CALGB 30901

Randomized Phase II Study of Maintenance Pemetrexed vs. Observation for Patients with Malignant Mesothelioma without Progression after First-Line Chemotherapy

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ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

CALGB 30901 Rationale

- Malignant pleural mesothelioma (MPM) is an uncommon tumor afflicting up to 3,000 patients annually in the United States.
- Pemetrexed and cisplatin, been approved by the FDA based on results of a randomized phase III trial, where treatment with pemetrexed and cisplatin was better than cisplatin alone with regard to response rates (41 vs. 17%), time to progression (6 vs. 4 months), and overall survival (12.1 vs. 9.3 months, p=0.02) (J Clin Oncol. 2003 Jul 15;21(14):2636-44).

CALGB 30901 Rationale

- Single arm study conducted in patients with mesothelioma who had at least stable disease after 6 cycles of pemetrexed-based chemotherapy demonstrated that maintenance therapy with pemetrexed in patients with mesothelioma was well tolerated, and demonstrated improved TTP and OS (3.4 and 6.0 months versus 8.5 and 17.9 months, respectively ($p < 0.0001$)(J Thorac Oncol 1:25-30, 2006).
- A phase III trial in advanced with mesothelioma confirmed that treatment with pemetrexed as a second-line regimen resulted in improved progression free survival over best supportive care ($p=0.148$) (although that trial was conducted in patients who had not received pemetrexed as part of their first-line therapy)(J Clin Oncol 26:1698-704, 2008.)
- Therapy with single agent vinorelbine in pemetrexed pre-treated patients achieved partial response in 15.2% cases, and stable disease in 33.9% cases. Median PFS and OS were 2.3 and 6.2 months, respectively (Lung Cancer. 2014 Jun; 84(3):265-70.).
- Treatment with gemcitabine and vinorelbine in patients pretreated with platinum and pemetrexed resulted in median PFS of 6.0 months, whereas OS was 11.2 months (Int J Clin Oncol. 2014 Aug;19(4):601-6).
- At present, role of maintenance therapy in mesothelioma is unknown**. Frequent practice is to continue first line therapy till progression.**

Promising Second Line Strategies:
A phase II study of intermittent sunitinib malate as second-line therapy in progressive malignant pleural mesothelioma.

- **METHODS:**

  Patients with mesothelioma and radiological progression after chemotherapy received oral sunitinib 50 mg daily for 28 of every 42 days. The primary endpoint was objective radiological response. Correlative biomarkers included serum mesothelin, vascular endothelial growth factor (VEGF)-A, VEGF-C, interleukin-8, sVEGFR-2, sVEGFR-3, and s-kit.

- **RESULTS:**

  Fifty-three patients received sunitinib between July 2006 and December 2009; 51 were assessable for response. Patients received a median of two cycles (range, 1-12); 40% required dose reduction. Fatigue was the most prominent toxicity**. Six patients (12%) had a confirmed radiological partial response, 34 (65%) had stable disease, and 11 (22%) had progressive disease as best response.** Six of 20 patients had a decrease in fluorodeoxyglucose positron emission tomographic total glycolytic volume of 15% or more. **Median overall survival was 6.1 months, and median time to progression was 3.5 months.** Correlative biomarkers did not predict treatment response.

- **CONCLUSIONS:**

  Sunitinib has activity in a subset of patients with pretreated MPM.

Promising Second Line Strategies: **Anti CTLA4 Therapy**

Study	Agent	Phase	Accrual	No. patients enrolled
MESOT-TREM-2008 (NCT01649024)	Tremelimumab second line	II	Completed	29
MESOT-TREM-2012 (NCT01655888)	Tremelimumab second line	II	Completed	29
D4880C00003 (NCT01843374)	Tremelimumab versus PBO second/third line	II	Recruiting	564

Cancer Immunol Immunother. 2015 Jan;64(1):105-12.

