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A Phase 1 Study Of VAC85135, A Neoantigen Vaccine Regimen Targeting Calreticulin And JAK2 Mutations, In Combination With Ipilimumab In Patients With Myeloproliferative Neoplasms

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Key Takeaway

In this Phase 1 study, the VAC85135 regimen was poorly immunogenic to *CALR* or *JAK2* neoantigens when administered alone or in combination with ipilimumab, a checkpoint inhibitor, in most patients. The lack of observed disease-modifying efficacy in any patient suggests the VAC85135 regimen was unable to generate productive neoantigen anti-tumor immunity within the study timeframe.

Conclusions

The VAC85135 regimen was well tolerated, with adverse event profiles consistent with that of ipilimumab.

The absence of robust immune responses, combined with lack of disease-modifying activity, does not support further development of the VAC85135 regimen for the treatment of MPNs.

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Poster

Supplementary material

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Acknowledgments

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Disclosures

Dr Otoukesh has no disclosures to report.

Introduction

- Myeloproliferative Neoplasms (MPNs), including essential thrombocythemia (ET), and primary myelofibrosis (MF), are slow-progressing, incurable diseases of the hematopoietic stem cell compartment[1,2]
- Treatment (tx) options are limited, and patients (pts) suffer high symptom burden and life-threatening complications[3]
- Disease-specific somatic mutations (mut) in calreticulin (*CALR*) and *JAK2* (*JAKV617F*) are drivers of MPNs, causing generation of immunogenic peptide epitopes hypothesized to be vaccine-targetable neoantigens[1,2]
- *VAC85135* is a heterologous prime-boost vaccine regimen comprising adenoviral and vaccinia vectors encoding polypeptides specific to mut*CALR* and *JAK2V617F* **(Figure 1)**

Methods

- VAC85135MPN1001 is a Phase 1, first-in-human, open-label, multicenter study to evaluate safety, vaccine-specific immune responses, mut*CALR* and *JAK2V617F* allele burden, and preliminary anti-tumor clinical activity of VAC85135 concurrently with ipilimumab, a checkpoint inhibitor (anti CTLA-4), in adult MPN pts with confirmed expression of mut*CALR* or *JAK2V617F* who provided informed consent
- Pts received a maximum of 9 vaccine doses over a 60-week (wk) tx course
- The dose regimen comprised two 9-wk tx cycles of heterologous prime-boost vaccinations followed by 3 boosters, and samples were collected longitudinally for biomarker evaluation **(Figure 2)**; dose escalation was guided by Bayesian Optimal Interval design using a 22% target dose-limiting toxicity (DLT) rate
- A safety lead-in cohort (C)0 received VAC85135 alone by intramuscular (IM) injection at a flat dose of $1x10^{11}$ virus particles for adenovirus and $1x10^{8}$ infectious units for vaccinia vector; the same flat dose of VAC85135 IM was co-administered with intravenous (IV) ipilimumab at 1 mg/kg (C1) or 3 mg/kg (C2)

Figure 1: VAC85135 construct design

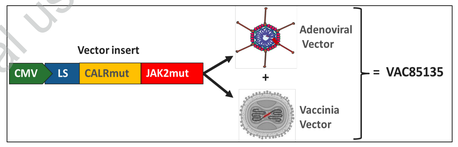
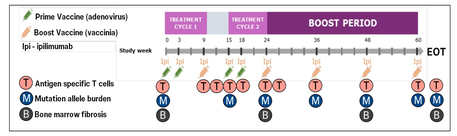


Figure 2: VAC85135 regimen and biomarker collection timepoints



Results

Safety

- 14 (MF, n=10, ET, n=4; mut*CALR*, n=12, *JAK2V617F*, n=2) pts were enrolled and received ≥1 study tx dose: C0 (n=3), C1 (n=8), and C2 (n=3)
- Overall, 9/14 (64.3%) pts reported tx-related adverse events (TRAEs; **Table 1**); most TRAEs were grade (G)1/2 (92.6%; **Supplementary Table 1)**
- G3 TRAEs included fatigue and splenomegaly (C1; **Supplementary Table 1)**
  - 4 TRAEs led to discontinuation of ipilimumab (C1: G3 immune-mediated splenomegaly and G1/2 diarrhea/colitis; C2: G2 immune-mediated diarrhea [met criteria for dose limiting toxicity (DLT)]; G1 worsening of musculoskeletal stiffness)
  - There were no TRAEs or related discontinuations in VAC85135-only treated pts
    - One pt in C0 experienced worsening G2 paroxysmal nocturnal hemoglobinuria and discontinued VAC85135 (unrelated to study tx)

