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LB-021

Intratumoral RNA-based TLR-7/-8 and RIG-I agonist CV8102 alone and in combination with anti-PD-1 in a phase I dose-escalation and expansion trial in patients with advanced solid tumors

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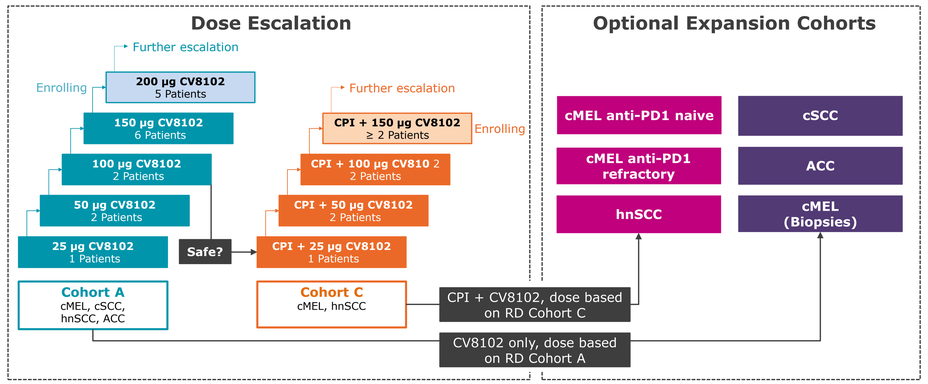
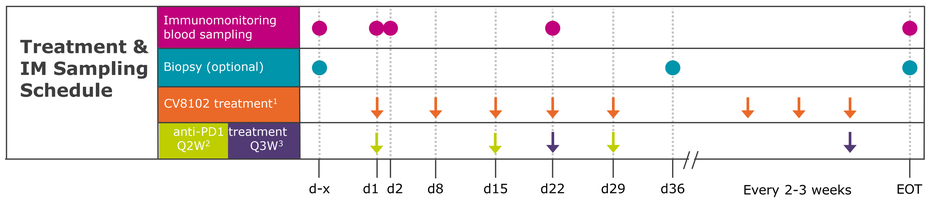
Background: CV8102 comprises a single-stranded non-coding RNA complexed with a cationic peptide. It acts as an agonist to TLR-7/-8 and RIG-I (Ziegler *et al.*, J Immunol 2017) to stimulate the innate and adaptive immune system. CV8102 was shown to induce an upregulation of inflammatory cytokines, chemokines and IFN-γ related genes at the injection site along with an activation of T, NK, NKT and migratory dendritic cells in the draining lymph nodes (Heidenreich *et al.*, Int J Cancer 2015). Intratumoral CV8102 demonstrated dose-dependent anti-tumor activity and synergized with systemic PD-1 inhibition in preclinical models. In this phase I trial we are investigating CV8102 as single agent and in combination with anti PD1 antibodies in patients with advanced melanoma, squamous cell carcinoma of skin or head and neck and adenoid cystic carcinoma.

1. Study Design CV-8102-008 – Phase I study of intratumoral CV8102

(dose escalation based on Bayesian design with flexible cohort sizes)





cMEL: cutaneous melanoma; cSCC: squamous cell carcinoma of the skin; hnSCC: squamous cell carcinoma of the head and neck; ACC: Adenoid cystic carcinoma

[1]Patients receiving single agent CV8102 with evidence of clinical benefit may receive further injections until progression. [2]Licensed anti-PD1 Nivolumab [3]Licensed anti-PD1 Pembrolizumab

