NOV-002 Plus Carboplatin Yields Disease Stability in Platinum-Resistant Ovarian Cancer

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Abstract

Background: Platinum remains the single most effective drug for the treatment of epithelial ovarian cancer; however with relapse and re-treatment most patients eventually become resistant to these drugs. Response rates to salvage chemotherapy in this population is 10-20%, with PFS typically < 8 weeks in 4th line. One mechanism of platinum resistance is thought to be mediated by changes in the cellular redox potential. Oxidized glutathione (GSSG), the active component of NOV-002, regulates the intracellular redox state via the glutathione (GSH) pathway. This study aims to determine tolerabilty, response rate and PFS to NOV-002 with carboplatin in women with platinum resistant ovarian, tubal or peritoneal cancer.

Methods: NOV-002 is given by IV bolus on lead-in day -1 at cycle 1, and on day 1 at subsequent cycles, followed by Carboplatin AUC 5. NOV-002 is then continued via daily SC injection, with 28 day cycles. Patients must be platinum refractory/resistant, with measurable disease and ≤ 3 prior lines. Fifteen patients are accrued in the first stage of the trial; if ≥ 2 responses, 10 additional patients will be accrued.

Results: Stage I accrual is complete. Patients were heavily pretreated with 12/15 having received 3 prior lines. Toxicity was mild-moderate with no grade 4 toxicity. There was no febrile neutropenia. The most common toxicities were nausea and fatigue, as well as abdominal pain and bowel obstruction thought to be related to underlying disease. To date, there is 1 PR, 7 SD and 5 PD, with 1 patient off-trial for patient discretion. PFS is 14 weeks. Treatment and evaluation are ongoing, with the possibility of accrual to the second stage if another PR is seen.

Conclusions: Patients tolerated this regimen extremely well, with most toxicity attributable to carboplatin alone. The PFS was longer than expected, with a significant proportion of these platinum resistant patients achieving clinical benefit with prolonged stable disease. Updated results will be available.

Selected eligibility criteria

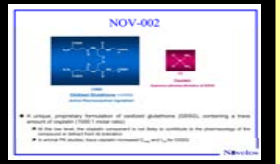
- Ovarian, tubal or peritoneal cancer
- Platinum resistant/ refractory
- No more than 3 prior lines
- Measurable disease

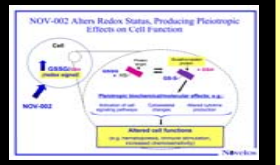
Prior Therapy

1 line: 1 pt
2 lines: 3 pts
3 lines: 11 pts

NOV-002 Background

- The active ingredient in NOV-002 is **oxidized glutathione**
- Changes in the ratio of oxidized : reduced glutathione controls cellular redox state and can regulate protein function by the reversible formation of mixed disulfides between protein cysteines and glutathione (= **glutathionylation**).
- Protein glutathionylation by NOV-002 results in pleiotropic effects on cell functions including cell signaling pathways, cytoskeletal architecture and cytokine production and is associated with hematopoiesis, immune stimulation and increased chemosensitivity of tumor cells.
- NOV-002, in combination with standard chemotherapy, is also the subject of an ongoing pivotal Phase 3 trial in advanced non-small cell lung cancer and an exploratory Phase 2 trial for neoadjuvant treatment of breast cancer.





Treatment

Day 1: NOV-002 60 mg IV push* followed 60 minutes later by Carboplatin AUC 5 given over 30-60 minutes

Days 2-28: NOV-002 60 mg SC given daily by patient self-injection (1 cycle = 28 days)

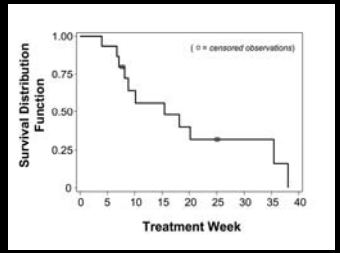
At cycle 1* ***only* *a lead-in dose of NOV-002 120 mg IV push is given as two 60 mg boluses, 3 hours apart on day –1*

Toxicity

- No grade 4 toxicity
- Grade 3 toxicity included: (1 each) DVT, abd pain, bowel obstruction, depression, syncope, fatigue, neuropathy, and 2 cases of platinum allergy. None thought related to NOV-002.
- There was no febrile neutropenia
- Hematologic toxicity was mild with only grade 1-2 events

Efficacy

- **Tumor responses** CR: 0, PR:1, SD: 8, PD: 6
- The criterion for continuing to Stage II of the study (≥ 2 responses) was not met, though the regimen demonstrated clinical benefit (CR+PR+SD) in 60% of patients
- **Progression-Free Survival:** **Median: 15.4 wks**
  Mean: 19.4 wks (range 4-38 wks)



CONCLUSIONS

- This is a well-tolerated regimen with no apparent additive toxicity of NOV-002
- Toxicity was limited to what would be expected from carboplatin alone
- Hematological toxicity was mild, suggesting possible mitigating effect of NOV-002
- Median PFS was 15.4 weeks, which is longer than historical controls of ~8 wks (Berkenblit *et al.* Gyn Onc, 2004) in similar heavily-pretreated pts
- Mean PFS was 19.4 weeks, indicating some patients derive prolonged clinical benefit
- NOV-002 deserves further study in ovarian cancer

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