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COMPLEMENT C3 INHIBITION WITH PEGCETACOPLAN ABROGATES NEUTROPHIL SUPPRESSOR FUNCTION AND INHIBITS CIRCULATING NEUTROPHIL EXTRACELLULAR TRAPS IN PATIENTS WITH RECURRENT EPITHELIAL OVARIAN CANCER

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Background: Persistent malignant effusions (MEs) are common in recurrent ovarian cancer (OC) and other advanced solid tumors. Using malignant ascites fluid supernatants (ASC) from patients with OC as an authentic and clinically relevant component of the tumor microenvironment (TME), we observed that neutrophils acquire a complement-dependent T cell suppressor phenotype in the TME characterized by suppression of T cell proliferative, cytokine and metabolic responses. Similar results were observed in ME from other solid tumors showing generalizability. In addition, ASC induced neutrophil extracellular traps (NETs) a distinct mode of neutrophil death characterized by externalization of chromatin and proteases. NETs have been implicated in tumor progression and immune evasion in mice. We designed a clinical trial to investigate whether complement inhibition can control MEs in patients with recurrent OC. Systemic pegcetacoplan (APL-2) is a peptide complement C3 inhibitor approved for paroxysmal nocturnal hemoglobinuria; its use in cancer is novel. As part of the rationale, we posited that pegcetacoplan would abrogate neutrophil suppressor function and inhibit NET generation.

Methods: This trial included two sequential safety lead-in cohorts: (i) pegcetacoplan alone for 2 weeks followed by addition of pembrolizumab (anti-PD1) (n=3), and (ii) pegcetacoplan with pembrolizumab and bevacizumab (anti-VEGF) (n=3). Following DSMC approval, the phase 2 randomization involved 3 cohorts: (i) bevacizumab (standard of care), (ii) pegcetacoplan plus pembrolizumab, and (iii) pegcetacoplan plus pembrolizumab and bevacizumab. Primary endpoints were safety and ME control. Correlative studies included assessment of the effect of pegcetacoplan-based regimens on neutrophil suppressor activity

against T cells and NET markers (citrullinated histone 3, myeloperoxidase levels) using baseline and on-treatment serum and ME samples.

Results: The best observed response was stable disease (SD), achieved in 5 of 8 patients. Interim data suggest that pegcetacoplan exerts a therapeutic impact on MEs, with 3 patients achieving long lasting SD without requiring therapeutic drainage since starting the trial. Pegcetacoplan-based regimens partially abrogated the capacity of ME to induce neutrophil suppressor function in co-cultures of healthy donor neutrophils and T cells incubated in ME. Pegcetacoplan-based treatments, including single-agent pegcetacoplan from the initial safety lead-in cohort, significantly reduced serum markers of NET formation, although this effect was not observed in ME samples. Pegcetacoplan treatment did not significantly affect serum or ME soluble complement activation products.

Conclusions: Our interim data suggest that pegcetacoplan can control ME in recurrent OC. If confirmed, our immunologic studies point to abrogation of neutrophil suppressor function and inhibition of circulating NETs as potential mechanisms for this benefit. Complement activation, NETs, and thrombosis create a self-amplifying loop that can drive vascular injury and thrombosis, VEGF production, and vascular leak that causes ME accumulation. Additional studies will clarify the extent that C3 inhibition disrupts this loop, including its effect on vascular injury markers. We expect these findings to be generalizable to other advanced solid tumors with refractory ME.