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Phase 1 Trial of CV301 in Combination With Anti-PD-1 Therapy in Non-Squamous NSCLC

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Abstract

Background: CV301 is an MVA-based vaccine encoding human Transgenes MUC1, CEA and TRICOM. A phase 1 dose-escalation trial (Gatti-Mays et al. 2019 CCR) concluded that CV301 is safe in advanced cancer and generated specific T cell responses against the encoded antigens. Preclinical data supports the rational for combining CV301 with PD-1 inhibitors. The primary objective of this trial (NCT02840994) was to evaluate safety and tolerability of this combination.

Methods: Patients with advanced non-squamous-NSCLC without actionable alterations in EGFR, ALK and ROS1 were eligible. Two priming doses of MVA-BN-CV301 (MVA) were administered in 4 separate subcutaneous (SC) injections of $4x10^8$ IU, 4 weeks apart, followed by boosting doses of Fowlpox-CV301 (FPV) given as a single injection of $1x10^9$ IU SC q2w for weeks 9-15, q4w for weeks 19-51 and q13w up to 17 doses for Cohort 1 (C1), q3w for weeks 7-22, q6w for weeks 28-52 and q12w up to 15 doses for Cohort 2 (C2). C1 included patients pre-treated with platinum-containing chemotherapy, who were considered eligible for nivolumab (N; 240 IV q2w). C2 included patients receiving front-line treatment with pembrolizumab (P; 200 mg IV q3w) after a minimum of 11 weeks of SD per RECIST.

Results: Between Oct 2017 and Sep 2018, 12 pts were recruited, 4 in C1 and 8 in C2. Median age was 64 years. 9 pts were female. Majority of patients were former smokers (9, 1 current, 2 never). As of Mar 2019 data cut-off, mean treatment duration was 272 days in C1 and 193 days in C2, with 7 pts continuing and 5 discontinued treatment. Both doses of MVA were administered to 3/4 pts in C1 and 7/8 pts in C2. CTCAE ≥ grade 3 AEs were observed in 3/4 pts in C1 and 3/8 pts in C2 with 1 fatal TEAE. IRAEs included 1 autoimmune hepatitis, and 1 pneumonitis fulfilling criteria of DLT. As of data cut, we observed 1 CR (C1), 10 SD and 1 discontinuation prior to first scheduled RECIST assessment.

Conclusions: The treatment of NSCLC with CV301 + N or P is feasible and tolerated, with no observed increase in the frequency or severity of expected AEs or IRAEs for each component of the combination.

Design & Treatment Schedule

NSCLC
2 Cohorts, 12 patients

Cohort 1 (C1)
NSCLC 2nd line
Nivolumab + CV301
N=4 patients

Cohort 2 (C2)
NSCLC 1st line
Pembrolizumab + CV301
N=8 patients

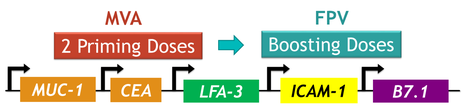
MVA-BN-CV301
2 Priming Doses + Anti-PD-1

Cohort 1 (C1):
2 weeks apart
Cohort 2 (C2):
3 weeks apart

FPV-CV301
Boosting Doses + Anti PD-1

Cohort 1 (C1):
Up to 17 doses
Cohort 2 (C2):
Up to 15 doses

BN-CV301 Construct



Tumor-associated antigens expressed on antigen-presenting cells (APC)

TRICOM (TRIad of COstimulatory Molecules) Genes for 3 costimulatory molecules to facilitate T cell /APC interaction and strengthen the anticancer immune response

Demographics

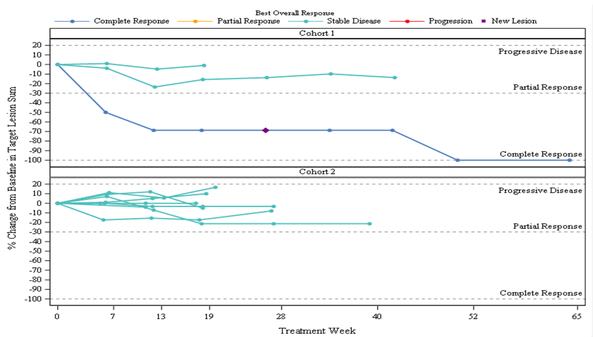
Age (Median)	64 years
Gender	9 Female 3 Male
Smoking	1 Current smoker 9 Former smokers 2 Never smoked

Best Overall Response

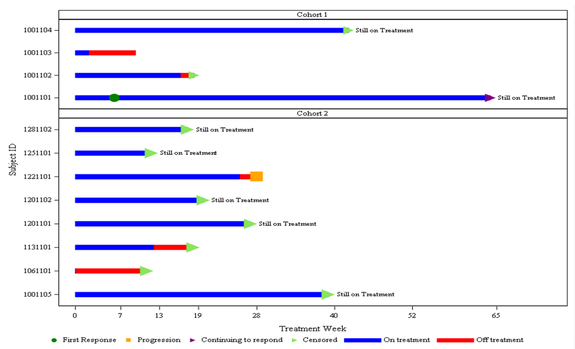
per RECIST v1.1, n (%)

Complete Response	1	(8.3)
Partial Response	0	(0)
Stable Disease	10	(83.3)
Progressive Disease	0	(0)
Unevaluable	1	(8.3)

Change in Tumor Burden



Subject Status per Cohort



Antigen Specific Responses

- Antigen specific responses to MUC-1 and CEA could be analyzed in 4 patients; cascade responses to Brachyury could be analyzed in 3 patients
- 4/4 patients developed T cell responses to at least 1 of the antigens tested
  - 4/4 patients developed MUC-1 responses
  - 3/4 patients developed CEA responses

