

NASDAQ: CNSP

December 11, 2024



CNS

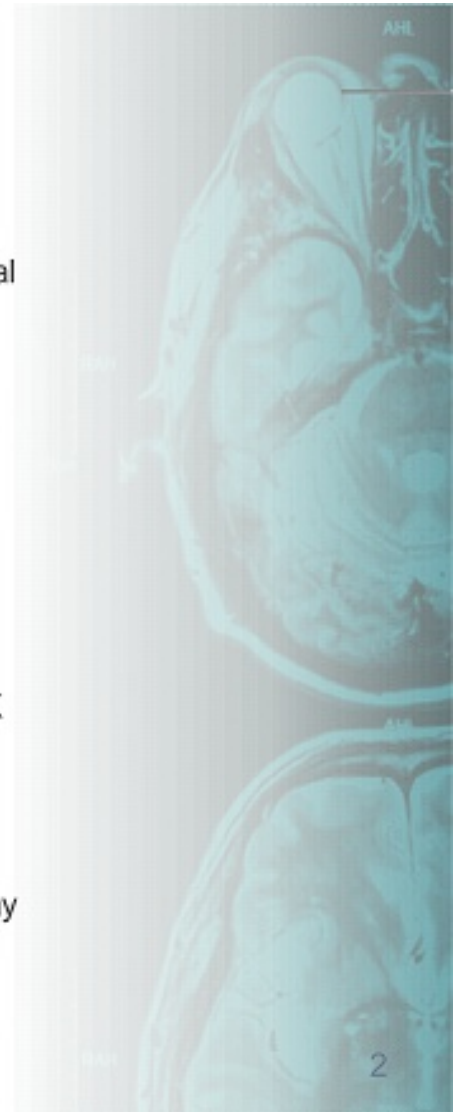
Pharmaceuticals

Virtual Analyst &
Investor Day

Forward Looking Statements

This presentation incorporates information from materials filed with the SEC and contains forward-looking statements. All statements contained herein other than statements of historical fact, including statements regarding our future results of operations and financial position, our business strategy and plans, and our objectives for future operations, are forward-looking statements. The words “believe,” “may,” “will,” “estimate,” “continue,” “anticipate,” “intend,” “expect,” and similar expressions are intended to identify forward looking statements. We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy, short-term and long-term business operations and objectives, and financial needs.

These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those described in the “Risk Factors” section of most recent Form 10-K as updated by any subsequent Form 10-Q filings. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties and assumptions, the future events and trends discussed in this presentation may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward looking statements.





John M. Climaco, Esq
President &
Chief Executive Officer



Sandra L. Silberman, MD, PhD
Chief Medical Officer



Zena Muzyczenko
Vice President,
Clinical Operations

Agenda

- Opening and Introductions
- CNS Pharma Overview
- Glioblastoma Multiforme: The Patient Journey and Unmet Need
- The Blood Brain Barrier and Overcoming This Significant Challenge
- Berubicin: A Novel Anthracycline Designed to Cross the Blood Brain Barrier
- Berubicin: Clinical Data and Path to Potential Approval
- TPI 287: A Novel, Blood Brain Barrier Permeable Abeotaxane
- CNS Pharma: Positioned for a Transformational 2025



Prof. Michael Weller, MD

- Director of Department of Neurology, Universitätsspital, Zurich, Switzerland since 2008
- Member of Swiss Neurological Society, German Society for Neurology, German Cancer Society, European Association for Neuro-Oncology, Society for Neuro-Oncology, European Society of Medical Oncology, and American Society of Clinical Oncology
- Member of the Board, European Organisation for Research and Treatment of Cancer
- President, Swiss Neuro-Oncology Society
- Chairman of the Department of General Neurology at the University Hospital Tübingen, Germany, where he had previously received his education in clinical neurology
- Postdoctoral fellowship at the Department of Clinical Immunology, University Hospital Zurich, Switzerland, followed where he identified death receptor targeting as a potential treatment strategy for malignant gliomas
- Received several awards in recognition of his contributions to cancer research, including the German Cancer Award in 2007
- Dr. Weller was involved in major practice-changing clinical trials including the registration trial for temozolomide in glioblastoma
- Has co-authored more than 600 original publications in peer-reviewed journals, including *The New England Journal of Medicine*, *Science*, *Nature*, *Nature Medicine*, *Lancet Oncology*, *PNAS*, *The Journal of Clinical Investigation*, and *The Journal of Clinical Oncology*
- Dr. Weller has been a member of the ESMO Open Editorial Board since 2016 and was a member of the ESMO Educational Committee, 2012-2016. He has also been a member of ESMO CNS Tumors Faculty Group since 2012



Samuel Goldlust, MD

- Board-certified and fellowship-trained neuro oncologist with Saint Luke's Cancer Specialists
- Specialized training in neuro-oncology and extensive experience treating patients with primary and metastatic brain tumors as well as the neurological complications of cancer
- Passionate about research and focused on the development of novel and more effective treatments for glioblastoma and other brain tumors, including options when standard chemotherapy, radiation and surgery have proven ineffective
- Completed his residency training in neurology at New York University Hospitals and was selected to serve as Chief Resident
- Received fellowship training in neuro-oncology at Memorial Sloan Kettering Cancer Center and was promoted to Chief Fellow in his final year
- Dr. Goldlust frequently treats conditions like Brain Cancer, Hypothalamus Cancer and Cancer of Cerebral Meninges along with other conditions at varying frequencies



Erin Dunbar, MD

- Founding physician of the Brain Tumor Center and Director of Neuro-Oncology at Piedmont Atlanta Hospital, Piedmont Atlanta, GA
- She specializes in the comprehensive care of brain and spine tumor patients who are battling both primary and metastatic tumors
- Completed fellowships in Neuro-oncology at Johns Hopkins University, in Hospice and Palliative Medicine at the Malcom Randall VA Medical Center and in Medical-oncology at the University of Florida
- Avid clinical researcher and a collaborator with organizations, including the National Cancer Institute and other national brain tumor centers



CNS Pharma Overview

John M. Climaco, Esq
President &
Chief Executive Officer

Overview

Lead Program: Berubicin, a Novel Anthracycline

- First drug of its class to appear to cross the blood-brain barrier
- **A clinical trial designed to be pivotal now fully enrolled**
- The primary analysis of data in the 1st half of 2025
- No evidence of cardiotoxicity in hundreds of patients
- Developed at **MD Anderson Cancer Center – Ranked #1 in Cancer Care in the US**