Table 1: Treatment-related Adverse Events

TRAEs, n (%)	Cohort 0 (n=3)	Cohort 1 (n=8)	Cohort 2 (n=3)	Overall (N=14)
Any TRAE	0	7 (87.5)	2 (66.7)	9 (64.3)
Most common TRAEs (any grade, ≥10% overall)				
Diarrhea	0	1 (12.5)	1 (33.3)	2 (14.3)
Nausea	0	1 (12.5)	1 (33.3)	2 (14.3)
Fatigue	0	1 (12.5)	1 (33.3)	2 (14.3)

Clinical Response

- No pts achieved a clinical response by European LeukemiaNet International Working Group-MPN Research and Treatment (ELN+IWG-MRT) criteria **(Table 2)**
  - Best overall response was no response (NR) in 4 ET pts and stable disease (SD) in 9 MF pts; 1 pt discontinued before the first disease evaluation

Table 2: Demographic and Disease Response

Cohort	Age, y/Sex	Diagnosis/ mutation type	Study day	Best response
Cohort 0	61/F	ET/*CALR* type 1	352	NR
	76/M	MF/*CALR* type 2	168	SD
	74/M	MF/*CALR* type 1	336	SD
Cohort 1	48/M	MF/*CALR* type 1	344	SD
	62/M	MF/*CALR* type 1	356	SD
	28/M	MF/*CALR* type 2	176	SD
	41/M	MF/*CALR* type 1-like	487	SD
	58/M	MF/*CALR* type 2	338	SD
	76/M	MF/*CALR* type 1	335	SD
	45/F	ET/*JAK2V617F*	446	NR
	43/F	ET/*JAK2V617F*	441	NR
Cohort 2[a]	61/M	ET/*CALR* type 2	218	NR
	64/F	MF/*CALR* type 1	253	SD

Disease was evaluated by overall clinical response per revised response criteria by ELN+IWG-MRT consensus report. [a]One pt (60/M with MF/CALR type 1) discontinued all tx at Wk 15 prior to first disease evaluation at Wk 24.

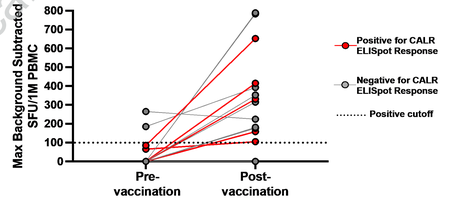
Pharmacokinetics

- The ipilimumab pharmacokinetic exposure (dose-normalized C_{max}) in the current study is similar to reported data in the ipilimumab study CA184007[4]

Vector immunogenicity

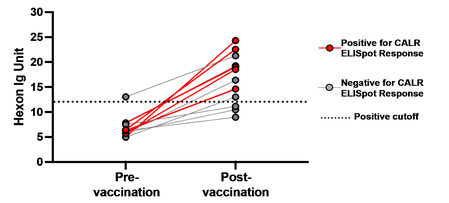
- Vaccine bioactivity was confirmed by evaluating antigen specific T cell and humoral immune responses to the hexon peptide constituent of the adenovirus vector by interferon (IFN)-γ ELISpot using pt PBMCs and anti-hexon antibody in pt serum by semi-quantitative ELISA
- Positive IFN-γ ELISpot was observed post-vaccination in 11/14 (78.6%) pts (C0, n=1; C1, n=8; C2, n=2) **(Figure 3)**
- Increased levels of anti-hexon antibodies were observed in 14/14 (100%) pts post-vaccination compared to pre-vaccination **(Figure 4)**

