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Early Safety From a Phase 1, Multicenter, Open-label Clinical Trial of Talimogene Laherparepvec (T-VEC) Injected Into Liver Tumors in Combination With Pembrolizumab

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Joel Randolph Hecht[1], Miklos Pless[2], Antonio Cubillo[3], Aitana Calvo[4], Hong Jae Chon[5], Chunxu Liu[6], Wendy Snyder[6], Emily Chan[6], Marya Chaney[7], Jason Chesney[8], Aleix Prat[9]

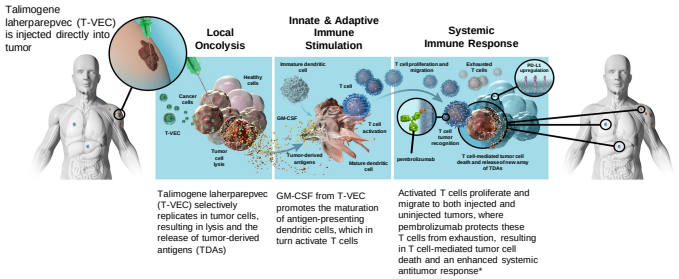
[1]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [2]Kantonsspital Winterthur Department of Oncology, Winterthur, Switzerland; [3]HM Universitario Sanchinarro, CIOCC, Madrid, Spain; [4]Hospital General Universitario Gregorio Marañon, Madrid, Spain; [5]CHA Bundang Medical Center, CHA University, Bundang-Gu, South Korea; [6]Amgen Inc., Thousand Oaks, CA , USA; [7]Merck & Co., Inc., Kenilworth, NJ, USA; [8]James Graham Brown Cancer Center, University of Louisville, Louisville, KY, USA; [9]Hospital Clínic, University of Barcelona, Barcelona, Spain

INTRODUCTION

- Talimogene laherparepvec (T-VEC) is a genetically modified, oncolytic HSV-1 designed to selectively replicate within tumors and produce GM-CSF to enhance systemic antitumor immunity[1]
- The safety and efficacy of T-VEC in the treatment of advanced melanoma has been demonstrated as monotherapy, and is currently being evaluated in combination studies with checkpoint inhibitors[2,3,4]
- T-VEC has also demonstrated tolerable safety for intrahepatic injection from early stage-study[5]
- This phase 1b, multicenter, open-label, dose-escalation study (NCT02509507) evaluates the safety of intrahepatic injection of T-VEC in combination with intravenous (IV) pembrolizumab in patients with hepatocellular carcinoma (HCC) or non-HCC liver metastases

METHODS

Figure 1: Proposed mechanism of action for T-VEC in combination with pembrolizumab



Talimogene laherparepvec (T-VEC) selectively replicates in tumor cells, resulting in lysis and the release of tumor-derived antigens (TDAs)

GM-CSF from T-VEC promotes the maturation of antigen-presenting dendritic cells, which in turn activate T cells

Activated T cells proliferate and migrate to both injected and uninjected tumors, where pembrolizumab protects these T cells from exhaustion, resulting in T cell-mediated tumor cell death and an enhanced systemic antitumor response*

*This figure depicts the proposed mechanism of action and is not meant to imply clinical efficacy
GM-CSF, granulocyte-macrophage colony-stimulating factor; PD-L1, programmed death-ligand 1; TDA, tumor-derived antigen; T-VEC, talimogene laherparepvec.

Figure 2: Methods, treatment, objectives, and patients

- Eligible patients were ≥ 18 years old, had progressive HCC or breast cancer, colorectal cancer, gastroesophageal cancer, melanoma, non-small cell lung cancer, or renal cell cancer liver metastases, with measurable liver tumors suitable for injection
- This analysis includes three of 12 part 1 cohorts: A5, A6, and B5 (see Hecht et al. 2018 for entire study design)
- Data cutoff for this analysis was December 13, 2019

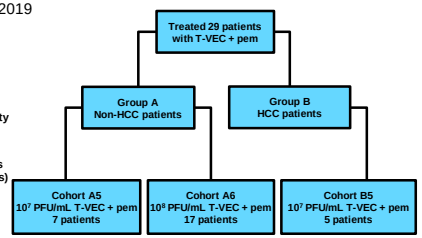
T-VEC: 10^6 PFU/mL on day 1, followed by either:
Cohort 5: ≤ 4mL of 10^7 PFU/mL every 21 days
Cohort 6: ≤ 4mL of 10^8 PFU/mL every 21 days