Pipeline Expansion with In-License of TPI 287

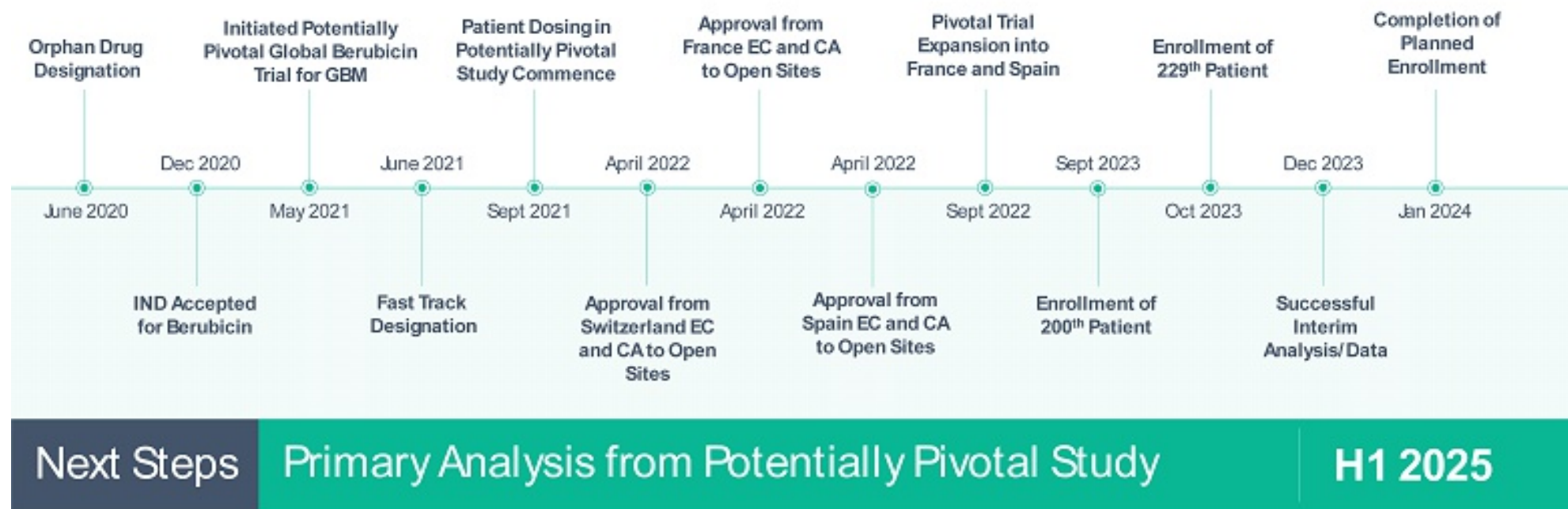
- Late-stage, novel, blood brain-barrier permeable taxane-derivative (abeotaxane) for treatment of brain malignancies
- Studies in over 350 patients to date, include clinical trials as monotherapy and combination with bevacizumab
- Orphan Designation for 7 years granting US marketing exclusivity
- Fast Track Designation expediting review of data

A Focused and Targeted CNS Oncology Pipeline

Program	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Highlights
Berubicin	Glioblastoma Multiforme (GBM)	Potentially Pivotal				<ul style="list-style-type: none"> • Study fully enrolled • Primary analysis data expected H1 2025
TPI 287	Glioblastoma Multiforme (GBM)					<ul style="list-style-type: none"> • Recently in-licensed • Plan to engage with regulators to design potential registration study

Proven Execution and Milestones

Berubicin Development Program



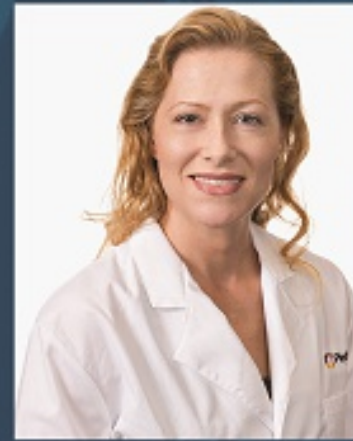
Glioblastoma Multiforme: The Patient Journey



Prof. Michael Weller, MD



Samuel Goldlust, MD



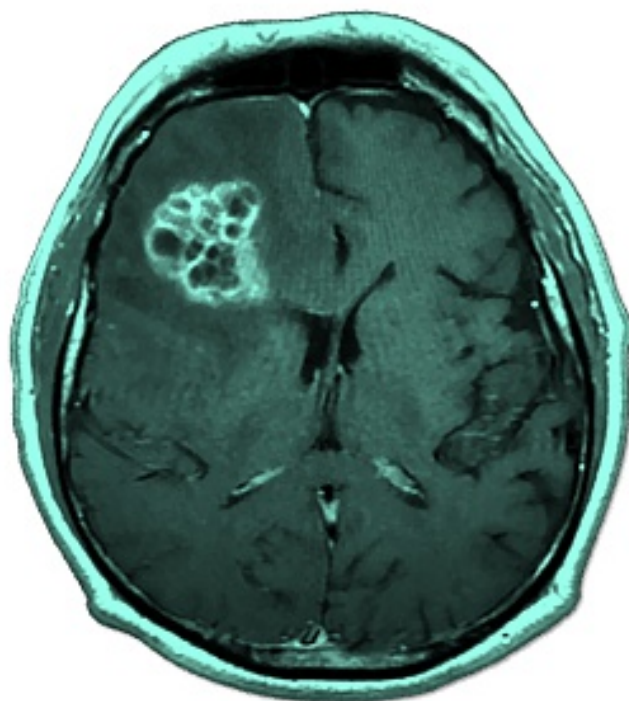
Erin Dunbar, MD

Glioblastoma Multiforme (GBM)

One of the most aggressive, deadly and treatment-resistant cancers that forms in the brain

Current standard of care ineffective in ~60% of patients

Can affect cognition, mood, behavior and organ function



12 – 18 MONTHS

Average Life Expectancy¹

>50,000

New Cases in the 8 Major Markets² Each Year³

>151,000

Forecast of Annual New Cases in the 8 Major Markets² by 2027³

~48%

Of All Primary Malignant Brain Tumors¹







1: <https://braintumor.org/take-action/about-gbm/>

2: 8 Major Markets includes USA, France, Germany, Italy, Spain, UK, Japan and urban China

3: Global Data, "Glioblastoma Multiforme (GBM): Opportunity Analysis and Forecasts to 2027" (2017)

GBM: Treatment

Treatment depends upon the stage of disease, which may include:

