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CORE-001: Phase 2, Single Arm Study of Cretostimogene Grenadenorepvec (CG0070) Combined with Pembrolizumab in Patients with Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guerin (BCG)

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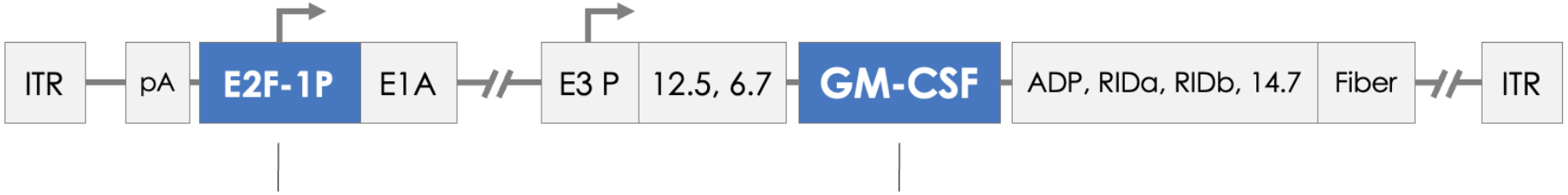
Cretostimogene Grenadenorepvec (CG0070)

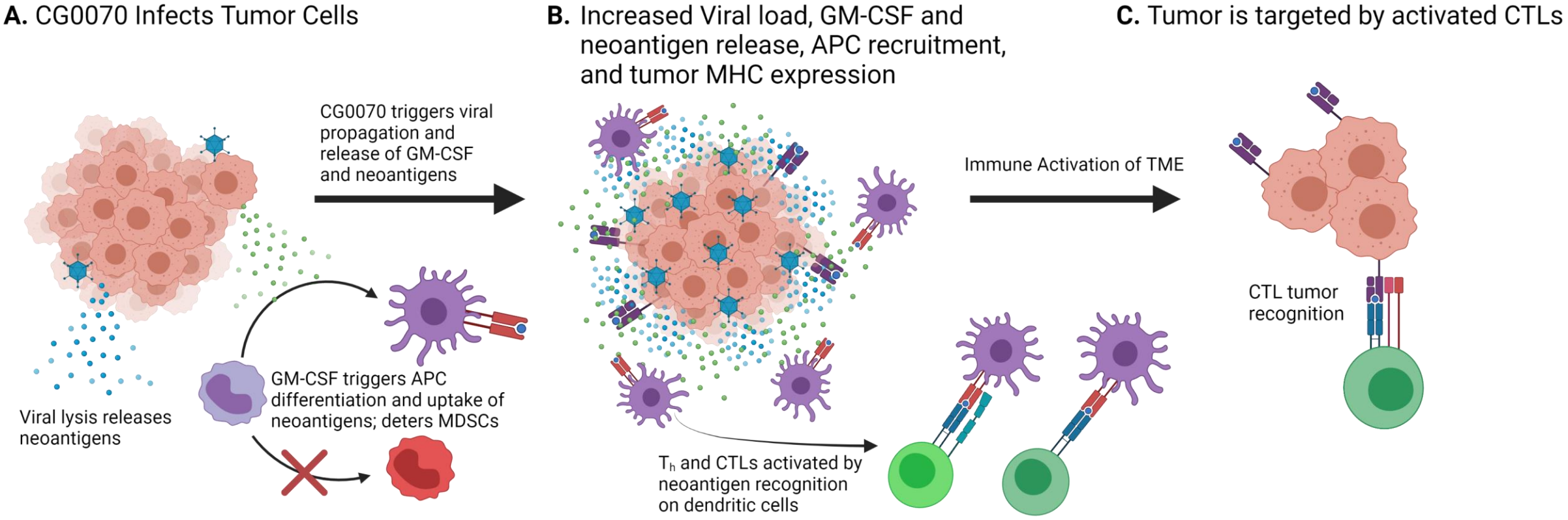
Cancer-selective Oncolytic Adenovirus Engineered to Preferentially Replicate in Tumor Cells



E2F Promoter along with **GM-CSF transgene** inserted into wild-type adenovirus backbone

