#2021

FINAL RESULTS FROM THE DOSE-ESCALATION STAGE OF A PHASE 1/2 TRIAL OF TPI 287, A BRAIN PENETRABLE MICROTUBULE INHIBITOR, PLUS BEVACIZUMAB IN PATIENTS WITH RECURRENT GLIOBLASTOMA

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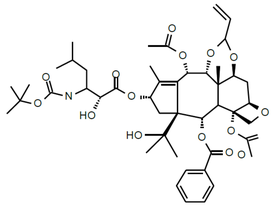
Background

TPI 287 is a novel anti-microtubule (MT) agent that readily penetrates the blood-brain barrier. Here we report final results from the Phase 1 portion of CB-017, a multi-center, dose-escalation Phase 1/2 trial designed to determine the maximum tolerated dose (MTD) and efficacy of TPI 287 in combination with bevacizumab (BEV) in patients with BEV-naïve recurrent glioblastoma (GBM).



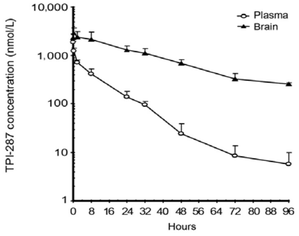
TPI 287

Third-generation taxane

Evades inactivation by P-glycoprotein

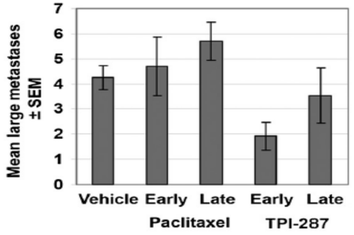
Readily penetrates the BBB

Well defined mechanism of action



PK analysis after single injection of 20 mg/kg TPI 287 in mouse

Fitzgerald et al., *Molecular Cancer Therapeutics* (2012)



Large brain metastases formation in mice 28 days after left ventricular 231-BR cell inoculation. TPI 287 or paclitaxel dosed 18 mg/kg 3x, either on days 3, 7, 11 ("early") or 18, 22, and 26 ("late") inoculation.

CB-017 Methods

- Treatment administered in 6 week cycles: TPI 287 (fixed IV dose every 3 weeks; 140-220 mg/m2 for Phase 1 stage) plus BEV (10 mg/kg every 2 weeks).
- MRI obtained at the start of every cycle. Response assessed via RANO.
- Median PFS and OS calculated based on Kaplan-Meier analysis
- Key eligibility criteria

  Histologically proven GBM

  Disease progression following TMZ and radiation

  Up to two prior recurrences

  No prior anti-angiogenic therapy

  KPS ≥ 70

Demographics

Median age	55 yrs (41, 76)
Male	65%
Karnovsky performance status (KPS)	
100	4 (17%)
90	13 (57%)
80	4 (17%)
70	2 (9%)
Median prior lines therapy	2 (1, 3)
MGMT promoter status	
methylated	1 (11%)
unmethylated	8 (89%)
unknown	14

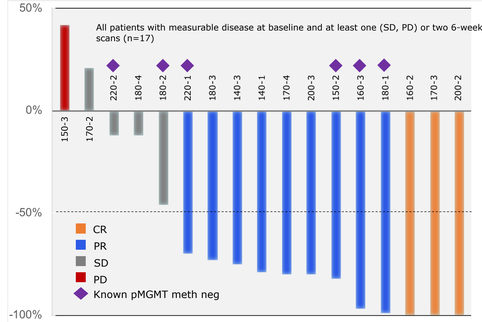
low doses: 140, 150, 160, and 170 mg/m2; high doses: 180, 200, and 220 mg/m2

Clinical results

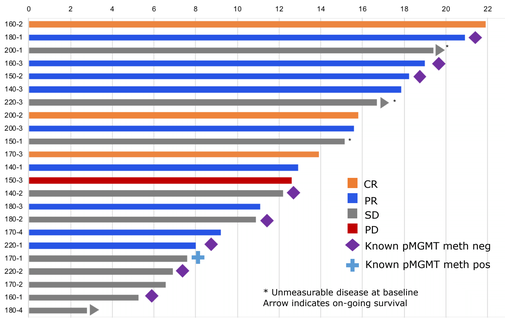
ORR	12/20 (60%)*
CR	3/20 (15%)
PR	9/20 (45%)
SD	10/23 (43%)
PD	1/23 (4%)
Med. PFS	5.5 mo. [95% CI 4.1, 8.2]
6-mo. PFS	40%
Med. OS	13.4 mo. [95% CI 10.9, 17.9]
1 yr OS	64%