Figure 3. VAC85135 regimen ± ipilimumab induces adenovirus (hexon) specific T cell immune responses



Pt peripheral blood mononuclear cells (PBMCs) and serum were collected pre-vaccination (wk 0) and at various timepoints post-vaccination (wks 9, 15, 24, 36, 48, 60, end of treatment (EOT)). Antigen specific T cell responses to adenovirus hexon peptides were assessed in pt PBMCs by IFN-γ ELISpot. Maximum spot forming unit (SFU)/1 million (M) PBMC from any timepoint post-vaccination is shown. Positivity was defined as 100 SFU/1M PBMC after background (dimethyl sulfoxide; DMSO-stimulated) subtraction. Assay limit of detection (LOD) was 23 SFU.

Figure 4. VAC85135 regimen ± ipilimumab induces adenovirus (hexon) humoral immune responses

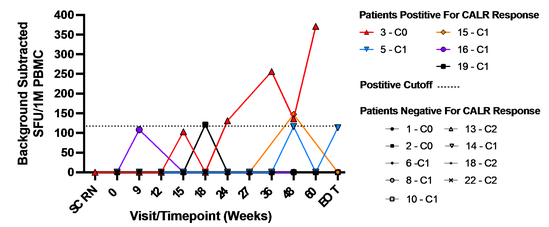


Pt PBMCs and serum were collected pre-vaccination (wk 0) and post-vaccination at wk 15. Anti-adenovirus hexon antibodies were detected by semi-quantitative ELISA in pt serum. Positive response criteria ≥12 hexon unit post-vaccination.

Mutant *CALR* Immunogenicity

- Positive IFN-γ ELISpot immune responses to a mut*CALR* peptide pool predicted to be recognized by MHC class I were observed post-vaccination in 5/14 (35.7%) pts (C0, n=1; C1, n=4) with confirmed *CALR* mutations **(Figure 5)**
- Immune response was maintained in pt 3 from C0 over the tx course starting after dose 3; immune responses in 4 C1 pts were transient and were observed only after dose 7 in 2 of 4 pts **(Figure 5)**
- No pts with confirmed *JAK2* mutations were positive for immune responses to mut*JAK2* antigens by IFN-γ ELISpot (data not shown)

Figure 5. VAC85135 regimen ± ipilimumab induces transient mutant *CALR* specific T cell responses in 5/14 patients

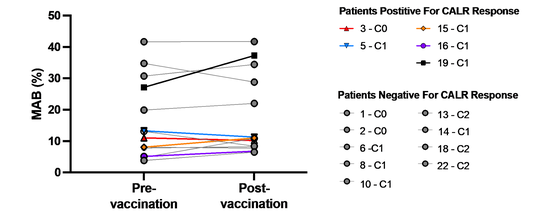


Pt PBMCs were collected at various timepoints (screening, SCRN; EOT) and assessed by IFN-γ ELISpot for antigen specific T cell responses to a pool of peptides present in type 1 mut*CALR* predicted to bind MHC I. ELISpot positivity was defined as 100SFU/1M PBMC after background (DMSO stimulated) subtraction. Assay LOD was 23 SFU.

Disease Biomarkers

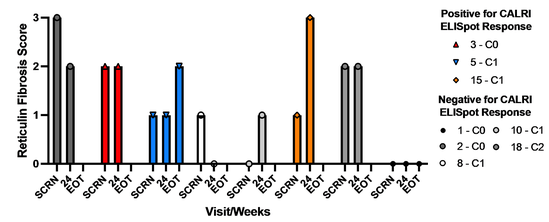
- No pt had reduced mut*CALR* or *JAKV617F* allele burden at any post-vaccination timepoint (**Figure 6**)
- Consistent reductions in reticulin fibrosis were not observed in post-vaccination bone marrow biopsies **(Figure 7)**

Figure 6. VAC85135 regimen ± ipilimumab does not reduce mutant *CALR* or *JAK2* allele burden



Pt blood was collected pre-vaccination (wk 0) and at various timepoints post-vaccination (wks 15, 24, 36, 48, 60, EOT) and frequency of mut*CALR* or *JAK2V617F* alleles were evaluated by next generation sequencing. Mutant allele burden at the latest post-vaccination timepoint collected for each patient is shown compared to pre-vaccination (wk 0).

