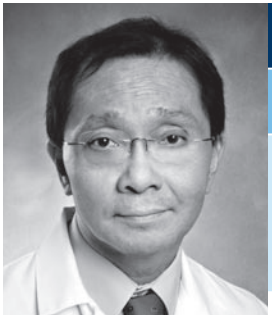

INTERVIEW

## Patrick Y Wen, MD

Dr Wen is Director of the Center for Neuro-Oncology at Dana-Farber/Brigham and Women's Cancer Center and Professor of Neurology at Harvard Medical School in Boston, Massachusetts.

### Tracks 1-13


**Track 1** Pivotal Phase II trial of bevacizumab for recurrent GBM

**Track 2** Infiltrating pattern of relapse after bevacizumab in GBM

**Track 3** Efficacy and safety of XL184 in recurrent GBM

**Track 4** Radiographic artifact versus durable response with bevacizumab in GBM

**Track 5** Six-month progression-free survival as a clinically meaningful endpoint in recurrent GBM

**Track 6** Pseudoprogression versus true disease progression after chemoradiation therapy for GBM

**Track 7** Clinical trials of cediranib in GBM

**Track 8** Perspective on the use of bevacizumab for patients with brain metastases

**Track 9** Antiedema versus antitumor effect of VEGF inhibitors in GBM

**Track 10** Approach to integrating bevacizumab in the treatment algorithm for recurrent GBM

**Track 11** Risk-benefit ratio of bevacizumab for patients with GBM receiving anticoagulation for thromboembolism

**Track 12** **Case discussion:** A 48-year-old woman with GBM experiences disease recurrence with an infiltrating pattern of relapse after a clinically meaningful response to bevacizumab

**Track 13** Mesenchymal phenotype as a distinct aggressive vascular subtype of GBM


## Select Excerpts from the Interview

### Tracks 2-3

**DR LOVE:** Would you discuss the novel multitargeted tyrosine kinase inhibitor XL184, which is being evaluated in GBM?

**DR WEN:** The interest in this class of drugs is tremendous. XL184 in particular inhibits not only VEGFR2 but also MET and RET. We presented initial Phase II results with two doses of XL184 for patients with recurrent GBM at ASCO 2010 (Wen 2010a; [2.1]). The original Phase II dose garnered from the Phase I studies was 175 mg, but that dose was toxic. Dose reduction to 125 mg daily was better tolerated, patients remained on treatment longer and results were more favorable. Response rates were approximately 30 percent, which

**2.1** **Efficacy of XL184 for Recurrent Glioblastoma Multiforme**

| | Prior anti-angiogenic therapy | | | |
|---|---|---|---|---|
| | No | | Yes | |
| **Cohort** | XL184 175 mg N = 34 | XL184 125 mg N = 37 | XL184 175 mg N = 12 | XL184 125 mg N = 22 |
| **Median PFS** | 16 weeks | 16 weeks | NR | 7.9 weeks |
| **ORR, n (%)** | 7 (21) | 11 (30) | 1 (8) | 0 |

PFS = progression-free survival; NR = not reported; ORR = overall response rate

- XL184 shows encouraging clinical activity in patients with recurrent glioblastoma.
  - Clinical activity was observed in both populations of patients with anti-angiogenic-naïve and pretreated disease.
- XL184 at the dose of 125 mg demonstrated improved tolerability compared to the 175-mg dose while retaining clinical activity.
  - Fewer treatment interruptions and lower rates of permanent discontinuation were observed at the lower dose.

Wen PY et al. *Proc ASCO* 2010a;**Abstract 2006**.

compares favorably with bevacizumab, and the six-month progression-free survival rate was approximately 26 percent.

In terms of side effects, patients exhibited hypertension, fatigue and some diarrhea. Another troublesome toxicity with this class of drugs is hand-foot syndrome, which often results in the need to reduce the dose. It's possible that further dose reduction of XL184 might be useful because it is a potent inhibitor of the VEGF receptor. Thus, a lower dose would probably still be effective.

I believe another important characteristic of VEGF receptor inhibitors is that by blocking VEGF you significantly decrease the edema around these tumors. It's a feature of all of these drugs that allows you to significantly reduce steroid use, and that is of real benefit to patients.

## Track 6

**DR LOVE:** Would you describe the phenomenon of pseudoprogression, which patients can experience after chemoradiation therapy for GBM?

**DR WEN:** Pseudoprogression can occur after patients have completed six weeks of radiation therapy with temozolomide. In approximately 40 percent of patients, the post-therapy scan at week four will appear worse. Approximately half of the time this is because of true tumor progression, but the other half of the time it's because of radiation therapy effects. Delineating between the two is extremely difficult.

This phenomenon occurs mainly in the first three months after radiation therapy, although occasionally it can occur later. A recent publication proposes that within the first three months of radiation therapy, patients should not

automatically be assumed to be experiencing disease progression based solely on the scan (Wen 2010b).

