INTRATUMORAL BO-112, A DOUBLE-STRANDED RNA (dsRNA), ALONE AND IN COMBINATION WITH SYSTEMIC ANTI-PD-1 IN SOLID TUMORS

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BACKGROUND

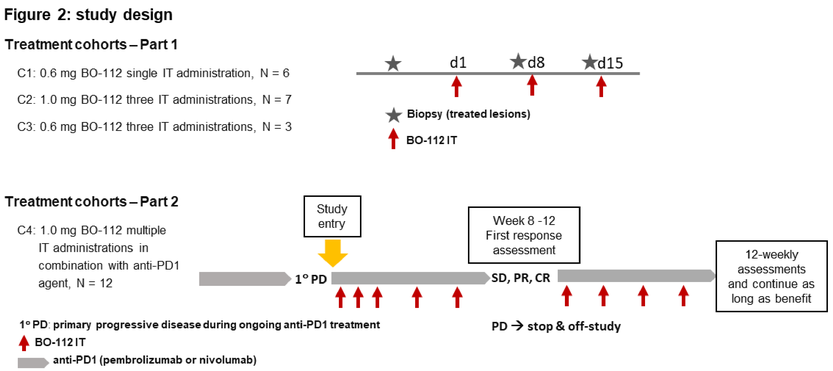
- BO-112 is a GMP preparation of dsRNA (poly I:C) formulated with the cationic carrier polyethylenimine that is capable to trigger both cancer cells and immune cells responses in preclinical cancer models towards immunogenic cell death and increase of immune-checkpoint inhibition effects (fig 1)

- Intratumoral BO-112 alone or combined with systemic anti-PD-1 is being analyzed in this 1st in human clinical trial (NCT02828098)

METHODS

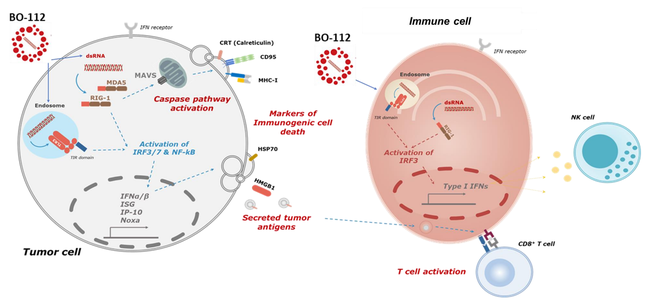
- 28 patients with solid tumors and metastases ≥1 cm amenable to IT injection were enrolled in 4 cohorts (C).
- C1: single IT BO-112 dose of 0.6 mg (N=6)
- C2: 1 mg IT BO-112 qw x 2-3 doses (N=7)
- C3: 0.6 mg IT BO-112 qw x 2-3 doses (N=3)
- C4: Primary anti PD-1 refractory patients were treated with 1 mg IT BO-112 qw x 2 or 3 doses before continuing nivolumab or pembrolizumab combined with BO-112, until progression, limiting toxicity or up to 1y (N=12).
- BO-112 injected into a single lesion, (if lesion responds, becoming too small, divide dose between original and additional lesion).

Figure 2: study design



MECHANISM OF ACTION OF BO-112

Figure 1: BO-112 mechanism of action



RESULTS: TOXICITY AND PHARMACOKINETICS

- Frequency of treatment-emergent adverse events of C1-4 are summarized in table 1.
- No safety signals were detected with the combination.
- BO-112 was not detected in blood.