Surgery	Chemotherapy Common Drugs	Radiation	Tumor Treating Fields
 <p>Craniotomy - a surgical procedure that involves removing a section of the skull to access the brain. The bone is replaced after surgery</p> <p>Resection of brain tumor or retrieve a sample of the brain tumor</p>	 <p>Temozolomide</p> <p>PCV - Procarbazine hydrochloride, Lomustine (CCNU) and Vincristine sulfate</p> <p>Bevacizumab</p>	 <p>Treatment that uses x-rays and other high-energy rays to kill abnormal cells</p>	 <p>Magnetic fields applied to the skull</p>

GBM Current Standard of Care

Standard of Care	US	Europe	Comments
Resection and Radiotherapy	X	X	First Line
Temozolomide	X	X	First Line*
Tumor Treating Fields	X		First Line
Lomustine (CCNU)	X		Second Line
PCV (Procarbazine, CCNU, Vincristine)	X		Second Line
Bevacizumab	X		Third Line
Clinical Trials	X	X	First, Second and Third Line

**Europe does not usually administer any drugs after the primary diagnosis in patients with an unmethylated MGMT promotor; the US usually provides Temozolomide to all patients*

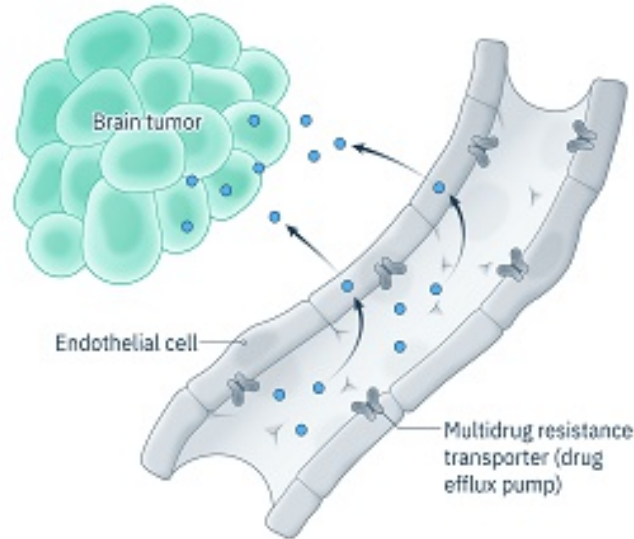


The Blood Brain Barrier and Overcoming This Significant Challenge

Sandra L. Silberman, MD, PhD
Chief Medical Officer

The Blood Brain Barrier (BBB)

Highly Selective, Semi-Permeable Barrier that Separates the Circulating Blood from the Brain



Key Functions

- **Protection:**
 - Blocks toxins, pathogens and potentially harmful molecules from entering the brain by transporters that bind to these substances and deliver them back to the bloodstream
- **Selective Permeability:**
 - Allows essential nutrients like glucose and amino acids to pass through while restricting larger or harmful molecules
- **Maintaining Homeostasis:**
 - Ensures a controlled environment for proper neuronal function

Drug Delivery to the Brain is Challenging Due to the BBB's Selective Nature, Limiting the Access and Effectiveness of Cancer Therapies in the Brain

Strategies for Therapies to Gain Access through the BBB

Liposomal Formulations

- Resemble the lipid bilayer of the endothelial cell membrane
- Can circumvent mechanisms that transport drugs out of the brain and that confer resistance to tumor cells

Intratumoral/Intracerebral or Intrathecal Administration:

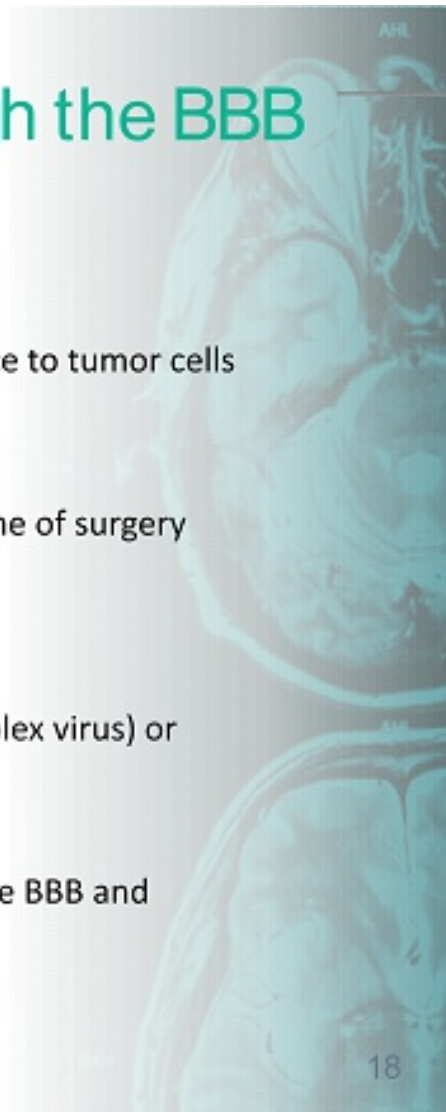
- Clinically established, useful to treat CNS disorders including brain tumors and seizures
 - Intratumoral: Injections or infusions of drugs directly into the tumor –available at the time of surgery
 - Intrathecal: Injections into the CSF - inadequate for delivery to tissue or cellular targets

Viral Vectors:

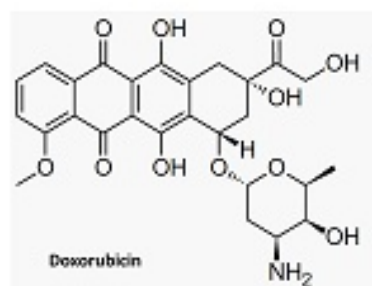
- Neurotropic viruses, i.e., viruses that can infect neural cells
 - Invade either by the neural network and axonal transport (eg rabies virus or herpes simplex virus) or invade the CNS from the bloodstream (retroviruses)

Ultrasound

- Ultrasound-mediated drug delivery – non-invasive using ultrasound to temporarily open the BBB and deliver drugs into the brain



Berubicin: A Novel Anthracycline Designed to Cross the Blood Brain Barrier



Berubicin

Molecule derived from the structure of other anthracyclines

Structure

- Discovered due to molecular modeling and structure-based rational design through computational chemistry
- Chosen based on its ability to circumvent P-glycoprotein and MRP1 (Multi-Drug Resistance Protein), which are part of the mechanisms that transport drugs out of resistant cells, as well as the normal brain due to the BBB