Gene / Protein	Function
E2F	Leads to selective viral replication in tumor cells, but not normal cells
E1A / E3	Viral gene retains wild-type adenovirus lytic ability
GM-CSF	GM-CSF activates and matures antigen-presenting cells

Cretostimogene Mechanism of Action



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Phase 1 Cretostimogene Monotherapy for High-Risk, BCG-Failure NMIBC, CIS-Containing or Papillary (NCT00109655)

N = 35 NMIBC CIS-containing or Ta/T1

Design: Dose-escalation, intravesical (IVe) administration

Trial Type: Open label

Regimen:
Multi-Schedule and Multi-Dose

Multi-Dose =
$1x10^{12}$ vp/mL, $3x10^{12}$ vp/mL, $1x10^{13}$ vp/mL, $3x10^{13}$ vp/mL

Multi-Schedule =
Single Dose, Every 28 Days, Weekly x 6

Endpoints: Safety, Dose and Schedule Determination

Safety and Efficacy Achieved, Dose & Schedule Identified for Phase 2 Study

CR at 3-Month

46%

16/35

Median Duration: 8.4 months, with responses ongoing at 17.0 months

CR by Schedule

Schedule	CR
Single Dose	3/13 (23%)
Every 28 Days	6/13 (46%)
Weekly x 6	7/9 (78%)
Multi-Dose (Every 28 Days + Weekly x 6)	13/22 (59%)
Total	**16/35 (46%)**

CR by Dose

Dose	CR
1×10^{12} vp	8/13 (62%)
3×10^{12} vp	4/9 (44%)
1×10^{13} vp	4/10 (40%)
3×10^{13} vp	0/3 (0%)

Burke J, et al. *J Urology*, 2012.

Phase 2 Cretostimogene Monotherapy for High-Risk, BCG-Failure NMIBC, CIS-Containing (NCT02365818)

46 Patients

Cretostimogene (CG0070)
Single-Arm, Open-Label

Primary Endpoint
CR Rate

Positive CR Rate & Duration of Response

CR at Any Time	CR at 6 Mo	CR at 12 Mo
65%	44%	28%
30/46	20/46	13/46

Favorable safety profile also achieved with most AEs being transient Grade 1-2 local urinary tract symptoms, and no Grade 4 or 5 AEs

Ref: Packiam et al. J Urol. Oncol. 2018; 36 (10) 440-447

BOND-003

Phase 3 Cretostimogene Monotherapy for High-Risk, BCG-Unresponsive NMIBC, CIS-Containing (NCT04452591)

N = 110 NMIBC CIS-containing

Design: Single-arm, intravesical (IVe) administration

Trial Type: Open label

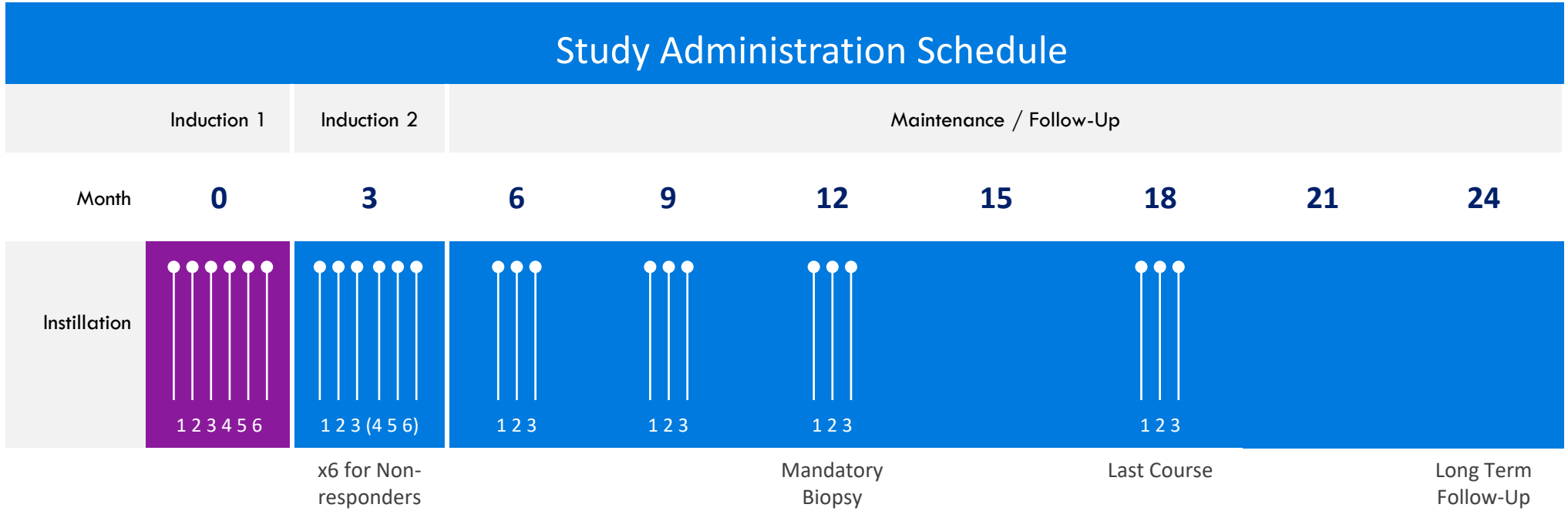
Regimen:
Induction course =
Weekly x 6 ($1x10^{12}$ vp/mL)