2. Patient Characteristics & Most Frequent Treatment Emergent Adverse Events (TEAEs)*

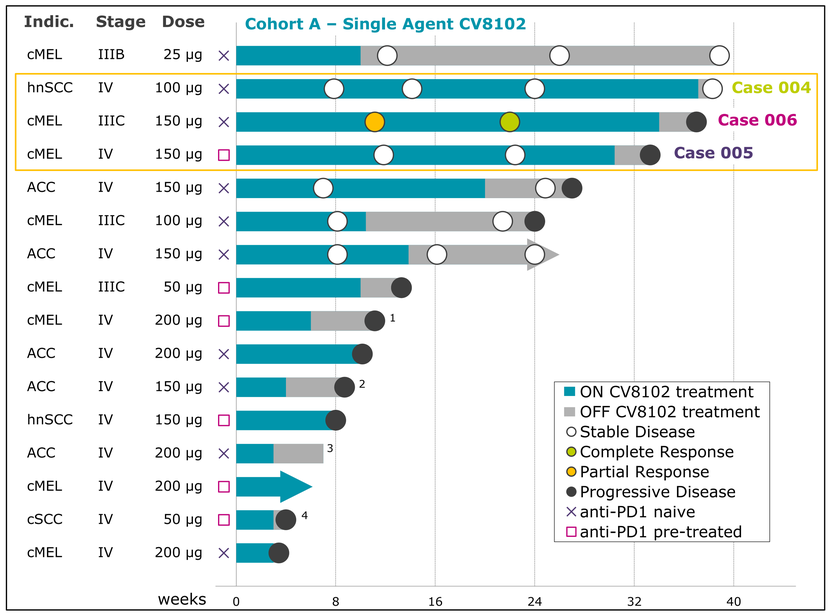
Characteristics	Number of patients (%)		
	Cohort A (n=16)	Cohort C (n=6)	All (n=22)
Age range (yrs)	35-91	50-85	35-91
Gender			
Male	7 (44)	2 (33)	9 (41)
Female	9 (56)	4 (67)	13 (59)
cMEL			
Stage IIIB	1 (6)	0 (0)	1 (5)
Stage IIIC	3 (19)	1 (17)	4 (18)
Stage IV	3 (19)	4 (67)	7 (32)
hnSCC			
Stage IV	2 (13)	1 (17)	3 (14)
cSCC			
Stage IV	2 (13)	0 (0)	2 (9)
ACC			
Stage IV	5 (31)	0 (0)	5 (23)
ECOG PS			
0	9 (56)	4 (67)	9 (41)
1	7 (44)	2 (33)	13 (59)
Pretreatment anti-PD1	6 (38)	6 (100)	12 (55)

AE Preferred Term	Number of patients with ≥1 TEAE (%)*				
	Cohort A (n=16)	Cohort C (n=6)	All (n=22)	Grade ≥3	Related Grade ≥3
Any adverse event	16	6	22 (100)	9 (41)	6 (27)
Fatigue	7	3	10 (45)	-	-
Headache	5	2	7 (32)	-	-
Influenza like illness	5	1	6 (27)	-	-
Chills	2	3	5 (23)	-	-
Pyrexia	4	1	5 (23)	-	-
Arthralgia	3	2	5 (23)	-	-
Injection site pain	4	1	5 (23)	-	-
Pain in extremity	3	2	5 (23)	-	-
C-reactive protein increased	3	1	4 (18)	-	-
Urinary tract infection	2	2	4 (18)	-	-

*TEAEs that occurred in ≥ 4 patients treated with CV8102±anti-PD1/safety population (n=22). Data cut-off Mar 15th 2019. No DLT observed within first 2 weeks of study drug treatment.

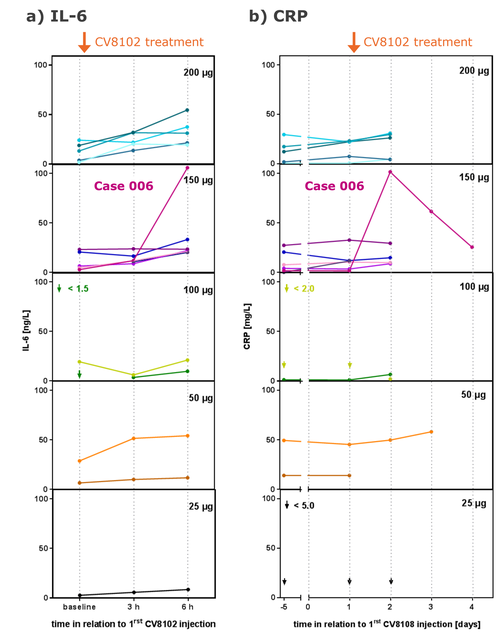
- 13 SAEs occurred in 10 patients and 17 ≥ grade 3 AEs occurred in 9 patients including 1 death due to disease progression (unrelated to CV8102)
- 4 related SAEs occurred in 4 patients: G2 CRP increase, inpatient observation after multiple AE (G1 fever, G1 chills, G3 hypertension, G1 tachycardia), both reported as SAE due to prolonged hospitalization for safety monitoring, G2 tumor pain requiring further diagnostic clarification, G3 abscess at site of injected lesion requiring therapeutic intervention
- 11 ≥ grade 3 related AEs occurred in 6 patients: Cohort A, transient elevation of liver enzymes (3 pat) and abscess at site of injected lesion (1 pat); Cohort C: hypertension, inpatient observation after multiple AE (G1 fever, G1 chills, G3 hypertension, G1 tachycardia), elevated serum lipase (1 pat) and elevated serum amylase (1 pat)