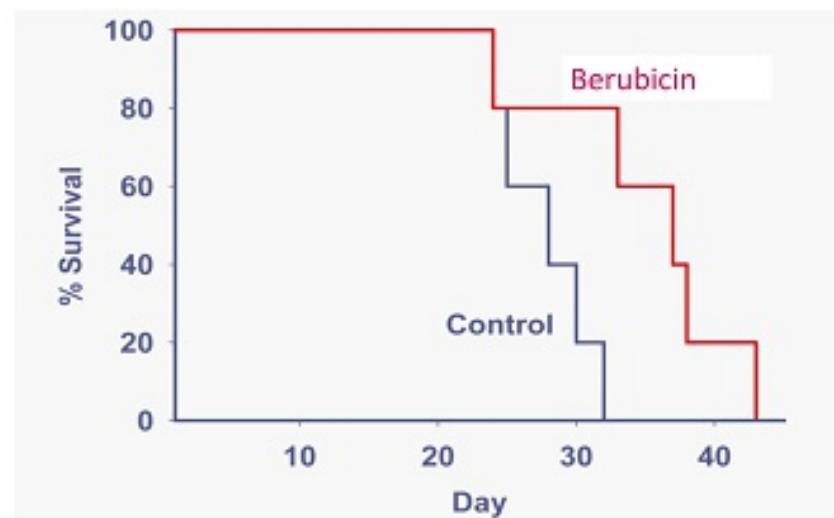
Activity:

- The mechanism of action is comparable to other anthracyclines; poisoning Topoisomerase II and disrupting DNA repair
- Berubicin is more potent than Doxorubicin in cellular assays
- Levels of Berubicin are higher in multidrug-resistant cells
- Berubicin increases the survival of mice with orthotopic gliomas

Berubicin Increases Survival in Mouse Glioma Model

Tumors in the natural setting require compounds to cross the BBB to be effective

- Nude mice (*nu/nu*) were seeded with U-87 MG cells by direct intracerebral injection
- Implanted mice were treated with two doses of Berubicin by intraperitoneal (i.p.) injection at 10 mg/kg on Day 1 and 5 mg/kg on Day 10
- U-87 MG tumor-bearing mice treated with Berubicin showed a 33% increase in survival relative to placebo-treated control animals





Berubicin: First-In-Human Trial

Sandra L. Silberman, MD, PhD
Chief Medical Officer

Berubicin: First-In-Human Trial Design

35

Subjects

with recurrent or refractory glioblastoma multiforme (GBM) or other primary brain cancers

29 were GBM,
4 AO and 2 AA

DOSE

Intravenous berubicin over **2 hours for 3 consecutive days (one course) every 21 days**

Doses were escalated using an accelerated titration design and ranged from **1.2 to 9.6 mg/m²/day**

PRIOR THERAPIES

The median number of prior therapies was **(5) five**

71% of the patients had received at least four prior therapies, including any combination of chemotherapy, radiation and resection

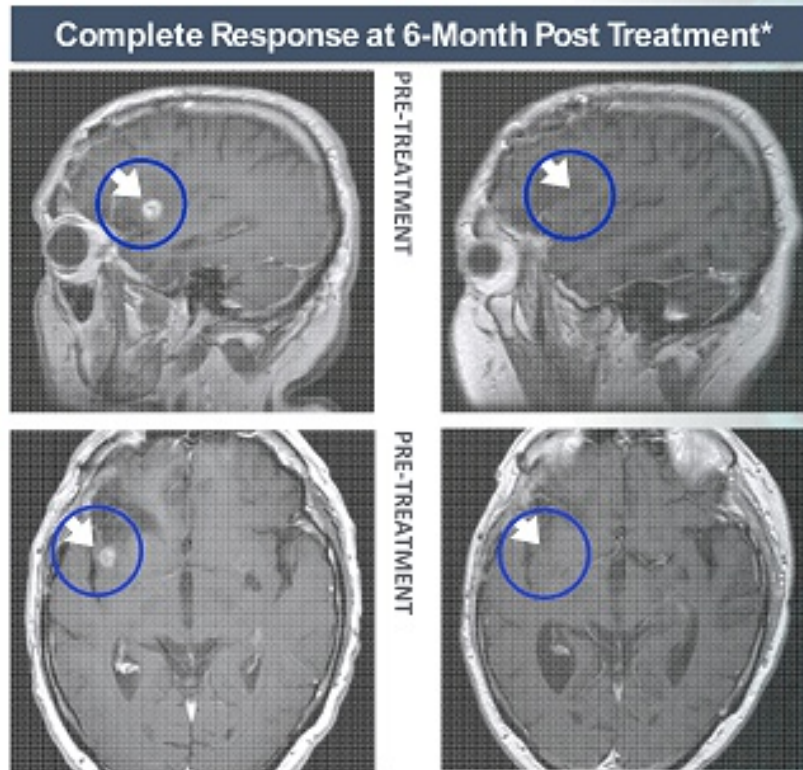
Berubicin: Results of Phase 1 Dose-Finding and PK Study

44%
of subjects
demonstrated "stable
disease or better"

Two responses with
up to **80%** tumor
shrinkage

Extremely well
tolerated with a good
safety profile (**no off-
target toxicities**)

**DURABLE COMPLETE
RESPONSE (CR)** - One
subject remains
cancer-free ~17 years
following treatment



* This does not always mean the cancer is cured. Also called a complete remission:
www.cancer.gov/publications/dictionaries/cancer-terms/def/complete-response

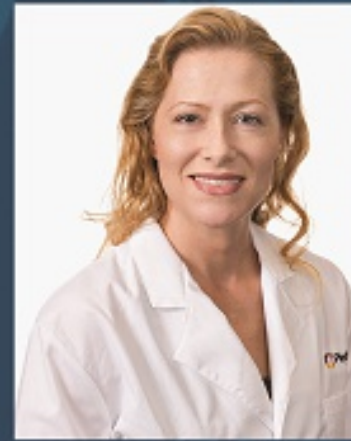
Berubicin: Clinical Data Generated to Date



Prof. Michael Weller, MD



Samuel Goldlust, MD



Erin Dunbar, MD



Established Clinical Global Infrastructure and Network

Zena Muzyczenko
Vice President,
Clinical Operations

Clinical Development Infrastructure Optimized for Brain Cancer Drug Development

Relationships	Program Development Infrastructure & Efficiencies
<ul style="list-style-type: none">• Deliberate establishment of a global, CNS focused network• Commitment to work in this disease• Deep understanding of the landscape of clinical trials in GBM	<ul style="list-style-type: none">• Seamless transition to our next asset• Built to last• Set up for success