Pembrolizumab: 200 mg IV on day 1 and every 21 days thereafter

DLT rate: evaluated with the modified toxicity probability interval up-and-down design

1° Primary objective: to assess the maximum tolerable concentration (MTC) of T-VEC injected into liver tumors based on the incidence of dose limiting toxicities (DLTs)

2° Secondary objectives: ORR, BOR, DRR, response in injected and uninjected lesions, DCR, PFS, and OS



PFU: plaque-forming unit; IV: intravenous; DLT: dose-limiting toxicity; MTC: maximum tolerate concentration; pem: pembrolizumab; ORR: objective response rate; BOR: best overall response; DRR: durable response rate; DOR: duration of response; DCR: disease control rate; PFS: progression-free survival; OS: overall survival

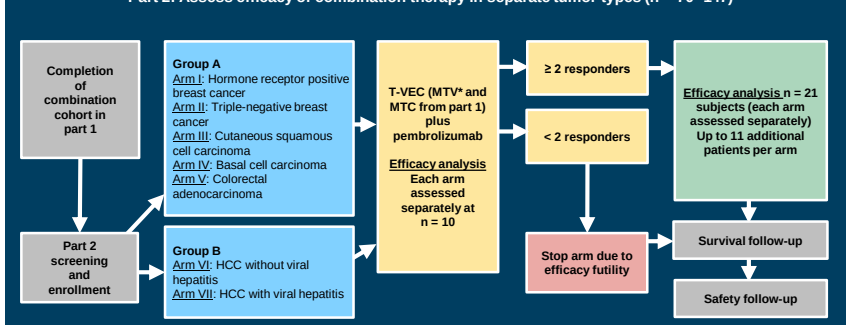
CONCLUSIONS

Combination treatment is feasible and tolerable at data cutoff

- Of 29 patients treated with combination T-VEC plus pembrolizumab at the time of the data cutoff
  - One DLT of cholestatic hepatitis was observed in a patient with colorectal adenocarcinoma (cohort A5)
  - No DLTs were observed in cohorts A6 and B5
  - MTC was 10^8 PFU/mL in non-HCC patients
- Exploration of MTC in the HCC population is ongoing

***T-VEC intrahepatic injection** in combination with **IV pembrolizumab** at standard doses in patients with HCC or liver metastases has thus far been demonstrated as **feasible and tolerable** to continue further investigation*

Figure 3: Future study plans for expanded tumor types



*MTV determination of 8 mL in part 1. HCC: hepatocellular carcinoma; MTC: maximum tolerated concentration; MTV: maximum tolerated volume

RESULTS

Table 1: Baseline patient characteristics

	Cohort A5 (N = 7)	Cohort A6 (N = 17)	Cohort B5 (N = 5)	All (N = 29)
Male – n (%)	5 (71.4)	9 (52.9)	4 (80.0)	18 (62.1)
Age – median (range), years	56 (30–76)	61 (38–76)	69 (31–69)	61 (30–76)
Disease stage at initial diagnosis – n (%)				
Stage I	-	2 (11.8)	1 (20.0)	3 (10.3)
Stage II	-	5 (29.4)	-	5 (17.2)
Stage III	2 (28.6)	5 (29.4)	1 (20.0)	8 (27.6)
Stage IV	5 (71.4)	5 (29.4)	-	10 (34.5)
Unknown	-	-	3 (60.0)	3 (10.3)
Child-Pugh score – n (%)				
A5	6 (85.7)	15 (88.2)	5 (100.0)	26 (89.7)
A6	1 (14.3)	2 (11.8)	-	3 (10.3)
Type of primary cancer – n (%)				
Breast adenocarcinoma	-	2 (11.8)	-	2 (6.9)
Colorectal adenocarcinoma	4 (57.1)	6 (35.3)	-	10 (34.5)
Gastroesophageal cancer (adenocarcinoma or squamous cell carcinoma)	-	3 (17.6)	-	3 (10.3)
Uveal melanoma (malignant melanoma)	2 (28.6)	4 (23.5)	-	6 (20.7)
Carcinoma, non-small cell lung	1 (14.3)	1 (5.9)	-	2 (6.9)
Clear cell renal cell carcinoma	-	1 (5.9)	-	1 (3.4)
Hepatocellular carcinoma	-	-	5 (100.0)	5 (17.2)
Prior therapies, n (%)				
Anticancer therapy	6 (85.7)	16 (94.1)	5 (100.0)	27 (93.1)
Number of prior lines – median (range)	4 (1–5)	3 (1–6)	2 (1–4)	3 (1–6)
Radiotherapy	5 (71.4)	8 (47.1)	-	13 (44.8)
Surgery	4 (57.1)	15 (88.2)	1 (20.0)	20 (69.0)