3. Best Overall Response and Duration by RECIST as assessed by investigators (preliminary data with cut-off March 15th 2019)



[1]Patient withdrawn from treatment due to grade 2 pain of injected tumor; [2&4]Patient withdrawn from treatment due to disease progression; [3]Patient withdrew consent due inconveniences involved with intratumoral injection into laryngeal tumor

4. Single Agent CV8102 (Cohort A) IL-6 and CRP Levels after First Injection



Preliminary data with cut-off March 15th 2019

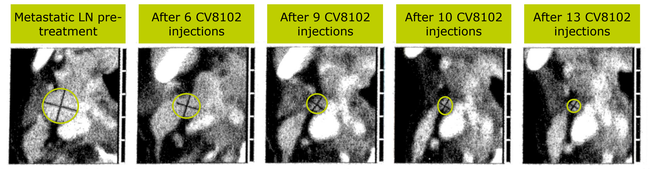
Blood samples are taken at baseline, three and six hours after first CV8102 injection for express IL-6 serum measurement. Additionally, CRP levels are determined routinely.

a) IL-6 levels at baseline, 3 and 6 hours post-treatment. A marked rise in IL-6 was observed for Case 006 from three to six hours post-treatment time points.

b) CRP levels at screening, day 1 (pre-treatment) and post-treatment time points day 2, 3 and 4. CRP levels day 3 and day 4 are only measured in case of further hospitalization. Case 006 had a transient increase in serum CRP at day 2.

5. CV8102: Single Agent Activity in Three Patients

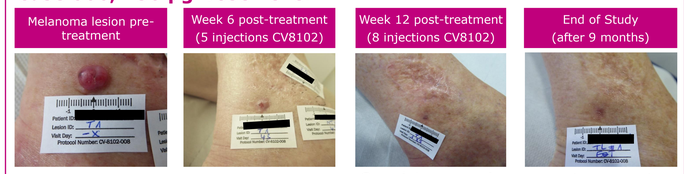
Case 004, 100 µg Dose Level



91-year-old male patient with stage IV hnSCC with large buccal and small lip lesion and a contralateral cervical metastatic LN

- Buccal and lip lesions remained stable for 9 months (study duration)
- Untreated metastatic LN showed ongoing regression

Case 006, 150 µg Dose Level



longest diameter 12 mm

Partial regression, longest diameter 8 mm

Complete regression with minimal remaining palpable skin induration

No locoregional recurrence after 9 months

74-year-old female patient with stage IIIC melanoma with multifocal in-transit metastases

- Marked transient rise in serum IL-6 and CRP following the first intratumoral injection
- Partial regression of the injected tumor lesion after 5 injections of CV8102
- Complete regression of in-transit metastases on MRI, complete regression of all skin metastases with minimal residual palpable induration of the injected lesion at week 12
- Patient continued to receive injections at monthly intervals for 9 months without locoregional recurrence
- New intraabdominal soft tissue lesion after 9 months

Case 005, 150 µg Dose Level

64-year-old male patient with stage IV melanoma, progression after initial PR on Pembrolizumab

- Injected and non-injected contralateral paraortal LN lesion showed transient minor regression
- Disappearance of several non-target lesions
- Patient achieved radiological SD for > 6 months

(8 months follow up scan showed PD with new lesions)

6. Conclusion

- Intratumoral CV8102 single-agent and in combination with anti-PD1 appears well tolerated at doses up to 200 µg and 100 µg, respectively
- Evidence of single agent activity with shrinkage of injected and non-injected lesions was observed including a complete response in a melanoma patient
- Dose escalation of CV8102 ± anti-PD1 is ongoing and expansion cohorts are planned after determination of the phase 2 recommended dose

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