Antitumor activity of CMP-001 (TLR9 agonist) alone or combined with immune modulators in syngeneic tumor models

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S. MAUBANT[1], J.-F. MIRJOLET[1], P. SLOS[1], F. BICHAT[1], A. MORRIS[2], A. M. KRIEG[2]
[1]Oncodesign, Dijon (FRANCE);[2]Checkmate Pharmaceuticals, Cambridge, MA (USA)

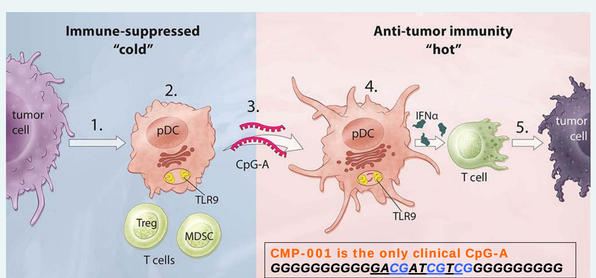
For more information: contact@oncodesign.com / amorris@checkmatepharma.com

INTRODUCTION

Background

Targeted blockade of checkpoint receptors such as PD-1 or CTLA-4 with antagonist monoclonal antibodies (mAbs) has shown impressive and durable clinical responses in patients with advanced cancer. An alternative and complimentary strategy for boosting anti-tumor immunity is to promote T-cell activation through co-stimulatory receptors such as OX40 and 4-1BB. OX40 is of particular interest, as treatment with an activating anti-OX40 mAb augments T-cell differentiation and cytolytic function leading to enhanced anti-tumor immunity. However, each of these immune modulators provides benefits to only a subset of patients, highlighting the critical need for more effective combinatorial therapeutic strategies.

Toll-Like Receptor 9 (TLR9) agonist CpG oligodeoxynucleotides (ODN) are another class of immune modulators. **CMP-001**, a CpG-A ODN formulated within a virus-like particle, is designed to activate TLR9 in plasmacytoid dendritic cells (pDC) within the tumor or tumor-draining lymph nodes. Resting or immature pDC promote tumor growth, but when activated by CpG-A, the resulting mature pDC promotes a robust anti-tumor immune response. Activation of pDC causes secretion of very large quantities of type I interferons, increased expression of costimulatory molecules, and recruitment and activation of other DC subsets to enhance tumor antigen presentation to T-cells, culminating in the generation of effective anti-tumor T-cell responses.

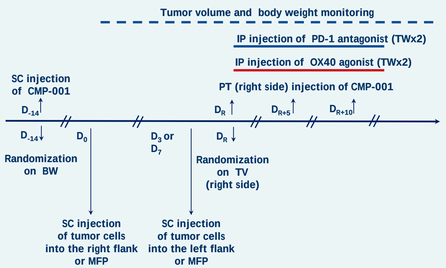


1. Tumor recruits immature pDC.
2. Immature pDC maintain immune-suppressed "cold" tumor micro-environment.
3. Intra-tumoral injection of CpG-A converts tumor microenvironment from "cold" to "hot"
4. Activated pDC produces type I IFN, chemokines; recruits T cells into "hot" tumor microenvironment.
5. T cells specific to tumor neoantigens mediate local and systemic tumor regression.

Only CpG-A selectively activates pDC - the strongest known type I IFN and T cell inducer in humans => converting tumors from "cold" to "hot"

The aim is to investigate the antitumor activity of CMP-001 alone or in combination with a PD-1 antagonist and/or an OX40 agonist in a variety of syngeneic tumor models: CT-26 colon tumor model, 4T1 breast tumor model, LLC-1 lung tumor model, MBT-2 bladder tumor model and RenCa kidney tumor model.

