

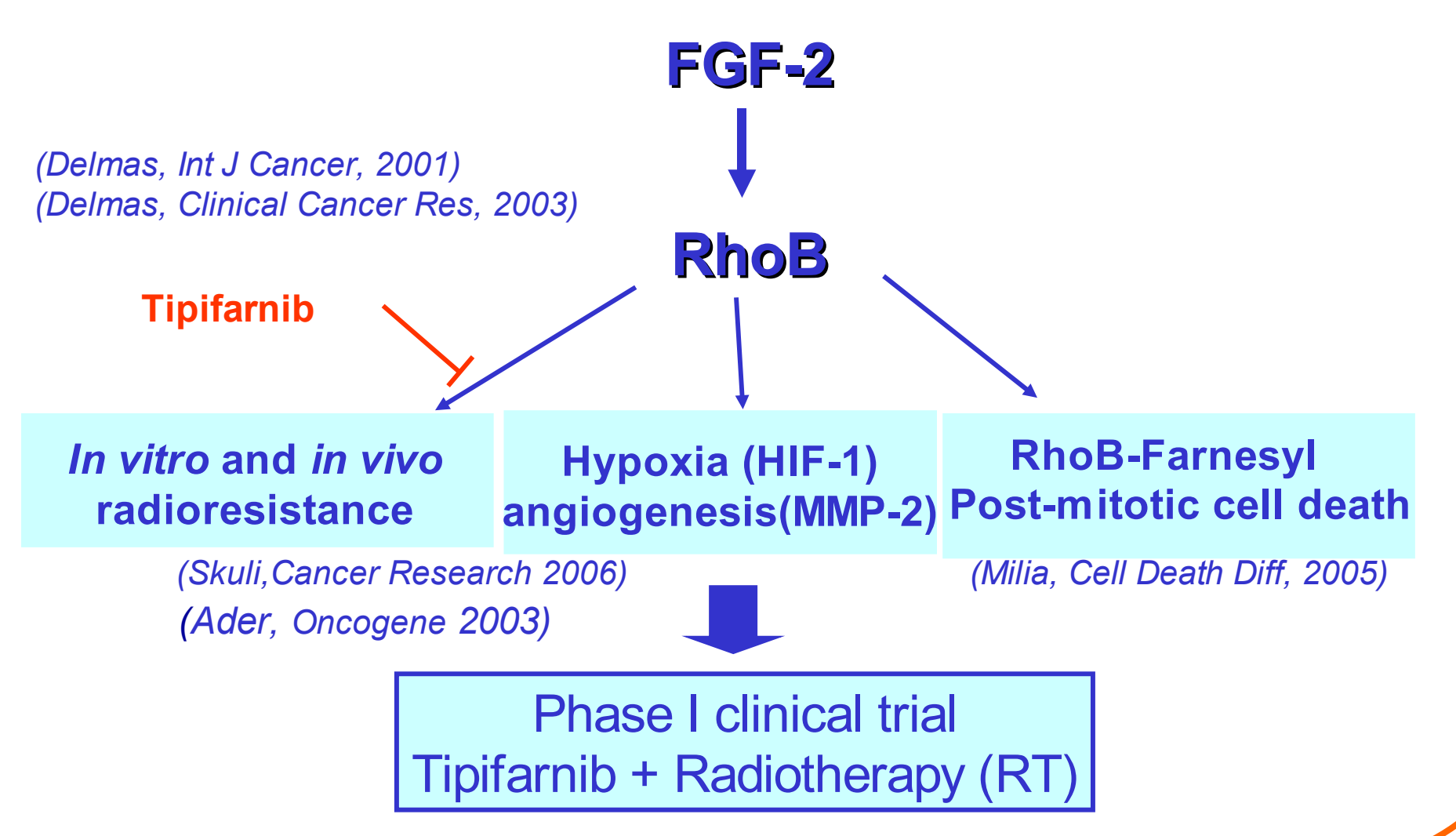
Phase I Trial Of The Farnesyltransferase Inhibitor Tipifarnib (R115777) In Combination With Radiotherapy In Patients With Newly Diagnosed Glioblastoma

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#1122

Introduction

Previous results from our laboratory



Patient evaluations

Toxicity

- Baseline evaluations were performed within 7 days from study entry and included a complete medical history, physical examination, determination of performance status, complete blood count, serum chemistries
- Patients were assessed for adverse events and toxicity, complete blood count and chemistry were checked weekly during radiotherapy and cycle 1 of the adjuvant treatment, then every two weeks thereafter