## Track 7

**DR LOVE:** What are the current data with cediranib in GBM?

**DR WEN:** Cediranib is a potent pan-VEGF receptor inhibitor with some inhibitory activity against PDGF. It doesn't inhibit MET at all. We reported a Phase II study of cediranib for recurrent GBM (Batchelor 2010; [2.2]).

When this trial was initiated, the cediranib dose was 45 mg/day, but that dose was difficult for patients to tolerate. A dose reduction to 30 mg/day was better tolerated. I believe the most striking side effect with the lower dose was hypertension, which was prominent. It was treatable but often required more than one antihypertensive agent.

Combining cediranib with radiation therapy is also of interest. Preclinical data suggest this class of agents might potentiate radiation therapy, thus the rationale for using it with radiation therapy for brain metastases (Eichler 2010). Some trials are also evaluating cediranib with radiation therapy and temozolomide for newly diagnosed glioblastoma (NCT00662506, NCT01062425).

**2.2 Phase II Study of Cediranib for Patients with Recurrent Glioblastoma**

| | Alive and progression free at six months (APF6) | Partial response (by MRI three-dimensional measurements) |
|---|---|---|
| Cediranib (N = 31) | 25.8% | 56.7% |

"Potential advantages of cediranib relative to bevacizumab include oral bioavailability; a shorter half-life (22 hours v 21 days), which should allow more rapid clearance of drug in the event of serious toxicity such as hemorrhage; multiple tyrosine kinase targets and the ability to target intracellular VEGF receptors.

We observed that cediranib treatment results in a radiographic response proportion, APF6 proportion, median PFS and median OS that compare favorably with data from historical controls.

These data are also comparable to data obtained in phase II studies of bevacizumab in this patient population. The frequency of drug discontinuation due to toxicity was low and comparable to other anti-VEGF therapies. The safety profile of cediranib in patients with glioblastoma was acceptable, and there were no CNS hemorrhages or increased risk of thromboembolic complications."

Batchelor TT et al. *J Clin Oncol* 2010;28(17):2817-23.

## Track 8

**DR LOVE:** What is your perspective on the use of anti-VEGF therapies, specifically bevacizumab, for patients with brain metastases?

**DR WEN:** When bevacizumab was first administered in this setting, the concern was that its use would cause brain metastasis bleeding. Meta-analyses are now evaluating patients on trials who either developed brain metastases while receiving bevacizumab or were allowed to enroll on bevacizumab trials with known brain metastases.

The risk of hemorrhage in these patients is low — on the order of one or two percent (Rohr 2009; [2.3]). I believe that for most patients with brain metastases bevacizumab is a safe agent. For patients with brain metastases who exhibit many symptoms and for whom no other interventions are available, bevacizumab may be helpful. ■

**2.3**

**Rates of Cerebral Hemorrhage with Bevacizumab in Patients with Brain Metastases from Various Solid Tumors: A Retrospective Analysis of (A) 13 Phase II or III Trials, (B) the ATHENA and SAiL Trials and (C) Two Open-Label Studies for Patients with Treated CNS Metastases**

| Data set | Patients with CNS metastases | Rates of cerebral hemorrhage | |
|---|---|---|---|
| | | Bevacizumab | No bevacizumab |
| **A** | Bevacizumab (n = 91), no bevacizumab (n = 96) | 3.29% | 1.04% |
| **B** | N = 321 | 0.93% | — |
| **C** | N = 131 | 0.80% | — |

- Risk of cerebral hemorrhage does not appear to be disproportionately high for patients who have received bevacizumab.
- Patients with CNS metastases should not, in general, be excluded from bevacizumab therapy.

Rohr UP et al. *Proc ASCO* 2009;**Abstract 2007**.

## SELECT PUBLICATIONS


Batchelor TT et al. **Phase II study of cediranib, an oral pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma.** *J Clin Oncol* 2010;28(17):2817-23.

Brandsma D et al. **Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas.** *Lancet Oncol* 2008;9(5):453-61.

Cloughesy T et al. **Updated safety and survival of patients with relapsed glioblastoma treated with bevacizumab in the BRAIN study.** *Proc ASCO* 2010;**Abstract 2008**.

Eichler AF et al. **A phase I study of cediranib plus whole-brain radiation therapy in patients with brain metastases from non-small cell lung cancer.** *Proc ASCO* 2010;**Abstract TPS177**.

Friedman HS et al. **Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma.** *J Clin Oncol* 2009;27(28):4733-40.

Rohr UP et al. **Safety of bevacizumab in patients with metastases to the central nervous system.** *Proc ASCO* 2009;**Abstract 2007**.

Wen PY et al. **Phase II study of XL184 (BMS 907351), an inhibitor of MET, VEGFR2, and RET, in patients (pts) with progressive glioblastoma (GB).** *Proc ASCO* 2010a;**Abstract 2006**.

Wen PY et al. **Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group.** *J Clin Oncol* 2010b;28(11):1963-72.