RESULTS OF THE RANDOMIZED, PLACEBO-CONTROLLED PHASE I/IIB TRIAL OF CV9104 AN mRNA BASED CANCER IMMUNOTHERAPY IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)

A. Stenzl, S. Feyerabend, I. Syndikus, T. Sarosiek, H. Kübler, A. Heidenreich, R. Cathomas, C. Grüllich, Y. Loriot, S. L. Perez Gracia, S. Gillessen, U. Klinkhardt, A. Schröder, O. Schönborn-Kellenberger, V. Reus, S.D. Koch, H.S. Hong, T. Seibel, K. Fizazi, U. Gnad-Vogt

BACKGROUND

- CV9104 is a novel prostate cancer immunotherapy based on sequence-optimized, free and protamine-complexed mRNA encoding the antigens PSA, PSMA, PSCA, STEAP1, PAP and MUC1
- Safety and immune responses to the predecessor therapy CV9103 encoding 4 of the antigens have been described previously[1]
- We assessed whether immunotherapy with CV9104 on top of standard of care (SOC) results in longer overall survival than placebo plus standard of care in patients with mCRPC

METHODS

Study design

- Study scheme is presented in Figure 1

Patient eligibility

- Men with chemo-naïve, asymptomatic or minimally symptomatic mCRPC progressing after surgical castration or GNRH-analogue therapy, no visceral metastases, at least one 2nd-line antihormonal manipulation

Endpoints

- The primary endpoint was overall survival (OS)
- Key secondary endpoints: radiographic progression-free survival times rPFS1, rPFS2 and rSPFS (Figure 2), time to symptom progression and cellular and humoral immune responses

Immune response

- Antigen specific cellular immune responses were measured ex vivo in pre- and post-treatment blood samples

Statistical analysis

- The planned primary analysis was performed following 96 death events; for analysis of OS, a Cox proportional hazards regression model with adjustment for selected prognositc co-variates was used

Figure 1: Study design and treatment schedule

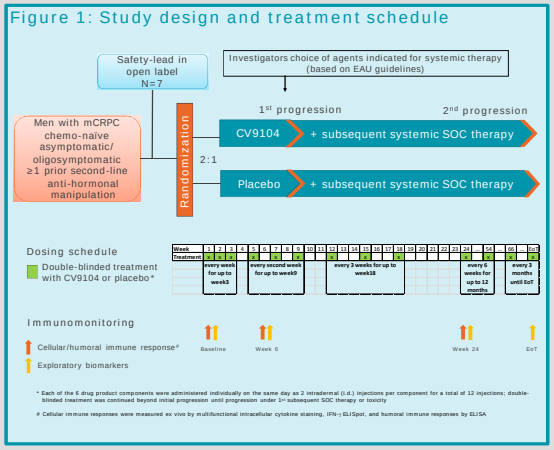
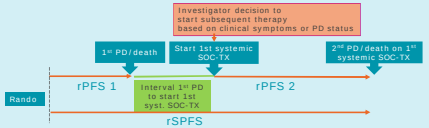


Figure 2: Assessment of PFS time-to-event endpoints



Tumor assessments according to PCWG2 criteria (investigator assessment)
PFS 1-period : every 3 months up to 12 months on study treatment, thereafter every 6 months
PFS 2-period: every 6 months

RESULTS

Patients

- Between Nov 2012 and Dec 2013, 197 patients were randomized 2:1 to either CV9104 or placebo (corresponding to the ITT population)
- Baseline characteristics were balanced between treatment arms (Table 1)
- 192 patients received at least one treatment (Safety population)
- Drug exposure was similar in both treatment arms: median duration of treatment was 9.5 (CV9104) vs 10.4 months (P)
- Use of 2nd subsequent therapies was fairly balanced (Table 2)

Table1: Patient demographics and disease characteristics

Characteristic	CV9104 (N=134)	Placebo (N=63)
Age (years), Median (IQR)	70.8 (12)	69.5 (12)
Country, N (%) *		
Germany	49 (36.6)	23 (36.5)
Poland	27 (20.1)	13 (20.6)
Other	58 (43.3)	27 (42.9)
ECOG Performance Status, N (%) *		
0	103 (76.9)	45 (71.4)
>0	31 (23.1)	18 (28.6)
Gleason Score at Diagnosis, N (%) *		
<8	58 (43.3)	29 (46.0)
8	33 (24.6)	9 (14.3)
9	35 (26.1)	21 (33.3)
10	3 (2.2)	3 (4.8)
Time Since First Diagnosis (months), Median (IQR)	56.6 (89)	53.8 (73)
Metastases Pattern, N (%)		
Bone Metastases only	53 (39.6)	22 (34.9)
Lymph Node Metastases only	30 (22.4)	12 (19.0)
Bone and Lymph node Metastases only	38 (28.4)	22 (34.9)
Other	13 (9.7)	7 (11.1)
Number of bone metastases, N (%)		
0	35 (26.1)	14 (22.2)
1-4	31 (23.1)	19 (30.2)
≥5	68 (50.7)	30 (47.6)
PSA (ng/mL) at baseline , Median (IQR)	31 (61)	52 (118)
Predicted Survival Halabi 2003, months *		
Median (IQR)	21.7 (6)	20.0 (6)
Predicted Survival Halabi 2014, monthsMedian (IQR)	29.6 (7)	28.9 (8)
Previous Prostate Cancer Therapy, N (%)		
Prostatectomy	47 (35.1)	19 (30.2)
Orchiectomy	14 (10.4)	9 (14.3)
Radiotherapy	77 (57.5)	35 (55.6)
Bisphosphonate/Denosumab use at baseline , N (%)	52 (38.8)	28 (44.4)