Second induction course[1] =
Weekly x 6 ($1x10^{12}$ vp/mL)
for non-responders

Maintenance courses[2] =
Weekly x 3 ($1x10^{12}$ vp/mL)
for complete responders

Endpoints: Complete Response (CR) at Any Time

Study Administration Schedule



[1] Second induction course of weekly x 6 for non-responders at month 3
[2] Maintenance course for complete responders starts at month 3 every 3 months for 1st year, and every 6 months for 2nd year
Note: Patients undergo urine cytology and cystoscopy every 3 months for first 2 years; mandatory, site-directed biopsy at month 12

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Phase 2 Cretostimogene + KEYTRUDA® for High-Risk, BCG-Unresponsive NMIBC, CIS-containing (NCT04387461)

N = 35 NMIBC CIS-containing

Design: Single-arm, intravesical (IVe) CG0070 + intravenous (IV) pembrolizumab

Trial Type: Open label

Regimen:

CG0070 Induction =
Weekly x 6 ($1x10^{12}$ vp/mL)

Second induction course[1] =
Weekly x 3 or 6 ($1x10^{12}$ vp/mL)
3 for responders, 6 for non-responders

Maintenance courses[2] =
Weekly x 3 ($1x10^{12}$ vp/mL)
for complete responders

Pembrolizumab =
Every 6 weeks (400 mg)
through Year 2

Endpoints:

Complete Response (CR) at Any Time, CR at 12 months (Duration of Response)