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Eligibility

- Malignant pleural mesothelioma not amenable to surgery
- CR, PR or SD after 4-6 cycles of pemetrexed and cisplatin or carboplatin
- Randomization before Cycle 5 D1 in patients receiving additional treatment, or before Day 22 of cycle 4 in patients receiving only 4 cycles of therapy.
- Treatment on maintenance arm should not start earlier than 3 weeks after starting last cycle of first line therapy.
- Age ≥18 years
- Performance status 0-1

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Schema

Pemetrexed + Cisplatin or Carboplatin (4-6 cycles)

↓ CR, PR or SD

Enrolled and Randomized

Stratify:

Cisplatin vs. Carboplatin

Epithelioid Histology vs. Other

< 6 vs. 6 cycles

↓ Arm A

Observation to PD

↓ Arm B

Pemetrexed to PD or intolerable toxicity

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Study Information

- Primary endpoint: progression free survival
- CT scans performed every 6 weeks for 6 months, then every 9 weeks for 6 months, then every 12 weeks until progression for a maximum of 3 years
- Imaging correlative for volumetric measurements
- Tissue and blood correlates (TYMS, DYPD, MTHFR genetic variants, TYMS exp, SMRP)
- Treatment choice at progression is at physician's discretion
- Sample size: 60 eligible patients

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Initial Statistical Assumptions

- Pemetrexed and cisplatin had a median PFS of 6 months in phase 3 study.
- Arm A; a median PFS of 3 months during the maintenance phase
- Arm B; a 67% improvement in median PFS to 5 months
- Using a log rank test at a 1-sided significance level of 0.10, the study has approximately 86% power.
- Interim analysis at 44 cumulative events on both arms. The trial is subject to stopping early for either superiority or inferiority.

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Current Statistical Assumptions

- Pemetrexed and cisplatin had a median PFS of 6 months in phase 3 study.
- Arm A; a median PFS of 3 months during the maintenance phase
- Arm B; a 100% improvement in median PFS to 6 months
- Using a log rank test at a 1-sided significance level of 0.10, the study has approximately 91% power.
- 60 eligible patients (30 per arm) will be randomized to Arm A
- and Arm B with 1:1 allocation.
- Interim analysis at 44 cumulative events on both arms. The trial is subject to stopping early for either superiority or inferiority.