Dose reductions

Start Dose	First reduction	Second reduction
100 mg bid	100 mg od	not allowed
100+200 mg	100 mg bid	100 mg od
200 mg bid	100+200 mg	100 mg bid
300 mg bid	200 mg bid	100+200 mg

Response evaluation

- Baseline tumor measurements were taken within 7 days from entry of study by MRI
- MRI evaluation every 2 and then 3 months (volume)
- Spectro-MRI study (see Poster Laprie et al.)

- Study 2** (6 patients) : Only minor toxicities have been observed in these conditions (table 2). No increase in the radiation-induced toxicities was observed for any patient.

Table 1. Patient demographic and clinical characteristics

Characteristic	All patients	Study1	Study2
Total number of patients	13	7	6
Gender			
Male	8	4	4
Female	5	3	2
Age (years)			
Median	55	62	46
Range	28-74	53-74	28-71
ECOG performance status			
0	6	1	5
1	3	2	1
2	4	4	0
Extent of resection			
Biopsy	8	4	4
Incomplete resection	4	3	1
Gross total resection	1	0	1
Recursive partitioning analysis Class			
III	3	0	3
IV	4	3	1
V	6	4	2
Anti epileptic drugs used			
EIAED	2	2	0
Non-EIAED	6	4	2

Abbreviations : EIAED, enzyme-inducing antiepileptic drug ; ECOG, Eastern Cooperative Oncology Group

Table 2. Non DLT toxicities by dose level

Toxicities	Dose Level 1			Dose level 2	
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2
Anorexia				1	1
Arthralgia		1			
Constipation		2			
Diarrhea					1
Dry skin	1				
Dysgeusia	1	1		1	
Fatigue	2	1	1	1	1
Glaucoma	1				
Hepatotoxicities		2			
Mouth dryness	1				
Myalgia		1			
Nausea	1				2
Oedema	1				
Rash	2	2			
Stomatitis	1	1		1	1

Abbreviations : DLT, Dose limiting toxicity

Patients and design

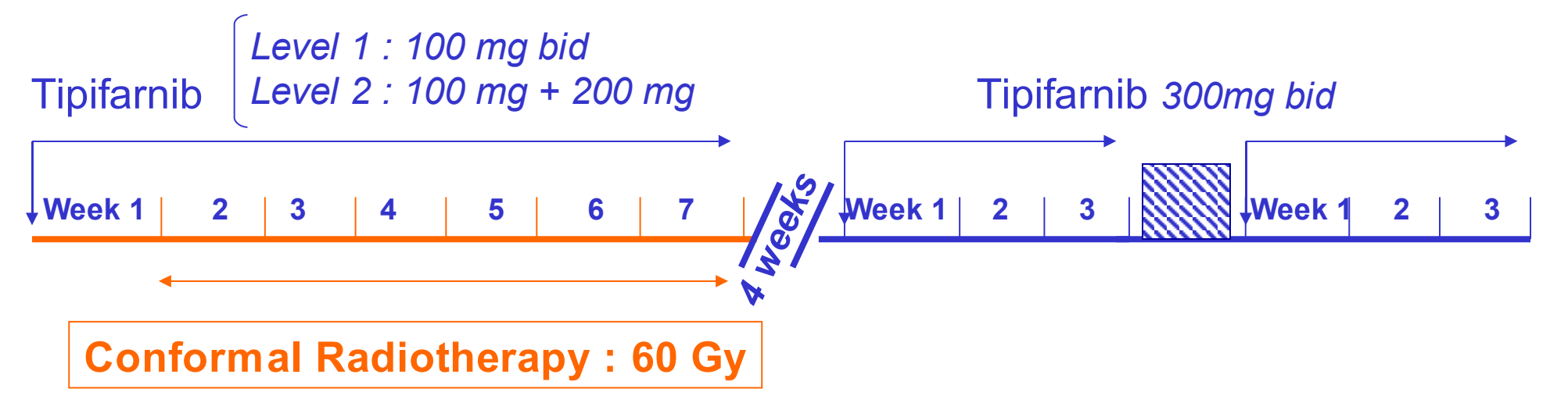
Purpose :

- To test feasibility and tolerability of oral administration of **tipifarnib** bid and **radiotherapy** in patients with newly diagnosed glioblastoma
- The primary endpoint was MTD.
- Secondary endpoints included efficacy outcomes of best objective response, time to progression, and overall survival (OS).

