Improved Progression-Free Survival among Women with Measurable Recurrent Ovarian Carcinoma Treated with CA4P Plus Bevacizumab: A Post-Hoc Analysis of GOG-0186I*

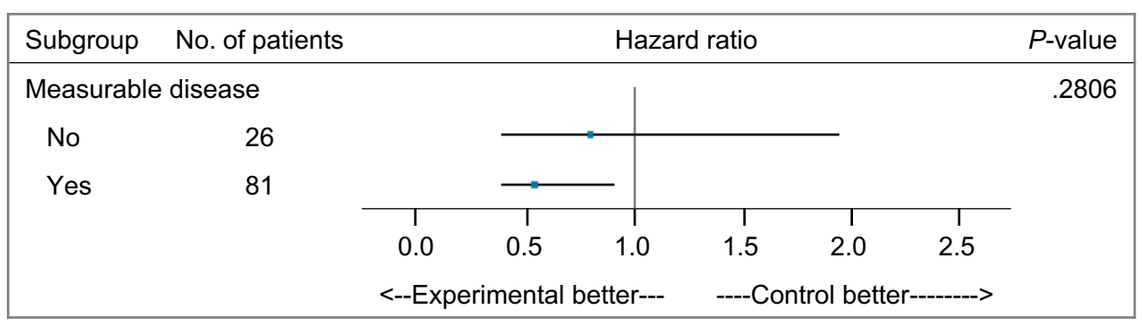
K.S. Tewari[1], N.E.D. Abrouk[2], R.L. Coleman[3], C. Aghajanian[4], R. Couchenour[5], J. Nelson[5], R. Mannel[6], P.A. DiSilvestro[7], D.G. Mutch[8], L.M. Randall[1], J. Farley[9], S.C. Rubin[10], M.W. Method[11], F.B. Stehman[12], B. J. Monk[13]

[1]University of California Irvine, [2]Innovexe, LLC, [3]University of Texas MD Anderson Cancer Center, [4]Memorial Sloan Kettering Cancer Center, [5]Mateon Therapeutics, Inc. [6]University of Oklahoma Health Sciences Center, [7]Women and Infants Hospital of Rhode Island, [8]Washington University School of Medicine, [9]Dignity Health St. Joseph's Hospital and Medical Center, [10]Fox Chase Cancer Center, [11]Indiana University School of Medicine, [12]Indiana University Health, [13]University of Arizona

Background

- Vascular Targeted Therapies (VTTs) are classified into 2 categories:
  - anti-angiogenics (AAs) which inhibit angiogenesis
  - vascular disrupting agents (VDAs) which obstruct tumor vasculature[1,2]
- The mechanism of actions of AAs and VDAs are complementary[3,4,5]
  - VDAs target established vasculature leading to tumor cell necrosis while AAs target the VEGF rich outer rim preventing revascularization of the tumor
- Combretastatin A4-phosphate (CA4P) is a tubulin-binding VDA with demonstrated activity in combination with the AA, Bevacizumab (Bev), in both Phase 1 and 2 studies[4,5]
- The phase 2, GOG-0186I study randomized recurrent ovarian carcinoma (OC) patients (n=107) previously treated with ≤3 prior regimens to CA4P 60 mg/m^2 + Bev 15 mg/kg or Bev alone q3wks, until progression or toxicity
  - The study demonstrated combination VTT therapy (CA4P+Bev), significantly improved progression-free survival (PFS) compared to Bev alone in recurrent OC
    - Median PFS was 7.3 months for CA4P+Bev vs. 4.8 months for Bev alone (HR, 0.69, 90%CI [0.47 to 1.00]; 1-sided *P*=.049) [5]
- VDA activity appears enhanced based on tumor size
  - In preclinical studies, VDA activity increased as tumors became larger[6,7]
    - As tumors become larger, a smaller percentage of tumor cells depend on normal tissue vasculature at tumor rim
  - In GOG-0186I, patients with measurable disease had improved PFS response with CA4P+Bev compared to Bev alone (Figure 1)[5]

Figure 1: Progression-free survival for measurable disease.