*covariate of the primary analysis

Table 2: First subsequent SOC therapies

First subsequent cancer therapy	CV9104	Placebo
Docetaxel	46 (34.3)	24 (38.1)
Abiraterone	57 (42.5)	24 (38.1)
Enzalutamide	2 (1.5)	1 (1.6)
Other	12 (9.0)	6 (9.5)
No first subsequent therapy	17 (12.7)	8 (12.7)

Efficacy

- There was no significant difference in OS between the treatment arms (HR 1.11, 95% CI 0.70-1.76, one sided p=0.33) (Figure 3)
- There were also no significant differences in the rPFS endpoints and time to symptom progression (Table 3)

Figure 3: Kaplan Meier OS (ITT population)

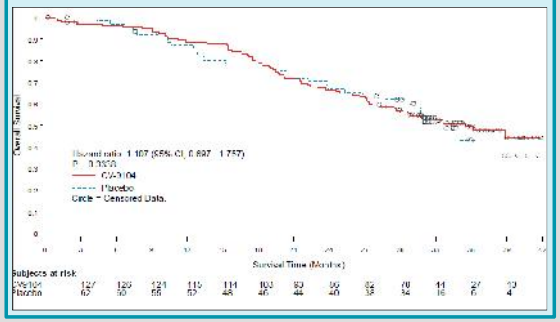


Table 3: Summary of key time-to event efficacy data

Parameter, mon (95%CI)	CV9104	Placebo
Median OS time (ITT population)	35.5 (28.4-NE)	33.7 (28.7-NE)
Median OS time (Per Protocol Population)	36.3 (27.6-NE)	33.7 (23.9-NE)
Median rPFS1 time	5.5 (2.9-8.1)	2.9 (2.8-8.2)
Median rPFS2 time	10.8 (6.7-15.8)	8.3 (5.4-14.2)
Median rSPFS time	21.7 (16.1-26.5)	17.7 (12.6-23.0)
Median time to start of 1st systemic SOC therapy,	6.11 (4.4-7.4)	4.0 (3.5-5.3)
Median FACT-P time to symptom progression	8.31 (5.3-11.1)	9.76 (4.1-19.8)

Immune responses

Overall, detected frequencies of ex vivo antigen-specific cellular and humoral immune responders were similar in both arms. Further analyses of immune cell populations in peripheral blood are ongoing.

Safety

- Incidence of Gr≥3 AEs (51.1% vs. 59.7%) or SAEs (44.5% vs 43.5%) was similar in both arms
- Mild to moderate injection site reactions and flu like symptoms were more frequent in the CV9104 arm

Table 4: TEAEs by MedDRA Preferred Term (≥10%)

MedDRA Preferred Term	CV9104 (N=137)	Placebo (N=62)
Injection site erythema	108 (78.8%)	25 (40.3%)
Pyrexia	52 (38.0%)	7 (11.3%)
Fatigue	34 (24.8%)	18 (29.0%)
Bone pain	29 (21.2%)	21 (33.9%)
Back pain	35 (25.5%)	13 (21.0%)
Influenza like illness	34 (24.8%)	8 (12.9%)
Arthralgia	28 (20.4%)	12 (19.4%)
Hypertension	22 (16.1%)	9 (14.5%)
Nausea	21 (15.3%)	9 (14.5%)
Oedema peripheral	18 (13.1%)	11 (17.7%)
Pain in extremity	20 (14.6%)	9 (14.5%)
Chills	25 (18.2%)	1 (1.6%)
Injection site pruritus	24 (17.5%)	1 (1.6%)
Anaemia	15 (10.9%)	8 (12.9%)
Diarrhoea	15 (10.9%)	8 (12.9%)
Asthenia	17 (12.4%)	5 (8.1%)
Urinary tract infection	15 (10.9%)	6 (9.7%)
Musculoskeletal pain	10 (7.3%)	8 (12.9%)

CONCLUSIONS

- CV9104 did not improve overall survival compared to placebo in this patient population with mCRPC
- There were also no significant differences in the rPFS endpoints and time to symptom progression
- Injection site reactions and flu like symptoms were more frequent in the CV9104 arm; incidence of ≥ grade 3 AEs was balanced between the treatment arms
- Cancer-mediated immunosuppression, tolerance to the prostate cancer self antigens and a suboptimal mode of administration for this protamine formulated mRNA vaccine as suggested by recent data[2] may have contributed to this outcome
- Further development of mRNA based cancer immunotherapies is ongoing with focus on improved formulations / modes of administration and combination with checkpoint blocking antibodies

REFERENCES

1 Kuebler et al., J Immunother Cancer; 2015; 3: 26.
2 Alberer et al., Lancet; 2017

Trial registration

Clinical trials.gov identifier NCT 01817738

Correspondence to

uro@stenzl.net