Berubicin: Designed-to-Be-Pivotal Clinical Trial and Path to Potential Approval

Sandra L. Silberman, MD, PhD
Chief Medical Officer

Berubicin

- ✓ 45 centers in 5 countries
- ✓ 252 patients randomized
- ✓ Pivotal endpoint 6-12 months

Announced Independent Data Safety
Monitoring Board (DSMB)
Recommendation on 12/18/23
Continuation of Clinical Trial of Berubicin
Without Modification

Primary Analysis from Trial Expected 1st Half 2025



Interim Analysis and Rationale

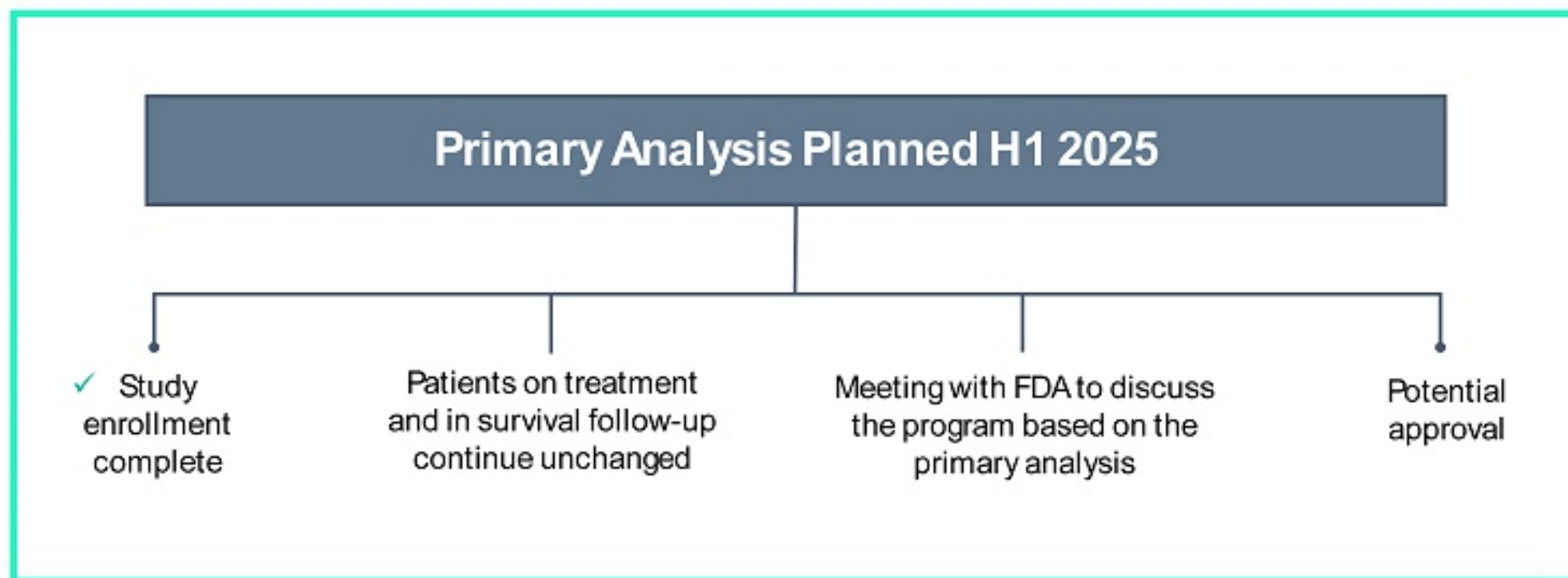
- **Independent Data Safety Monitoring Board (DSMB)**
 - Subject matter experts (oncologists, statistician)
 - Independently oversaw and monitored the clinical trial
 - Ensured the safety of the patients and the integrity of the data collected

- **DSMB made informed decisions about continuing, modifying or stopping the trial based on the accumulating safety and efficacy data**

- **Planned interim analysis to reject futility of investigational drug**
 - 07Dec2023 DSMB review of the interim safety and efficacy data
 - Concluded that CNS201 should be "Continued as planned (without modification)"



Berubicin: Next Major Milestone



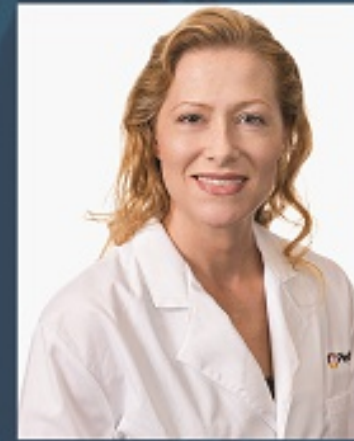
Berubicin: Potentially Pivotal Clinical Trial



Prof. Michael Weller, MD



Samuel Goldlust, MD



Erin Dunbar, MD



TPI 287

Late Stage, Novel Blood
Brain Barrier Permeable
Abeotaxane for Treatment of
Brain Malignancies

Sandra L. Silberman, MD, PhD
Chief Medical Officer

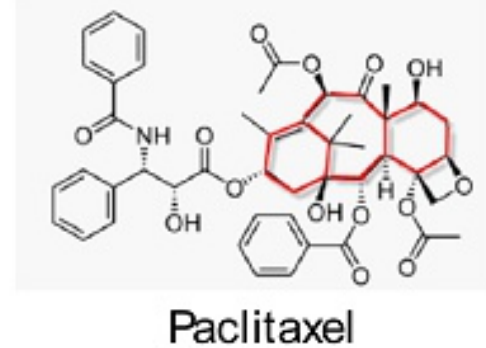
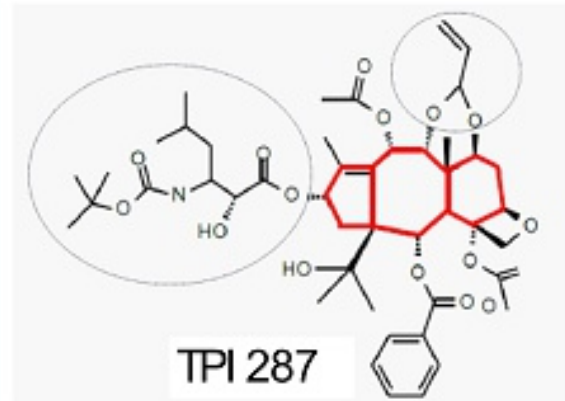
TPI 287: A Novel Taxane Derivative