Figure 7. VAC81535 regimen ± ipilimumab does not consistently reduce bone marrow fibrosis



Pt bone marrow biopsies were collected at SCRN, at 24 weeks post-vaccination and EOT. Reticulin staining was performed and the number, density and thickness of reticulin fibers were scored by a pathologist using a scale of 0 (absent) to 3 (dense).

References

1. Vainchenker W, et al. *F1000Res*. 2016:F1000. 2. Luque Paz D, et al. *Blood*, 2023;141(6):1909-1921. 3. How C-J, et al. Blood. 2024;144(Suppl 1): 3811. 4. Feng et al. *Brit J Clin Pharmacol*. 2014; 78(1):106-117.

Myeloproliferative Neoplasms

Presented by S Otoukesh at The European Hematology Association; June 12-15, 2025; Milan, Italy

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Supplementary Table 1. Treatment-related Adverse Events

	Cohort 0 VAC85135 only n=3	Cohort 1 VAC85135 + 1 mg/kg Ipilimumab n=8	Cohort 2 VAC85135 + 3 mg/kg Ipilimumab n=3	Overall N=14
Patients with 1 or more TRAEs related to any study agent in all treated patients	0	7 (87.5)	2 (66.7)	9 (64.3)
System organ class (preferred term)				
Gastrointestinal Disorders	0	3 (37.5)[a]	1 (33.3)[a]	4 (28.6)
Diarrhea	0	1 (12.5)	1 (33.3)[a]	2 (14.3)
Nausea	0	1 (12.5)	1 (33.3)	2 (14.3)
Abdominal pain	0	1 (12.5)	0	1 (7.1)
Colitis	0	1 (12.5)[a]	0	1 (7.1)
Enterocolitis	0	0	1 (33.3)	1 (7.1)
Proctitis	0	0	1 (33.3)	1 (7.1)
General Disorders And Administration Site Conditions	0	2 (25.0)[a,b]	1 (33.3)[a]	3 (21.4)
Fatigue	0	1 (12.5)[b]	1 (33.3)[a]	2 (14.3)
Injection site erythema	0	1 (12.5)[a]	0	1 (7.1)
Injection site mass	0	1 (12.5)	0	1 (7.1)
Pain	0	1 (12.5)	0	1 (7.1)
Musculoskeletal And Connective Tissue Disorders	0	2 (25.0)	1 (33.3)	3 (21.4)
Bone pain	0	1 (12.5)	0	1 (7.1)
Musculoskeletal stiffness	0	0	1 (33.3)	1 (7.1)
Pain in extremity	0	1 (12.5)	0	1 (7.1)
Nervous system disorders	0	1 (12.5)	1 (33.3)	2 (14.3)
Dizziness	0	0	1 (33.3)	1 (7.1)
Headache	0	1 (12.5)	0	1 (7.1)
Blood and lymphatic system disorders	0	1 (12.5)[b]	0	1 (7.1)
Splenomegaly	0	1 (12.5)[b]	0	1 (7.1)
Investigations	0	1 (12.5)	0	1 (7.1)
Decreased blood corticotrophin	0	1 (12.5)	0	1 (7.1)
Skin and subcutaneous tissue disorders	0	1 (12.5)	0	1 (7.1)
Rash	0	1 (12.5)	0	1 (7.1)
Vascular Disorders	0	1 (12.5)	0	1 (7.1)
Hot flush	0	1 (12.5)	0	1 (7.1)

TRAE, treatment-related adverse event.
[a]Grade 2 TRAEs. [b]Grade 3 TRAEs.
Based on a 20NOV2024 data-cut.

- Most TRAEs were Grade 1
- There were 4 Grade 2 TRAEs
  - Cohort 1: colitis (n=1); injection site erythema (n=1)
  - Cohort 2: diarrhea (n=1); fatigue (n=1)
- There were 2 Grade 3 TRAEs in Cohort 1
  - Fatigue (n=1); splenomegaly (n=1)

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