* 20/23 patients with measurable disease at baseline were evaluable for response

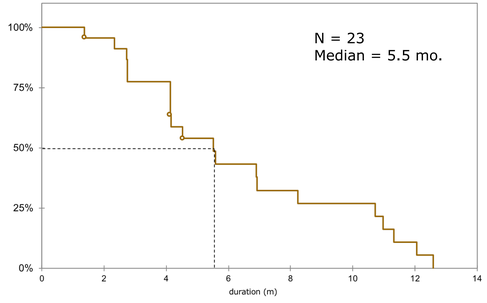
RANO Response



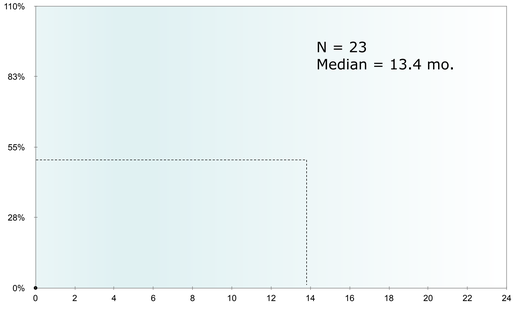
Patient survival



Progression-free survival

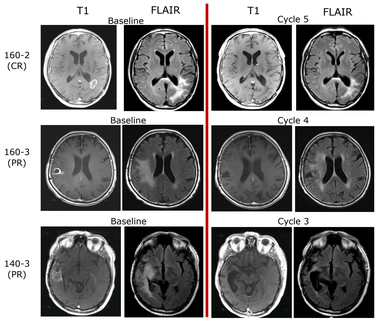


Overall survival



TRIAL	CB-017	ReACT 2	CABARET	BELOB	BRAIN	NCI '64E	AVAREG	EORTC '101	CABARET	BRAIN
REGIMEN:	**TPI 287 + Avastin**	Avastin	Avastin	Avastin	Avastin	Avastin	Avastin	CCNU+ Avastin	carbo+ Avastin	CPT-11 + Avastin
Patients	**23**	30	62	48	85	56	59	288	60	82
ORR	**60%**†	17%	6%	17%	26%	20%	26%	42%	14%	38%
Median PFS	**5.5 mo**	4.1 mo*	3.5 mo	3.0 mo	4.2 mo	3.9 mo	NA	4.1 mo	3.5 mo	NA
Median OS	**13.4 mo**	8.8 mo	7.5 mo	8.0 mo	9.2 mo	7.1 mo	7.3 mo	9.1 mo	6.9 mo	8.7 mo
1-year OS	**64%**^	30%*	25%*	26%	38%	33%*	NA	32%	17%*	38%

CB-017 Results as of Jan 24, 2017; ReACT 2: results SNO 2015; BELOB: SNO 2015 update and Taal et al. *Lancet Oncol.* (2014); CABARET: Field et al., *Neuro-Oncol.* (2015); BRAIN and NCI '64E: FDA Briefing Documents, ODAC March 31, 2009 and Friedman et al. *J. Clin. Oncol.* (2009); AVAREG: Brandes et al., *Annals Oncol.* (2014); EORTC 26101: SNO late-breaker 2015; NA: not available; † based on 20 evaluable patients; ^ n=20; * estimate.



Adverse Events

	Grade 1/2	Grade 3*
Alopecia	4	
Arthralgia	3	
Ataxia	3	1
Confusion		1
Diarrhea	4	
Dysphasia		1
Fatigue	6	1
General body pain	3	
Headache	3	
Hypertension		1
Hypoaesthesia	6	
Lymphocytopenia	4	1
Nausea	4	
Neutropenia	5	2
Peripheral neuropathy	11	

Grade 1/2 events in ≥3 patients probably associated with TPI 287; Grade 3 regardless of cause

* includes one episode of Grade 4 hypertriglyceridemia

Summary

- TPI 287 is well tolerated up to 220 mg/m2 with BEV in recurrent GBM
- Efficacy compares favorably to landmark rGBM studies:
- **60% overall response rate (3 CR; 9 PR)**
- **96% disease control rate (CR+PR+SD)**
- **13.4 mo. median and 64% 1-year OS**
- Active in patients harboring unmethylated MGMT promoters in tumors, a negative prognostic indicator for survival
- No DLTs reported; safety profile consistent with profiles of BEV and other anti-microtubule agents
- Results support further clinical development of TPI 287 for recurrent GBM