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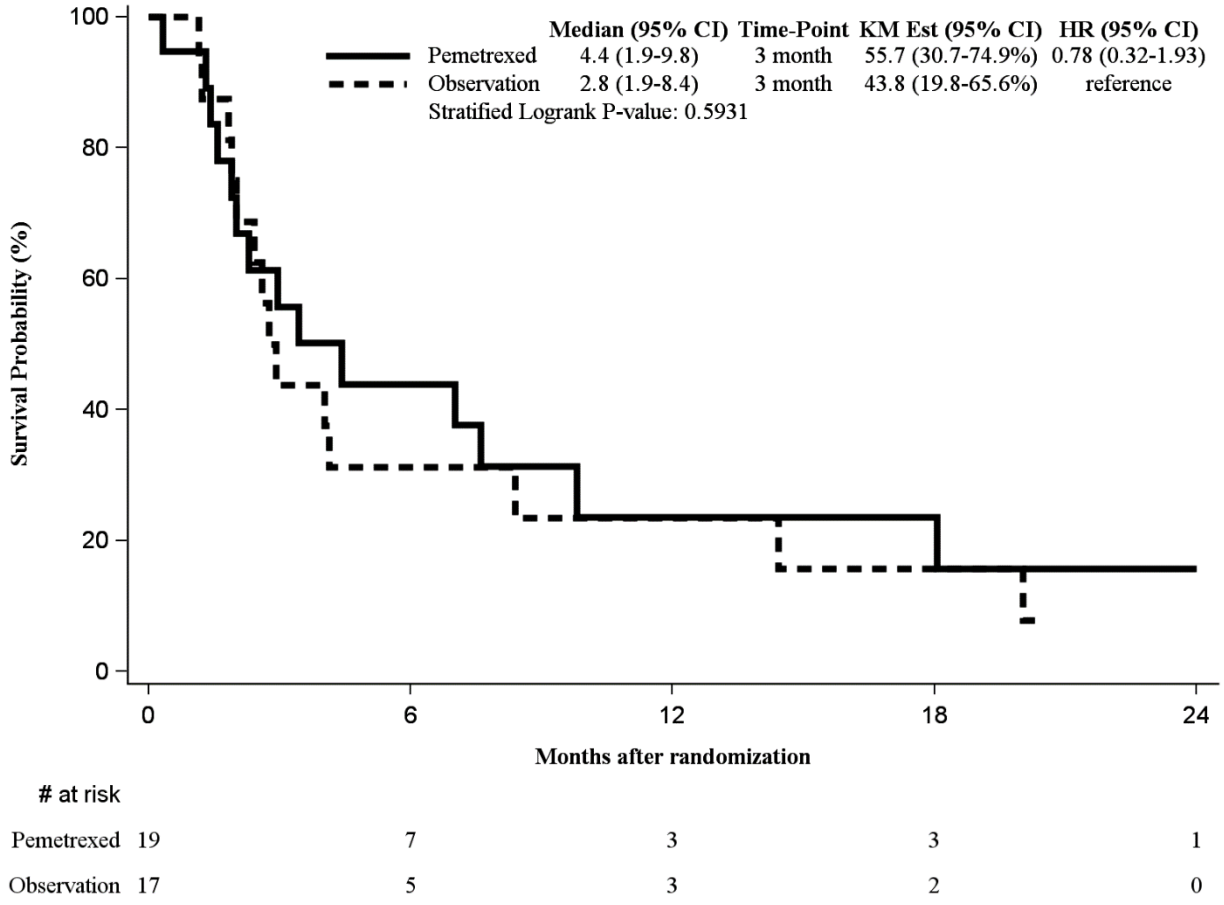
Current Accrual

- 67 pre-registered.
- Treated or on therapy: 50
- Arm A (Observation) : 25
- Arm B (Pemetrexed): 25