Table 2: Treatment exposure

	Cohort A5 (N = 7)	Cohort A6 (N = 17)	Cohort B5 (N = 5)	All (N = 29)
Doses for T-VEC – median (range)	3 (1–6)	3 (1–10)	6 (3–11)	4 (1–11)
Doses for pembrolizumab – median (range)	3 (1–6)	3 (1–10)	7 (3–11)	4 (1–11)
Treatment duration – median (range), days	88 (16–147)	75 (22–217)	150 (63–213)	88 (16–217)
Reason for discontinuing T-VEC – n (%)				
Adverse event	2 (28.6)	4 (23.5)	-	6 (20.7)
Patient request	-	1 (5.9)	-	1 (3.4)
Disease progression	5 (71.4)	8 (47.1)	1 (20.0)	14 (48.3)
Other	-	1 (5.9)	-	1 (3.4)
Reason for discontinuing pembrolizumab – n (%)				
Adverse event	2 (28.6)	3 (17.6)	-	5 (17.2)
Disease progression	5 (71.4)	10 (58.8)	1 (20.0)	16 (55.2)

Table 3: Patient treatment-emergent adverse events (TEAEs) were consistent across cohorts

	Cohort A5 (N = 7)	Cohort A6 (N = 17)	Cohort B5 (N = 5)	All (N = 29)
All TEAEs – n (%)	7 (100.0)	17 (100.0)	5 (100.0)	29 (100.0)
Grade ≥ 3	1 (14.3)	6 (35.3)	1 (20.0)	8 (27.6)
Grade ≥ 4	1 (14.3)	-	-	1 (3.4)
Leading to permanent discontinuation of T-VEC	2 (28.6)	4 (23.5)	-	6 (20.7)
Leading to permanent discontinuation of pembrolizumab	2 (28.6)	3 (17.6)	-	5 (17.2)
Serious adverse events	2 (28.6)	7 (41.2)	2 (40.0)	11 (37.9)
Fatal adverse events	-	-	-	-

- TEAEs leading to discontinuation of T-VEC include:
  - Cohort A5: one patient experienced ascites and one patient experienced cholestatic hepatitis
  - Cohort A6: one patient experienced hematoma, one patient experienced hemorrhage, one patient experienced spinal cord compression, and one patient experienced dyspnea, acute kidney failure, and lymphedema
- TEAEs leading to discontinuation of pembrolizumab include:
  - Cohort A5: one patient experienced ascites, and one patient experienced cholestatic hepatitis
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- **One DLT of cholestatic hepatitis was observed in a patient with colorectal adenocarcinoma (cohort A5)**
- **Patient was heavily pre-treated with a high tumor burden**

Table 4: The most common treatment-related TEAEs were pyrexia, chills, and nausea

	Cohort A5, A6, B5 pooled (N = 29) n (%)
Total	27 (93.1)
Pyrexia	23 (79.3)
Chills	11 (37.9)
Nausea	11 (37.9)
Fatigue	8 (27.6)
Vomiting	5 (17.2)
Aspartate aminotransferase increased	4 (13.8)
Arthralgia	3 (10.3)
Asthenia	3 (10.3)
Diarrhea	3 (10.3)
Hypotension	3 (10.3)
Influenza-like illness	3 (10.3)

Data cutoff at 10%

- No fatal TEAE/treatment-related fatal AE were observed

Best overall response observed as of April 1, 2020

- One patient in cohort A5, three patients in cohort B5, and four patients in cohort A6 had a BOR of SD
  - 6 of the 8 patients had SD for over 6 months
- One HCC patient in cohort B5 had a confirmed PR that progressed after 4.3 months
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Acknowledgments

- The authors thank the investigators, patients, and study staff who contributed to this study
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- Programming and statistical support was provided by Parexel
- The trial is sponsored and funded by Amgen Inc.