MUC1

PT #	Days vs Pre	CD4 CD107a	CD4 IFNg	CD4 IL-2	CD4 TNF	CD8 CD107a	CD8 IFNg	CD8 IL-2	CD8 TNF
1001101	D14	0	0	0	0	394	0	0	372
	D43	0	0	0	0	0	0	0	0
	D71	0	0	0	0	0	0	0	0
1001102	D14	0	0	420	34	0	0	67	0
	D43	0	0	0	0	0	0	0	0
	D155	0	0	0	0	0	0	362	0
1001103	D14	581	199	0	0	1519	1505	0	4653
	D43	260	391	0	0	5365	2321	0	5826
1001105	D21	0	0	0	0	0	0	0	0
	D106	0	6774	0	0	4828	9954	0	8343

CEA

PT #	Days vs Pre	CD4 CD107a	CD4 IFNg	CD4 IL-2	CD4 TNF	CD8 CD107a	CD8 IFNg	CD8 IL-2	CD8 TNF
1001101	D14	0	0	0	0	0	0	0	0
	D43	0	0	0	0	959	0	0	32
	D71	0	0	0	53	0	0	0	0
1001102	D14	0	0	0	513	79	0	0	505
	D43	161	2280	0	196	1840	949	880	0
	D155	553	0	0	0	1561	0	1317	0
1001103	D14	166	0	0	0	0	0	0	0
	D43	0	0	0	0	2248	2696	0	9334
1001105	D21	0	0	0	0	0	0	0	0
	D106	0	0	0	0	0	0	0	0

Brachyury

PT #	Days vs Pre	CD4 CD107a	CD4 IFNg	CD4 IL-2	CD4 TNF	CD8 CD107a	CD8 IFNg	CD8 IL-2	CD8 TNF
1001101	D14	0	0	0	0	0	0	0	0
	D43	0	0	0	0	0	0	0	0
	D71	0	0	0	0	93	0	0	0
1001102	D14	0	1552	0	216	53	0	84	0
	D43	96	0	0	0	4102	4979	983	962
	D155	243	0	0	0	0	0	973	0
1001103	D14	0	0	48	0	0	672	0	0
	D43	0	456	0	0	0	0	0	0

- Multifunctional TAA responses, defined as CD4 or CD8 T cells that express 2 or more of the following markers: IFNg, TNF, IL-2, or CD107a were also measured.
  - Multifunctional TAA specific T cells were generated after therapy in 50% of the patients to at least one of the antigens tested (using the criteria of a >10 fold increase post vaccination vs pre, or the presence of >1,000 multifunctional cells at post per $1x10^6$ PBMCs (if negative at pre)).

Scoring of Multifunctional TAA Response

+ (Low)	++ (High)
3x pre	10 x pre
Or if no pre, >100 post	*Or if no pre,* >1000 post

Frequency of Patients with Multi-functional TAA Response

	+ (Low)	++ (High)
MUC1	3/4 (75%)	1/4 (25%)
CEA	3/4 (75%)	1/4 (25%)
Brachyury	3/3 (100%)	2/3 (67%)
Any TAA	4/4 (100%)	2/4 (50%)

TEAEs by max. CTCAE Grade

Subject Level Incidence (N=12), n (%)

MedDRA Preferred Term	Grades 1&2	Grades 3&4	Grade 5
Injection site reaction	10 (83.3)	0	0
Headache	4 (33.3)	0	0
Diarrhea	3 (25.0)	0	0
Fatigue	3 (25.0)	0	0
Paraesthesia	3 (25.0)	0	0
Pruritus	3 (25.0)	0	0
Back pain	2 (16.7)	0	0
Confusional state	2 (16.7)	0	0
Constipation	2 (16.7)	0	0
Decreased appetite	2 (16.7)	0	0
Dysarthria	2 (16.7)	0	0
Dyspnoea	2 (16.7)	0	0
Hypotension	2 (16.7)	0	0
Infusion related reaction	2 (16.7)	0	0
Nasal congestion	2 (16.7)	0	0
Nausea	2 (16.7)	0	0
Pain in extremity	2 (16.7)	0	0
Pleural effusion	2 (16.7)	0	0
Pneumonitis [1]	1 (8.3)	0	1 (8.3)
Rash maculo-papular	2 (16.7)	0	0
Urinary tract infection	2 (16.7)	0	0
Autoimmune hepatitis [2]	0	1 (8.3)	0
Cerebrovascular accident	0	1 (8.3)	0
Neutropenia	0	1 (8.3)	0
Pneumonia	0	1 (8.3)	0
Weight increased	0	1 (8.3)	0
Proctitis [3]	1(8.3)	0	0

Note: Includes AEs with incidence >10% or with at least a Grade 3 severity.
[1] Grade 5 Pneumonitis case resulting included disseminated intravascular coagulation, vasculitis, and multiple organ dysfunction syndrome.
[2] Autoimmune hepatitis case included ALT increase, AST increase, and blood alkaline phosphatase increase.
[3] Proctitis Grade 2 assessed as IMAE and treated with steroids until complete remission permitted to continue treatment.

Conclusions

- Combination of CV301 with PD-1 inhibitors is safe and clinically active in advanced non-squamous NSCLC.
- Treatment results in generation of multifunctional tumor-associated antigen T-cell responses.
- These data support further evaluation of combination immunotherapy consisting of cancer vaccines and immune checkpoint inhibitors.

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DISCLAIMER:
C. Heery, M. Piechatzek, E. Wagner, E. Menius are employees of Bavarian Nordic.
All other authors declare that they have no financial conflicts to disclose.