Table 1: Treatment emergent adverse events

PART 1 – Cohorts 1-3	All TEAEs	Serious TEAEs	Grade 3-5 TEAEs
All TEAEs			
Number of subjects, N = 16 (%)	**16 (100)**	**5 (31)**	**6 (38)**
Number of events	110	6	13
TEAEs at least possibly related to BO-112			
Number of subjects, N = 16 (%)	**10 (63)**	**1 (6)**	**2 (13)**
Number of events	42	1	2
PART 2 – Cohort 4			
All TEAEs			
Number of subjects, N = 12 (%)	**12 (100)**	**6[a] (50)**	**8[a] (67)**
Number of events	153	7	9
TEAEs in ≥ 3 (25%) subjects: anaemia, asthenia, chills, decreased appetite, diarrhoea, dysgeusia, headache, injection site pain, myalgia, nausea, pruritus, pyrexia, respiratory disorder, syncope, vomiting			
TEAEs at least possibly related to BO-112			
Number of subjects, N = 12 (%)	**10 (83)**	**0**	**0**
Number of events	57	0	0
- of which not related to pembrolizumab or nivolumab	39	0	0
TEAEs in ≥ 3 (25%) subjects at least possibly related to BO-112: asthenia, chills, myalgia, pyrexia			
TEAEs at least possibly related to pembrolizumab or nivolumab			
Number of subjects, N = 12 (%)	**7 (58)**	**0**	**0**
Number of events	23	0	0
- of which not related to BO-112	5	0	0

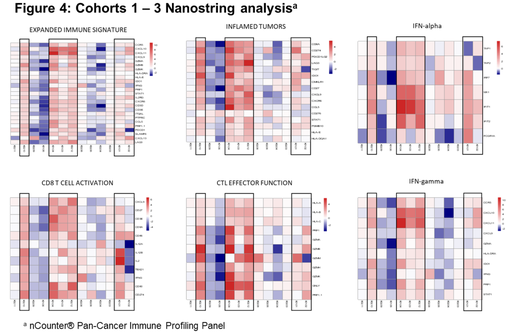
[a] There were 3 patients who died on study in Part 2: two due to disease progression and one unrelated Death NOS

RESULTS: IMMUNOBIOLOGICAL EFFECTS COHORTS 1-3

Table 2 – Cohorts 1 - 3

Increases in circulating immune cells	Number of patients N = 16 (%)
Lymphocytes	9 (56)
CD8+ T cells	8 (50)
CD4+ T cells (excl. regulatory T cells)	11 (69)
CD4+ regulatory T cells	14 (88)
NK cells	10 (63)
Monocytes	7 (44)
B cells	11 (69)
Dendritic cells	7 (44)
Tumor biopsy	**Number of patients N = 16**
Increased apoptosis	10 (63)
Increased necrosis	5 (31)
Increased CD8+	3 (19)
Increased CD4+	6 (38)

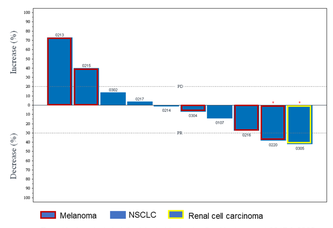
Figure 4: Cohorts 1 – 3 Nanostring analysis[a]



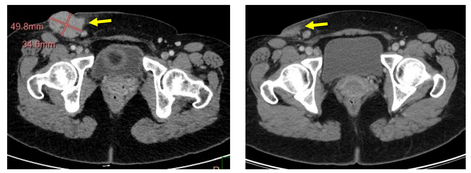
[a] nCounter® Pan-Cancer Immune Profiling Panel

RESULTS: RECIST 1.1 FROM COHORT 4 AND PATIENT EXAMPLE

Figure 4: Change in sum of target lesions at 1st scheduled assessment from baseline (RECIST v1.1)



Target lesions included the injected lesion in all subjects except 0217 & 0305



Pre BO-112 6-JUN-2018

Post BO-112+nivolumab 18-AUG-2018

Fig 5: patient 0220: female 48y, melanoma resistant to nivolumab. Arrow indicates the lesion injected with BO-112

Preliminary disease control rate at 1st assessment (8-12 weeks) was 7/12 (58%) and objective response rate 2/12 (17%), one PR in melanoma and one PR in renal cancer.

CONCLUSIONS

- BO-112 has demonstrated a manageable safety profile as single agent and combined with anti- PD-1.
- Its mechanism of action comprises direct antitumor effects and innate and adaptive immune system activation.
- Combination with anti PD-1 is feasible in anti PD-1 refractory patients.
- Preliminary efficacy analysis suggests the potential to halt or reverse primary resistance to anti-PD1 treatment.
- Cohort 4 (BO-112 + anti PD-1 in anti PD-1 refractory patients) is being expanded to include up to 30 patients.

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