Inclusion criteria

- Glioblastoma
- Age > 18 years
- Untreated, except biopsy or surgery (subtotal or growth total resection)
- Patients enrolled at least 1 week, but no more than 6 weeks, after biopsy or surgery.

Study 1



- Tipifarnib dose escalation during radiotherapy : 100mg increase/level – Starting dose 100 mg bid (level 1)
- No dose escalation for the adjuvant treatment
- Use of non- enzyme-inducible anti-epileptic drug (non-EIAED) was encouraged

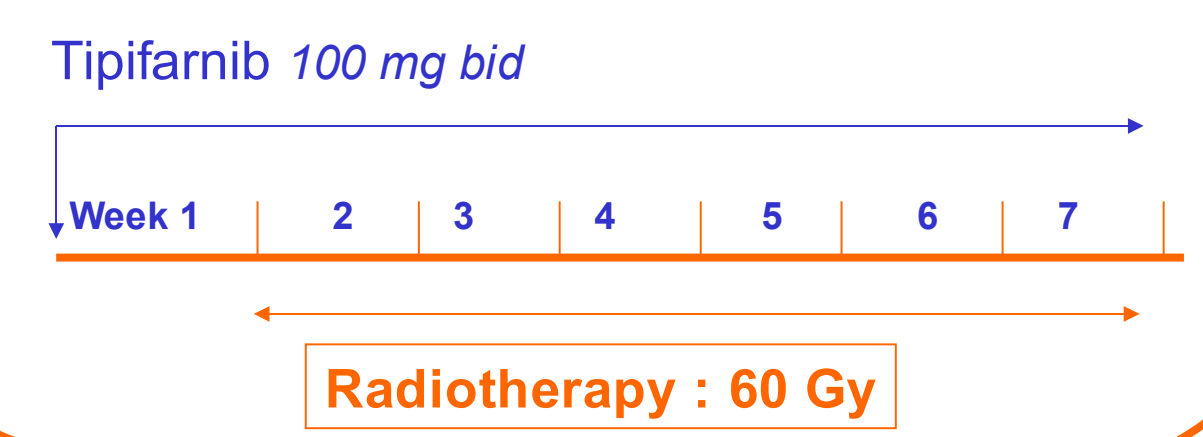
Results

Toxicity

- No DLT on dose level 1 (3 patients)
- On dose level 2 (300 mg daily) one patient died before the beginning of the radiotherapy. **3 patients experienced dose limiting toxicities** :
- One **sudden death** in the sixth week of concomitant treatment
- Two **acute pneumonitis** during the second and sixth week of concomitant treatment, one associated with a grade 4 neutropenia, a grade 2 thrombocytopenia, and a grade 3 phlebitis, the other one associated with a **bilateral pulmonary embolism** leading to death few days after DLT occurred.
- One of the three patients included at dose level 1, experienced a non febrile pneumonitis during the fourth cycle of adjuvant tipifarnib treatment

MTD : 300 mg daily

Study 2 (6 patients)



Responses for evaluable patients

- Study 1 :**
 - 2 stable diseases (26 % and 39 % reduction of the tumor volume during 6 and 4 months after the end of the concomitant treatment)
 - 1 progression 2 months after the end of the concomitant treatment
- Study 2 :**
 - 2 partial responses : 54 % and 64 % decrease of the irradiated tumor volume during 4 months and 18 months (date of analysis)
 - 2 stable diseases during 4 months after completion of the treatment
 - 2 progressions 2 months after the end of the concomitant treatment

Survival

- Median overall survival :
 - ✓9 months in study 1 including patients dead from toxicity
 - ✓11.5 months in study 2
 - ✓4 evaluable patients belonging to class V RPA : 10.91 months

Conclusion

Concomitant administration of tipifarnib and standard radiotherapy for newly diagnosed glioblastoma :

- MTD tipifarnib : 300 mg daily**
- Recommended dose for phase II : 100 mg bid**
- No increase of the radiation-induced toxicity
- Encouraging results
- Phase II :** tipifarnib 100 mg bid concomitant with standard radiotherapy with study of biological markers of response