- **Taxanes**

- A class of chemotherapy that binds to microtubules and prevents them from breaking down normally, which stops cancer cells from dividing
- A substrate for P-glycoprotein (Pgp), which is upregulated in cells that become taxane-resistant, and is part of the BBB

- **TPI 287**

- A derivative of taxane (abietaxane) that is not a substrate for Pgp
- Effective in taxane-resistance and able to cross the BBB



Readily Penetrates the Blood Brain Barrier in Animal Models

	COMPOUND	Blood ug*hr/ml	Brain ug*hr/g	Brain:Blood
Wild-type	paclitaxel	3.2	1.6	0.5
	docetaxel	8.7	2.5	0.3
	TPI 287	16.8	65.9	3.9
Pgp knock-out	paclitaxel	4.7	18.6	4.0
	docetaxel	9.0	15.4	1.7
	TPI 287	N/A	N/A	

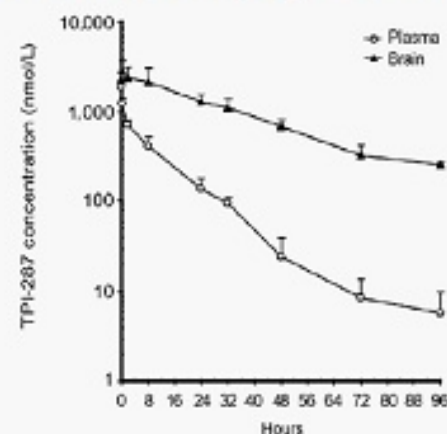
Single-dose IV bolus:

paclitaxel dosed 10 mg/kg AUC cal. 0-8 hr blood, 0-12 hr. brain (Cln Can Research. 9:2849, 2003).

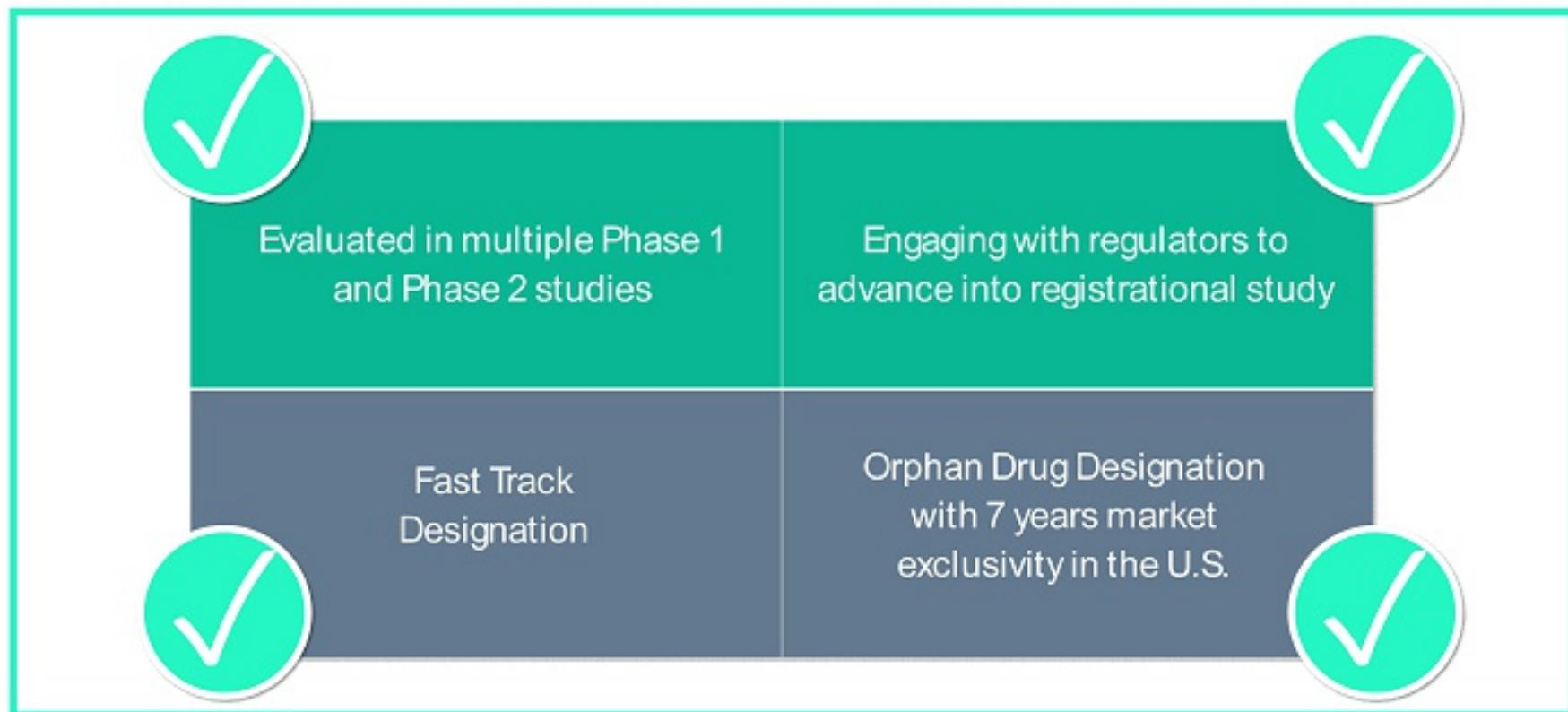
docetaxel dosed 33 mg/kg AUC cal. 0-8 hr blood, 0-12 hr. brain (Eur J Can. 40:1269, 2004).

TPI 287 dosed 20 mg/kg AUC cal. 0-96 hr blood and brain (Mol Can Ther. 11:1959, 2012).

~ 64x greater concentration in brain vs plasma 4 days after single dose in mouse.