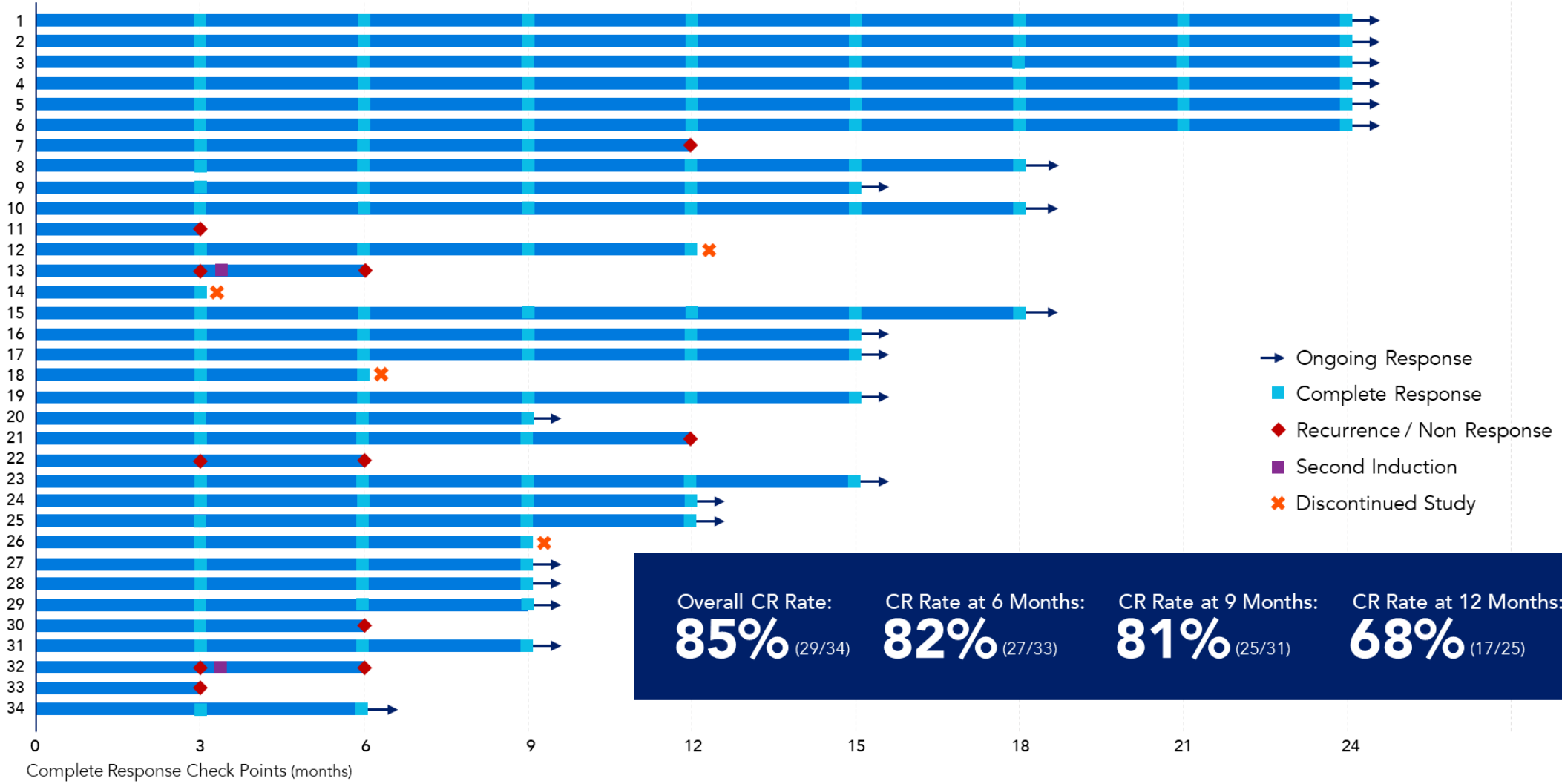
Study Administration Schedule

	Baseline	Enrollment	Induction 1 / Cycle 1	Induction 2 / Cycle 2	Maintenance / Follow-Up		
Week			Week 1-7	Week 13-19	Week 25-31 Week 37-43 Week 49-51	Week 73-79	Week 104+
Instillation			1 2 3 4 5 6 7	1 2 3 (4) (5) (6) 7	1 2 3 7	1 2 3 7	
	Complete Ta/T1 Resection	Urine Cytology & Cystoscopy	**Month 1 through Month 3** 6 doses of CG0070 2 doses of pembrolizumab	**Month 4 through Month 6** 3 to 6 doses of CG0070 2 doses of pembrolizumab	**Month 6 through 12** CG0070 every 3 months Pembro every 6 weeks	**Month 12 through 24** CG0070 every 6 months Pembro every 6 weeks	**Month 24+** Long Term Follow-Up

[1] Second induction course of weekly x 6 for non-responders at month 3. [2] Maintenance course for complete responders starts at month 3 every 3 months for 1st year, and every 6 months for 2nd year