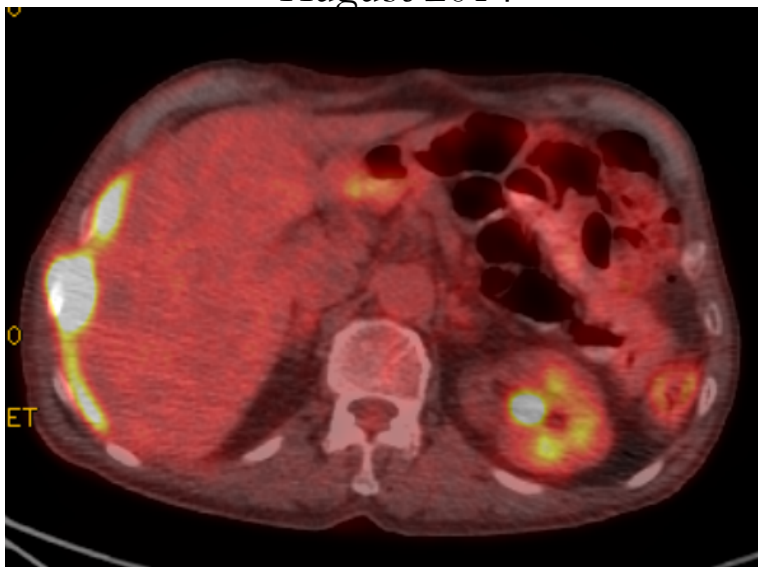
Interim Analysis, March 26, 2015



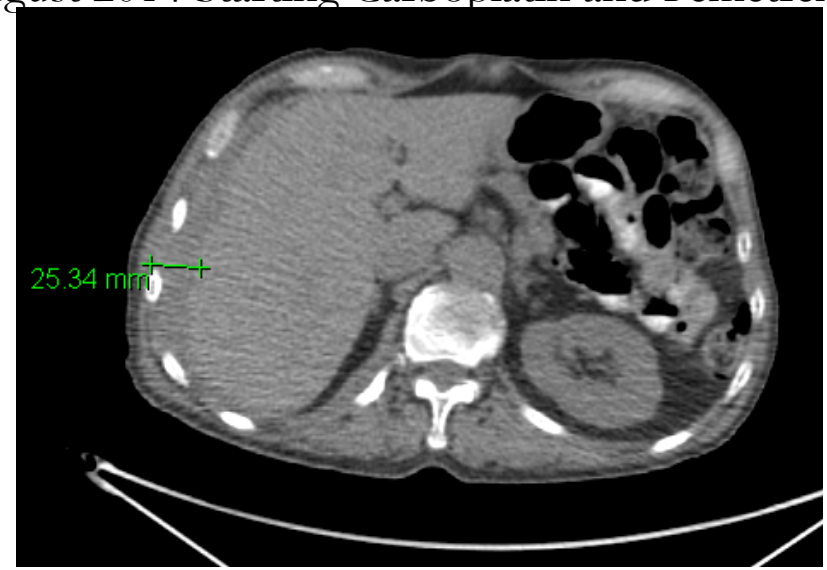
Mesothelioma Case on CALGB 30901

- 76 y. old man presented with history of dyspnea on minimal exertion, fatigue, productive cough with white sputum, and weight loss of 15 lbs over the past year. Consequently was found to have right sided pleural effusions and underwent pigtail catheter placement in June of 2014 to right pleural space. The fluid was found to be exudative, but no malignant cells were found and cultures were negative.
- Pt was then admitted again on July 2014 for effusion re-accumulation. Thoracentesis was performed which again showed exudative fluid. Cytology showed atypical mesothelial cells, but no malignancy.
- Subsequently patient underwent right thoracoscopy with pleural biopsy and right Pleurx catheter placement. Once in the pleural space, the operative report noted, "Diffuse tumor studding of the parietal and diaphragmatic pleural was seen. Adhesions of the lung to the chest wall at the right middle lobe." Pathology was consistent with mesothelioma.
- Patient then received four cycles of carboplatin and pemetrexed with partial response and minimal toxicity
- Consented to CALGB 3001 study and was randomized to pemetrexed.

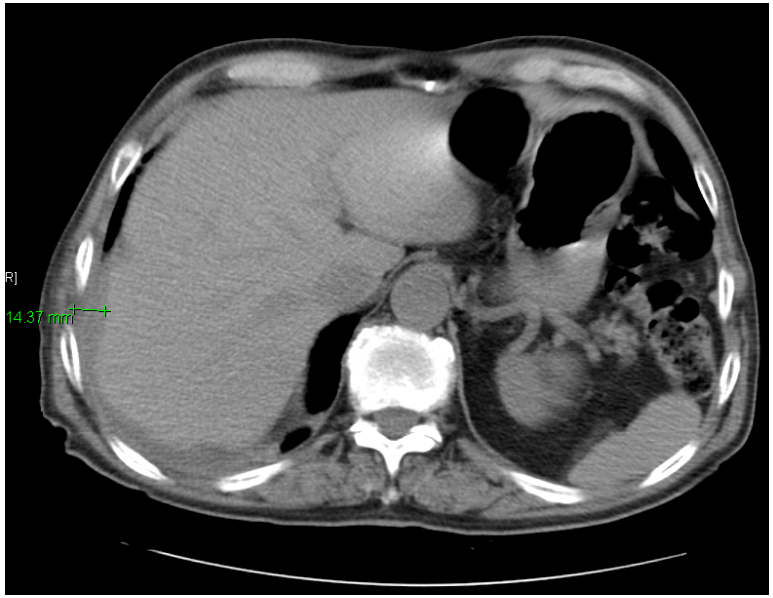
August 2014



August 2014 Starting Carboplatin and Pemetrexed



November 2014 Randomized to Pemetrexed



January 2015 Progression