Clinical Trials with TPI 287



TPI 287



Phase 1 trial of TPI 287, a microtubule stabilizing agent, in combination with bevacizumab in adults with recurrent glioblastoma

Samuel Goldlust, MD



Neuro-Oncology Advances

2021, 1-3, 287 | <https://doi.org/10.1093/advances/nab009> | Advance Access date 19 January 2021

Phase 1 trial of TPI 287, a microtubule stabilizing agent, in combination with bevacizumab in adults with recurrent glioblastoma

Samuel A. Goldlust¹*, Lewis B. Nabors², Sigmund Hou, Minish Mehila, Paul J. Dain³, Tara Benkers⁴, Samuel Singer⁵, Mayank Rao, Lori Cappello, Sandra L. Silberstein⁶, and George Farmer⁷

¹John Theurer Cancer Center, Rutgers University Medical Center, Newark, New Jersey, USA (S.A.G., S.F., L.C.); ²Department of Neurology, University of Alabama at Birmingham, Birmingham, Alabama, USA (L.B.N.); ³Baylor Neuroscience Institute, Memorial Hermann Health System, Houston, Texas, USA (S.M., M.A.); ⁴Department of Neurology, University of Rochester Medical Center, Rochester, New York, USA (N.M.); ⁵Long Island Brain Tumor Center of Neurological Surgery, P.C., Great Neck, New York, USA (L.P.D.); ⁶Swedish Neuroscience Institute, Swedish Medical Center, Seattle, WA, USA (T.E.); ⁷Centre for Biomarkers, New York, New York, USA (S.L.S., G.F.); ⁸Present affiliation: Sabet Solar's Cancer Institute, Sabet Solar's Hospital of Kansas City, Kansas City, Missouri, USA; ⁹Present affiliation: Merck & Co, Inc., North Wales, Pennsylvania, USA; ¹⁰Present affiliation: Brain Tumor Center at the Center for Advanced Medicine, Northwell Health, Lake Success, New York, USA; ¹¹Present affiliation: CNS Pharma, Houston, Texas, USA; ¹²Merck/Celltech, Houston, Texas, USA

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Abstract

Background. Recurrent glioblastoma (rGBM) has limited treatment options. This phase 1 protocol was designed to study the safety and preliminary efficacy of TPI 287, a central nervous system persistent microtubule stabilizer, in combination with bevacizumab (BEV) for the treatment of rGBM.

Methods. GBM patients with up to 2 prior relapses without prior exposure to anti-angiogenic therapy were eligible. A standard 3 + 3 design was utilized to determine the maximum tolerated dose (MTD) of TPI 287. Cohorts received TPI 287 at 100-200 mg/m² every 3 weeks and BEV 10 mg/kg every 2 weeks during 6-week cycles. An MRI was performed after each cycle, and treatment continued until progression as determined via response assessment in neuro-oncology criteria.

Results. Twenty-four patients were enrolled at 6 centers. Treatment was generally well tolerated. Fatigue, myelosuppression, and peripheral neuropathy were the most common treatment emergent adverse events. Dose-limiting toxicity was not observed, thus the MTD was not determined. Twenty-three patients were evaluable for median and 6-month progression-free survival, which were 5.5 months (mo) and 40%, respectively. Median and 12-month overall survival were 13.4 mo and 62%, respectively. The optimal phase 2 dose was determined to be 200 mg/m².

Conclusions. TPI 287 can be safely combined with BEV for the treatment of rGBM and preliminary efficacy supports further investigation of this combination.

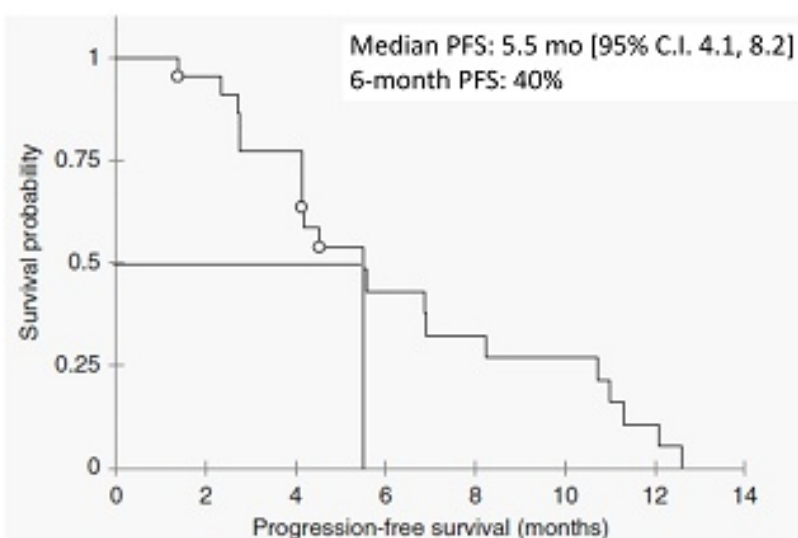
Key Points

- TPI 287 and bevacizumab were well tolerated in recurrent glioblastoma.
- Preliminary efficacy was encouraging.

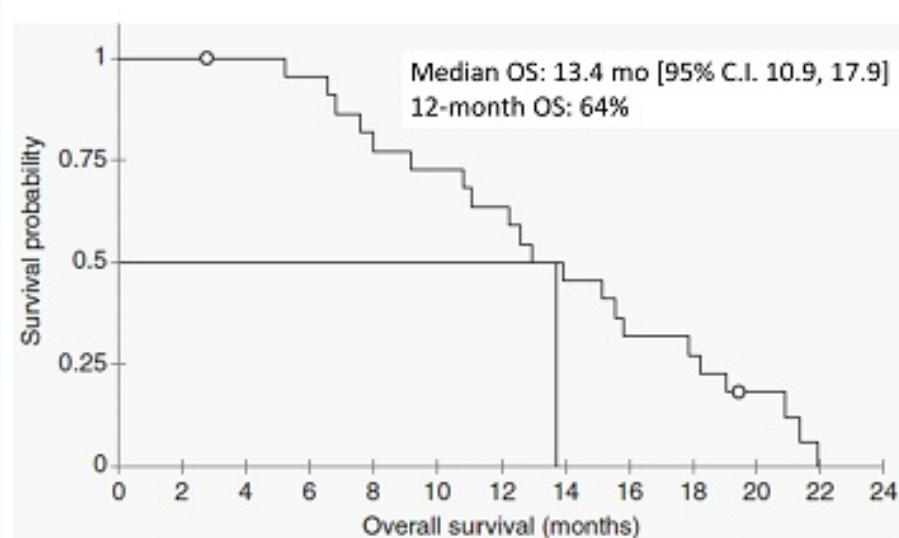
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TPI 287 in Combination with Bevacizumab for the Treatment of Recurrent Glioblastoma