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1. Liu, BL, et al. *Gene Therapy.* 2003; 10:292-303
2. Andtbacka, RH, et al. *J Clin Oncol.* 2015;33:2780-2788
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GM-CSF, granulocyte-macrophage colony-stimulating factor; HCC, hepatocellular carcinoma; IV, intravenous; HSV-1, herpes simplex virus type 1; T-VEC, talimogene laherparepvec.

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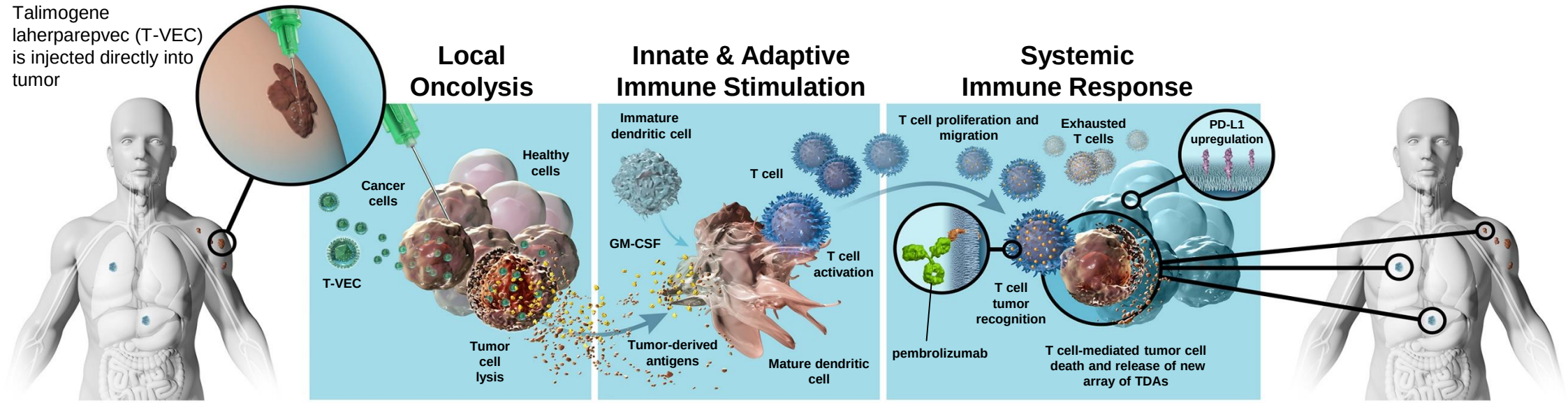
Proposed Mechanism of Action for T-VEC in Combination With Pembrolizumab



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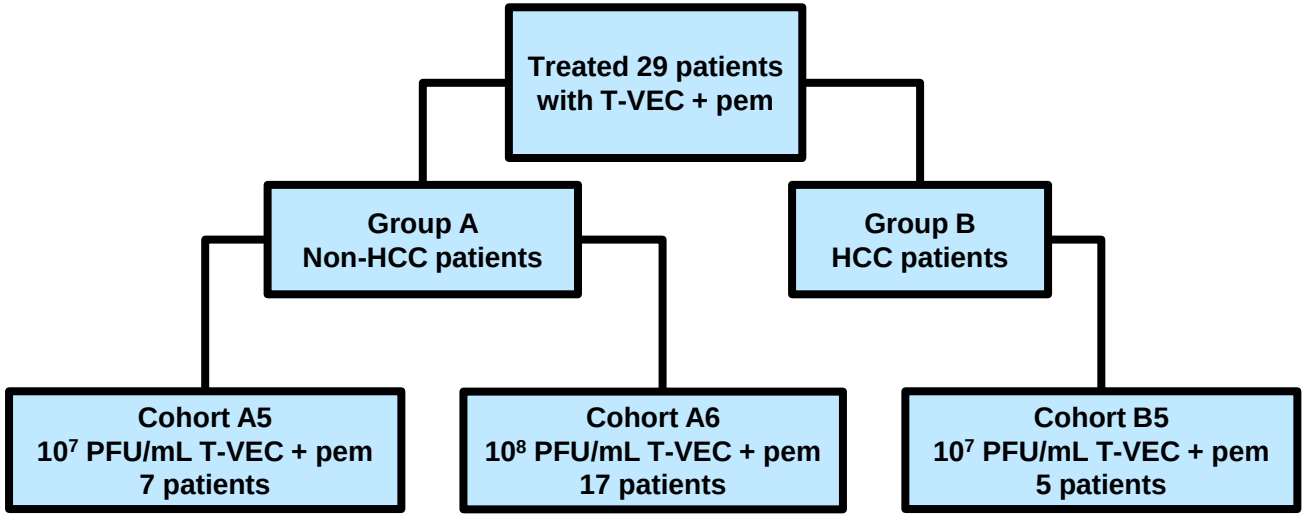