Study design

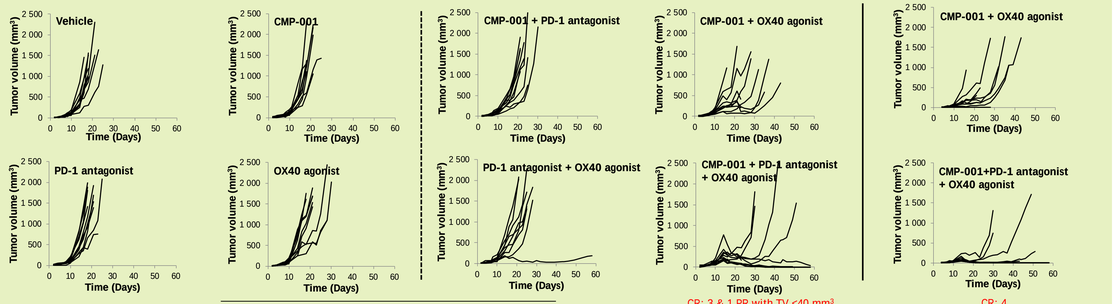


BW: body weight; D_R: day of randomization; IP: intraperitoneal; MFP: mammary fat pad; PT: peritumoral; SC: subcutaneous; TV: tumor volume; TWx2: twice weekly for 2 consecutive weeks.

Tumors were implanted into right and left flanks or MFP while only one tumor was injected with CMP-001. In addition to body weight and overall survival, tumor volume was monitored on both flanks or MFP to assess direct and abscopal/systemic anti-tumor activity.

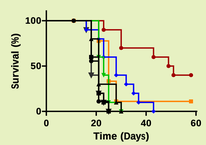
RESULTS

CT-26 model



CR: 3 & 1 PR with TV <40 mm³ — CR: 4

CR: complete response; PR: partial response; TV: tumor volume



Median Survival (days)	Group
18	Vehicle
21	CMP-001
21	PD-1 antagonist
21	OX40 agonist
23	CMP-001 + PD-1 antagonist
28*	CMP-001 + OX40 agonist
25*	PD-1 antagonist + OX40 agonist
50***	CMP-001+ PD-1 antagonist + OX40 agonist

- Complete responses were seen in both treated and untreated CT-26 tumors with combination of 3 immune modulators in ~40% of the mice.
- Increased median survival time of animals treated with the triple combination compared to vehicle alone, single agents or double combinations of immune modulators.

LogRank test (*versus* vehicle): *: $P < 0.05$; ***: $P < 0.001$

4T1, LLC-1, MBT-2 and RenCa models

4T-1

- Unexpected death of animals upon repeated treatments of OX40 agonist alone or combined with PD-1 antagonist but not in presence of CMP-001.

LLC-1

- No efficacy of any immune modulator alone or in combination.

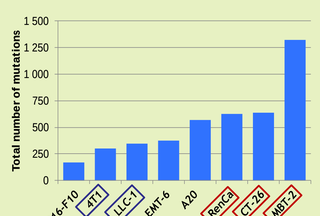
MBT-2 / **RenCa**

Group	T/C (D26) right	T/C (D26) left	Median Survival (days)	Median Survival (days)
Vehicle	100	100	26	33
CMP-001	69	12	28	33
PD-1 antagonist	62	51	29	33
OX40 agonist	65	76	28	32
CMP-001 + PD-1 antagonist	36	32	36	39
CMP-001 + OX40 agonist	39	12	33	37.5
PD-1 antagonist + OX40 agonist	49	12	34	34
CMP-001+ PD-1 antagonist + OX40 agonist	29	12	38.5*	43*

Tumor growth inhibition (T/C %) defined as the ratio of the median tumor volumes of treated groups *versus* Vehicle group was calculated. LogRank test (*versus* Vehicle): *: $P < 0.05$.

- Antitumor activity with increased median survival time in case of combination of CMP-001, PD-1 antagonist and OX40 agonist in MBT2 and RenCa.
- No complete response.

Exome sequencing and sensitivity to immune modulators



- Is there a link between response to combination of all three immune modulators and total number of mutations?

CONCLUSIONS

- **Clear distinctions in response to treatment were observed among evaluated syngeneic tumor models: CT-26 was the most responsive, with MBT-2 and RenCa also showing significant responses. Both LLC-1 and 4T1 were non-responders.**
- **The most efficacious results were registered in the CT-26 model. Each immune modulator yielded weak activity as a single agent, which was improved when combined with others.**
- **The best therapeutic efficacy was obtained with the combination of all three immune modulators whatever the responder model.**
- **These data support the clinical investigation of these combinations in patients with advanced cancer.**

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