2516 **Poster Discussion Session**

Phase I trial of adjuvant autogene cevumeran, an individualized mRNA neoantigen vaccine, for pancreatic ductal adenocarcinoma.

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Background: Pancreas ductal adenocarcinoma (PDAC) is a lethal cancer that claims ~90% of patients in <24 months of diagnosis. PDAC is also refractory to immunotherapy as most tumors exhibit an immune excluded/desert phenotype. However, although characterized by low mutation rates, most PDACs harbor mutations that can generate immunogenic neoantigens. Here, we report the results of a phase-I trial of autogene cevumeran, a systemic RNA-lipoplex individualized neoantigen-specific immunotherapy (iNeST) vaccine, to stimulate immunity against neoantigens in resected PDAC patients. **Methods:** We conducted an investigator-initiated, single-center, phase-I trial of adjuvant autogene cevumeran containing up to 20 neoantigens in each individualized vaccine, identified from resected PDACs using real-time next generation sequencing and bioinformatic neoantigen discovery. Following surgery, patients received atezolizumab (1 dose; week 6), autogene cevumeran (8 weekly doses starting week 9; doses 9,10 – weeks 17, 46), and modified (m) FOLFIRINOX (12 cycles; starting week 21). Primary endpoint: safety. Other endpoints: feasibility (actual vs. target treatment time), vaccine response (responder = positivity by two independent blood assays: IFNg ELISpot and T cell clonal expansion), and recurrence-free survival (RFS). Target accrual: n=20. **Results:** n=19 patients underwent surgery and received atezolizumab at 6.3 weeks (median; 95% CI 6.0–6.57) after surgery with no ≥ grade 3 (Gr3) adverse events. n=16/19 patients (84%) received autogene cevumeran at 9.4 weeks (median; 95% CI 9–10) after surgery. n=1/19 (5%) had insufficient neoantigens for vaccine manufacture. n=1/16 (6%) developed a vaccine-related Gr3 fever and hypertension. n=15/16 vaccinated patients (94%) received mFOLFIRINOX (median 12 cycles; 95% CI 7–12). Autogene cevumeran expanded polyclonal (median 7.5 clones, 95% CI 2–28), IFNg-producing neoantigen-specific $CD8^+$ T cells in 50% (n=8/16) of patients from undetectable levels to large fractions (median 2.9%, Table) of all blood T cells. At an early median follow-up of 15 months, vaccine responders (n=8) had a longer RFS vs. non-responders (n=8) (median not reached vs. 13.7 months, HR 0.08, 95% CI 0.01-0.5, $P = 0.007$). **Conclusions:** Autogene cevumeran is safe, feasibly manufactured in a clinically relevant timeframe, and immunogenic in PDAC. Vaccine induced neoantigen-specific immunity preliminarily correlates with improved PDAC outcome. Further clinical trials in PDAC are warranted. (This imCORE Network project was funded by Genentech Inc and BioNTech; additional funding from Stand Up To Cancer, Lustgarten Foundation). Clinical trial information: NCT04161755. Research Sponsor: Genentech Inc, BioNTech, Other Foundation.

Vaccine-induced T cells.

	Median % of all blood T cells (95% CI)		
	Pre-vaccine	*Post-vaccine*	*P* value
Non-responders (n=8)	0 (0-0)	0 (0-0.6)	0.001
Responders (n=8)	0 (0-0)	2.9 (0.2-10.4)	