CORE-001 Demographics and Baseline Characteristics		
	N	%
Subjects in dataset	35	
Gender		
Male	33	94.3
Female	2	5.7
Age (Years)		
<65	8	22.9
>65	27	77.1
ECOG		
0	27	77.1
1	7	20
2	1	2.9
BCG History: Number of prior instillations		
Median (range)	12 (9 - 30)	
Baseline High-risk NMIBC Disease status:		
Persistent high-risk NMIBC	21	60
Recurrent high-risk NMIBC	14	40
High-risk NMIBC T-Stage at study entry		
CIS with T1	3	8.55
CIS with Ta HG	3	8.55
CIS with Ta HG and T1	1	2.9
CIS	28	80
Geographical Region		
US	30	85.7
Non-US	5	14.3

CORE-001: Cretostimogene + KEYTRUDA® Combo for BCG-Unresponsive NMIBC



Overall CR Rate:	CR Rate at 6 Months:	CR Rate at 9 Months:	CR Rate at 12 Months:
85% (29/34)	82% (27/33)	81% (25/31)	68% (17/25)

CORE-001 Treatment Related Adverse Events

Preferred Term	Grade 1 (N%)	Grade 2 (N%)	Grades 1 and 2 (N%)
Bladder spasm	11 (31.4%)	4 (11.4%)	15 (42.9%)
Fatigue	11 (31.4%)	2 (5.7%)	13 (37.1%)
Pollakiuria	9 (25.7%)	1 (2.9%)	10 (28.6%)
Dysuria	7 (20.0%)	1 (2.9%)	8 (22.9%)
Hematuria	4 (11.4%)	1 (2.9%)	5 (14.3%)
Micturition urgency	3 (8.6%)	2 (5.7%)	5 (14.3%)
Diarrhea	4 (11.4%)		4 (11.4%)
Hypothyroidism	1 (2.9%)	3 (8.6%)	4 (11.4%)
Nocturia	3 (8.6%)	1 (2.9%)	4 (11.4%)
Urinary tract infection	3 (8.6%)	1 (2.9%)	4 (11.4%)
Abdominal pain	3 (8.6%)		3 (8.6%)
Alanine aminotransferase increased	2 (5.7%)	1 (2.9%)	3 (8.6%)
Aspartate aminotransferase increased	2 (5.7%)	1 (2.9%)	3 (8.6%)
Headache	3 (8.6%)		3 (8.6%)
Pruritus	2 (5.7%)	1 (2.9%)	3 (8.6%)
Arthralgia	1 (2.9%)	1 (2.9%)	2 (5.7%)
Asthenia	1 (2.9%)	1 (2.9%)	2 (5.7%)
Bladder discomfort	2 (5.7%)		2 (5.7%)
Blood glucose increased	2 (5.7%)		2 (5.7%)
Chills	2 (5.7%)		2 (5.7%)
Myalgia	2 (5.7%)		2 (5.7%)
Polyuria	2 (5.7%)		2 (5.7%)
Urinary incontinence	2 (5.7%)		2 (5.7%)
Urinary retention	1 (2.9%)	1 (2.9%)	2 (5.7%)
Urinary tract pain	2 (5.7%)		2 (5.7%)

An additional 34 grade 1-2 AE were experienced by a single patient

- Predominantly transient, grade 1-2 local genito-urinary AE
- Grade 3 AE included (4 total patients)
  - Autoimmune hepatitis
  - Reduced ejection fraction
  - Neutrophil count decreased
  - Alkaline phosphatase increased
  - Adrenal insufficiency
- Grade 4 / 5 AE – none observed
- AE profile generally consistent with prior studies of each agent alone
- No evidence of additive or synergistic toxicity

Conclusions

- Monotherapy activity of Cretostimogene grenadenorepvec in NMIBC after BCG failure has been established in two past studies of Cretostimogene Grenadenorepvec, V0046 and BOND-002

- The combination of Cretostimogene grenadenorepvec and pembrolizumab appears to be highly active in BCG-unresponsive NMIBC based on preliminary results of the CORE-001 study

- Studies of Cretostimogene grenadenorepvec alone (Phase 3 BOND-003, ongoing study) and in combination with checkpoint inhibitor therapy (Phase 3 PIVOT-001, planned study) will further elucidate the potential role of Cretostimogene grenadenorepvec based therapy for BCG-unresponsive NMIBC

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