BOR, best overall response; DCR, disease control rate; DOR, duration of response; DLT, dose-limiting toxicity; DRR, durable response rate; HCC, hepatocellular carcinoma; IV, intravenous; MTC, maximum tolerate concentration; ORR, objective response rate; OS, overall survival; pem, pembrolizumab; PFU, plaque-forming unit; PFS, progression-free survival; T-VEC, talimogene laherparepvec.

Results: Baseline Patient Characteristics

	Cohort A5 (N = 7)	Cohort A6 (N = 17)	Cohort B5 (N = 5)	All (N = 29)
Male – n (%)	5 (71.4)	9 (52.9)	4 (80.0)	18 (62.1)
Age – median (range), years	56 (30–76)	61 (38–76)	69 (31–69)	61 (30–76)
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Stage I	–	2 (11.8)	1 (20.0)	3 (10.3)
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Stage III	2 (28.6)	5 (29.4)	1 (20.0)	8 (27.6)
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Unknown	–	–	3 (60.0)	3 (10.3)
Child-Pugh score – n (%)				
A5	6 (85.7)	15 (88.2)	5 (100.0)	26 (89.7)
A6	1 (14.3)	2 (11.8)	–	3 (10.3)
Type of primary cancer – n (%)				
Breast adenocarcinoma	–	2 (11.8)	–	2 (6.9)
Colorectal adenocarcinoma	4 (57.1)	6 (35.3)	–	10 (34.5)
Gastroesophageal cancer (adenocarcinoma or squamous cell carcinoma)	–	3 (17.6)	–	3 (10.3)
Uveal melanoma (malignant melanoma)	2 (28.6)	4 (23.5)	–	6 (20.7)
Carcinoma, non-small cell lung	1 (14.3)	1 (5.9)	–	2 (6.9)
Clear cell renal cell carcinoma	–	1 (5.9)	–	1 (3.4)
Hepatocellular carcinoma	–	–	5 (100.0)	5 (17.2)
Prior therapies, n (%)				
Anticancer therapy	6 (85.7)	16 (94.1)	5 (100.0)	27 (93.1)
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Radiotherapy	5 (71.4)	8 (47.1)	–	13 (44.8)
Surgery	4 (57.1)	15 (88.2)	1 (20.0)	20 (69.0)

Results: Treatment Exposure

	Cohort A5 (N = 7)	Cohort A6 (N = 17)	Cohort B5 (N = 5)	All (N = 29)
Doses for T-VEC – median (range)	3 (1–6)	3 (1–10)	6 (3–11)	4 (1–11)
Doses for pembrolizumab – median (range)	3 (1–6)	3 (1–10)	7 (3–11)	4 (1–11)
Treatment duration – median (range), days	88 (16–147)	75 (22–217)	150 (63–213)	88 (16–217)
Reason for discontinuing T-VEC – n (%)				
Adverse event	2 (28.6)	4 (23.5)	–	6 (20.7)
Patient request	–	1 (5. 9)	–	1 (3.4)
Disease progression	5 (71.4)	8 (47.1)	1 (20.0)	14 (48.3)
Other	–	1 (5.9)	–	1 (3.4)
Reason for discontinuing pembrolizumab – n (%)				
Adverse event	2 (28.6)	3 (17.6)	–	5 (17.2)
Disease progression	5 (71.4)	10 (58.8)	1 (20.0)	16 (55.2)

T-VEC, talimogene laherparepvec.