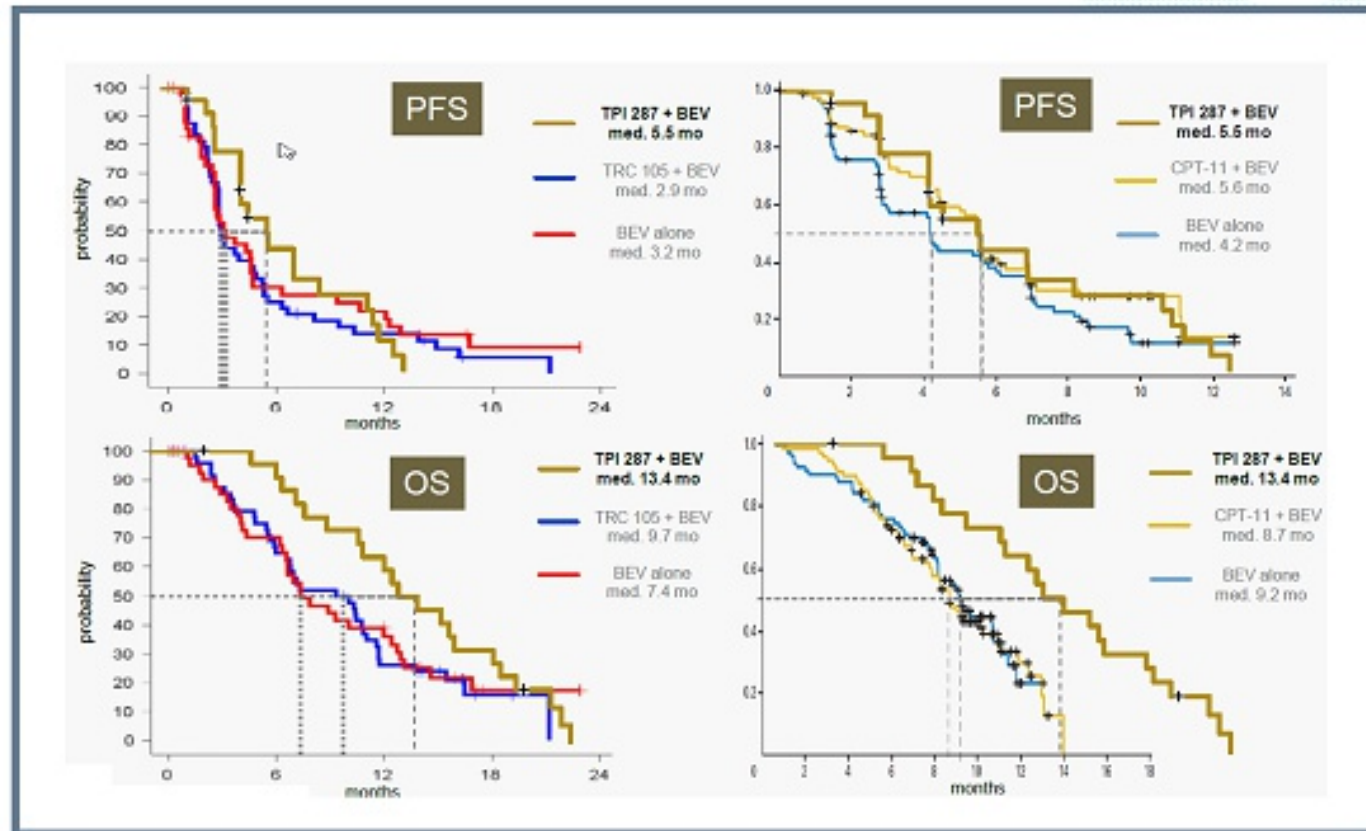
Progression-Free Survival



Overall Survival



Improved GBM Survival in Combination with Bevacizumab



* Graphs represent aggregate data from multiple studies

TPI 287:

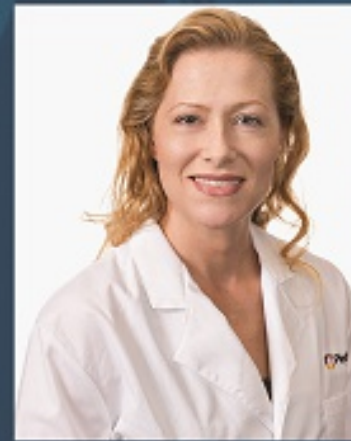
Late Stage, Novel Blood Brain Barrier Permeable Abeotaxane for Treatment of Brain Malignancies



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CNS Pharma Positioned for a Transformational 2025

Commercial Planning

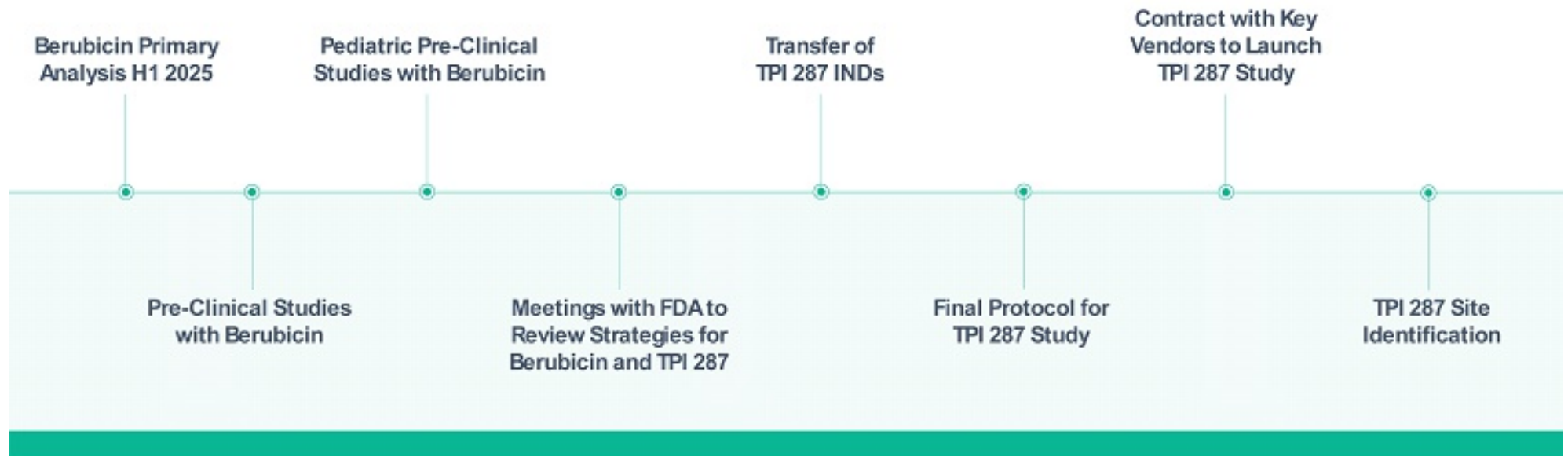
Key Appointment of Amy Mahery to Board of Directors

Commercial Strategy Under Development

Focus on Hiring the Right People

Medical Affairs/Medical Liaisons
Product Launch & Commercialization
Specialist

2025 Milestones





Q&A



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