- Objective of these post-hoc analyses was to assess relationship between treatment effects and measureable disease/tumor size

Methodology

- Post-hoc analyses of GOG-0186I were conducted in patients with measurable disease (>1cm) (RECIST) (n=81)
  - Tumor size: Sum of longest diameters (SLD) at baseline was used to analyze the groups of patients above and below the median baseline SLD for the population with measurable disease at baseline, 5.7cm
  - PFS and overall survival (OS) were estimated using Kaplan-Meier method
  - A Cox proportional hazards model was used to calculate HR and p values

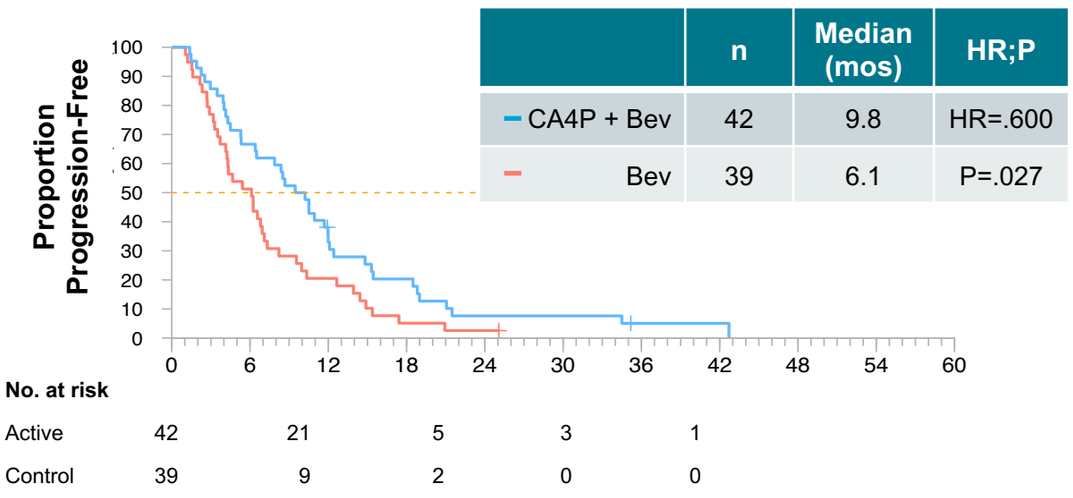
Results

- 81 patients of 107 patients had measurable disease
  - Median tumor size was 5.7cm
- In the measurable disease subgroup, treatment with CA4P+Bev compared with Bev alone significantly improved PFS (3.7 months; HR 0.600; P=0.027) (Figure 2)
  - A trend of improved OS was observed (5.6 months; HR 0.777; P=0.377)

*Supported by Grant: No. CA27469 from NCI to GOG Admin. Office; No. CA37517 to the GOG Statistical Office; No, 1U10CA180822 to NRG Oncology; and No. U1)CA180868 to NRG Operations