Results: Patient Treatment-Emergent Adverse Events (TEAEs) Were Consistent Across Cohorts

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Fatal adverse events	–	–	–	–

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  - **Patient was heavily pre-treated with a high tumor burden**

DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse events; T-VEC, talimogene laherparepvec.

Results: The Most Common Treatment-Related TEAEs Were Pyrexia, Chills, and Nausea

	Cohort A5, A6, B5 pooled (N = 29) n (%)
Total	27 (93.1)
Pyrexia	23 (79.3)
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Data cutoff at 10%

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Best overall response observed as of April 1, 2020

- One patient in cohort A5, three patients in cohort B5, and four patients in cohort A6 had a BOR of SD
  - 6 of the 8 patients had SD for over 6 months
- One HCC patient in cohort B5 had a confirmed PR that progressed after 4.3 months
- One CRC patient in cohort A6 had a confirmed PR that has continued for 8.3 months

AE, adverse event; BOR, best overall response; CRC, colorectal cancer; HCC, hepatocellular carcinoma; PR, partial response; SD, stable disease; TEAE, treatment-emergent adverse events; T-VEC, talimogene laherparepvec.

Conclusions

Combination treatment is feasible and tolerable at data cutoff

- Of 29 patients treated with combination T-VEC plus pembrolizumab at the time of the data cutoff
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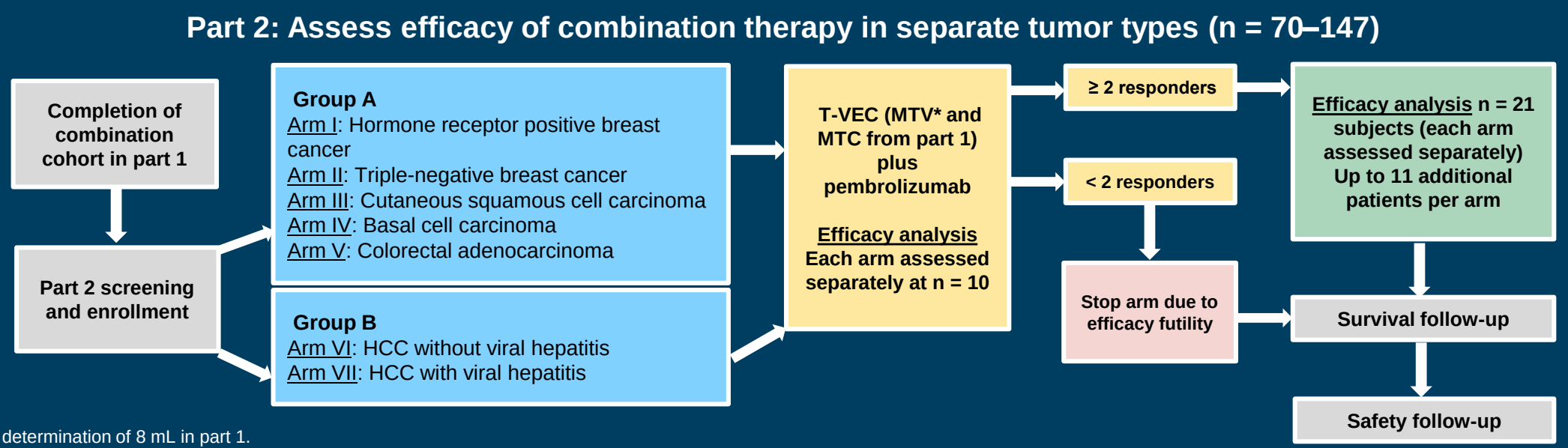
- Exploration of MTC in the HCC population is ongoing

DLT, dose-limiting toxicity; HCC, hepatocellular carcinoma; MTC, maximum tolerate concentration; PFU, plaque-forming unit; T-VEC, talimogene laherparepvec.

Key Takeaway and Future Study Plans

T-VEC intrahepatic injection *in combination with* ***IV pembrolizumab*** *at standard doses in patients with HCC or liver metastases has thus far been demonstrated as* ***feasible and tolerable*** *to continue further investigation*

Figure 3: Future study plans for expanded tumor types



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Acknowledgments

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