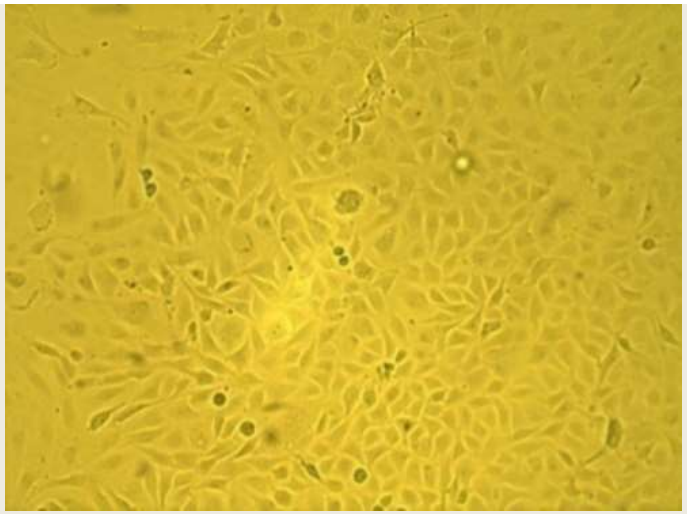
The effect of axitinib on GB1B proliferation

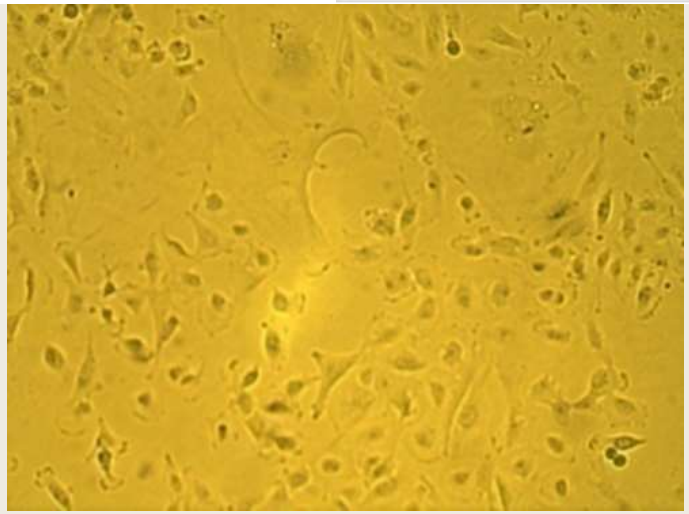


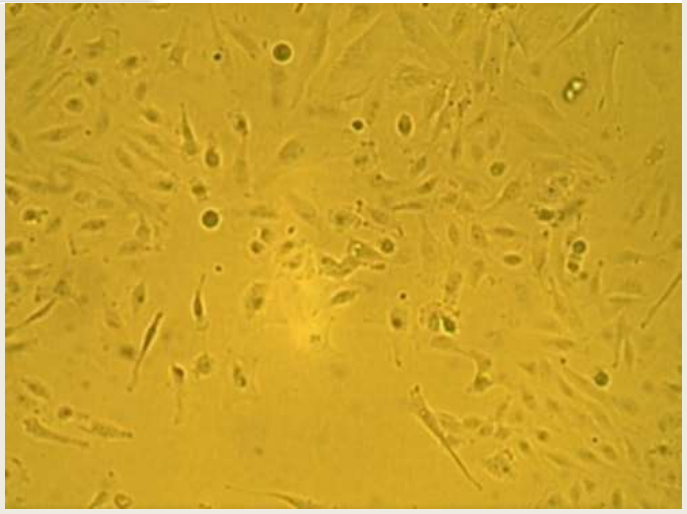
Control **3 days** **7 days**

The effect of sorafenib on GB1B proliferation









Control **3 days** **7 days**

The Challenges in Fulfilling the Promise of Precision Oncology

In, article by Langreth R et al, published in The Oncologist 1999 were listed some problems that limited the successful application of the personalized therapy:

-the poor efficacy of the existent medications
-disease heterogeneity and genetic variability
-technical limitations of molecular tests
-biomarker discovery and drug development are a challenging

The Challenges in Fulfilling the Promise of Precision Oncology

Limited knowledge-Gaps in research

-Understanding and addressing mechanisms of resistance

-Lack of effective drugs against most genomic aberrations

-a better use of omics data, artificial intelligence and machine learning is required to accelerate the implementation of a new medical practice

The Challenges in Fulfilling the Promise of Precision Oncology

Insufficient technologies

-technical limitations of molecular tests
-biomarker discovery and drug development are a challenging

long process with many obstacles
-bio-informatics and computational approaches for analyses of omics data are limited

The Challenges in Fulfilling the Promise of Precision Oncology

Very expensive

- Targeted therapies are quite costly in comparison to their traditional counterparts, and existing health insurance models have not been structured to reimburse for these types of treatments.