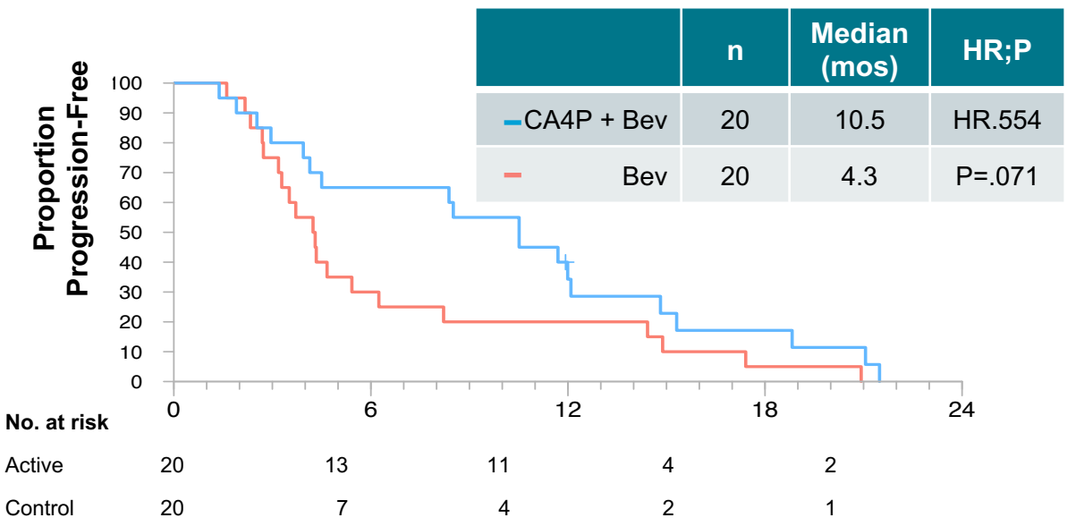
Results, cont'd

Figure 2: Progression-free survival for measurable disease.



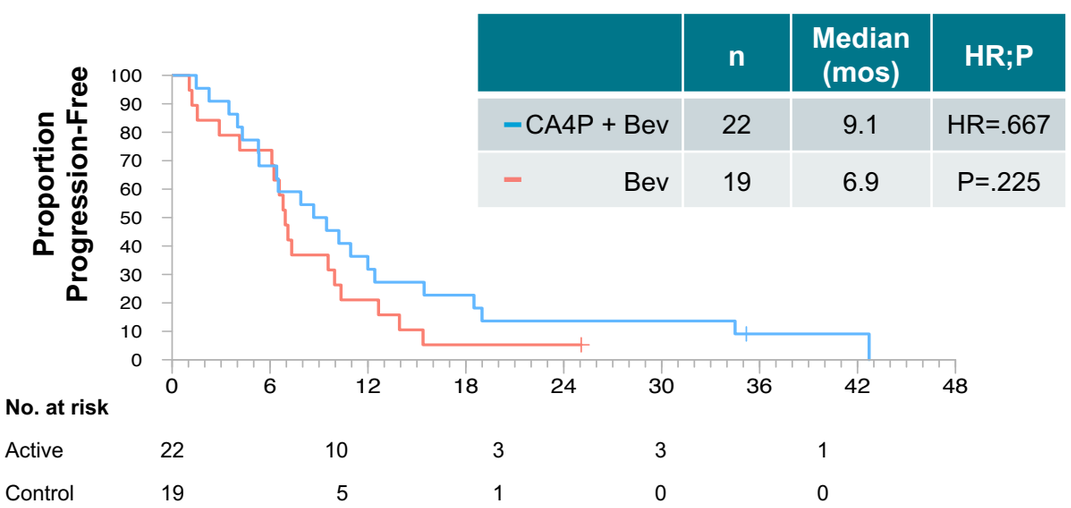
- In 40 patients with larger tumors (>5.7cm), PFS increased (6.2 months) in CA4P+Bev versus Bev alone (Figure 3)

Figure 3: Progression-free survival for tumor size >5.7 cm.



- For those patients (n=41) with smaller tumors (<5.7cm), PFS increased (2.2 months) in CA4P+Bev versus Bev alone (Figure 4)

Figure 4: Progression-free survival tumor size ≤ 5.7 cm.



- Adverse events were as reported previously

Conclusions

- A significantly greater response in PFS was seen in patients with measurable disease treated with CA4P+Bev vs. Bev alone
  - Numerical trends for improvements in OS were observed
- These data show a trend (improved HR) with increasing tumor size when CA4P is added to Bev compared to Bev alone
  - This difference was not statistically significant, but it is hypothesis generating and should be prospectively studied
- No new safety signals were noted

References

1. Galbraith SM et al. *Anticancer Res* 2001; 21:93-102.
2. Vincent L et al. *J Clin Invest* 2005; 115:2992-3006.
3. Siemann DW et al. *Anticancer Res* 2008; 28:2027-2031
4. Nathan P et al. *Clin Cancer Res 2012;* 18:3428-3439
5. Monk et al. *J Clin Oncol* 2016; 34(19):2279-86.
6. Landuyt et al. *Eur J Cancer* 2000; 36:1833-1843
7. Siemann DW et al. *Int J Rad Onc Biol Phys* 2005; 62:846-854