Completion of Acclaim-1 Dose Escalation: Recommended Phase 2 Dose of Quaratusugene Ozeplasmid Gene Therapy and Osimertinib

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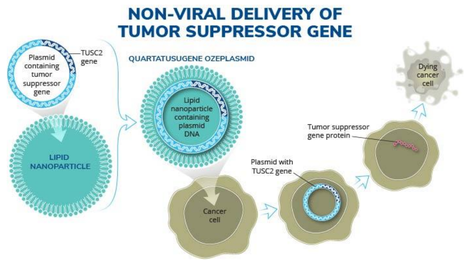
Introduction

- TUSC2 is a tumor suppressor gene often deleted or inactivated in NSCLC
  - TUSC2 expression is decreased in 82% of patients with NSCLC
- Quaratusugene ozeplasmid gene therapy consists of a plasmid containing the TUSC2 gene encapsulated in a lipid nanoparticle
  - Restores TUSC2 expression in cancer cells
- Quaratusugene ozeplasmid enhances responses to EGFR inhibitors[1] and increases NK and CD8+ T-cell tumor infiltration[2]



Major Eligibility Criteria

- Adult patients with Stage III or IV NSCLC
- EGFR mutation
- ECOG PS 0-1
- Achieved clinical response (including stable disease) for ≥ 4 months with osimertinib or osimertinib containing regimen
- Progression on osimertinib or osimertinib-containing regimens
- Asymptomatic brain metastases allowed
  - Off steroids ≥ 7 days
- Adequate hematologic, renal, and hepatic function

Phase 1 Trial Design

- Quaratusugene ozeplasmid was administered IV every 21 days in combination with osimertinib 80 mg PO daily
  - 3 dose levels (0.06, 0.09, and 0.12 mg/kg) of quaratusugene ozeplasmid were used
  - Osimertinib dose did not change
  - Standard dose escalation with 3-6 patients/dose level was used
- Dexamethasone, acetaminophen, and diphenhydramine were given prior to each treatment to prevent delayed infusion related reaction
- Efficacy was evaluated after every even cycle of treatment using RECIST 1.1 criteria
- Safety was evaluated using CTCAE v5
- Dose limiting toxicities (DLTs) were generally defined as ≥ Grade (Gr) 3 adverse events (AEs) during Cycle 1 of treatment

Enrollment and Dose Limiting Toxicities

	0.06 mg/kg	0.09 mg/kg	0.12 mg/kg	Total
# Patients	3	4◊	5^	12
M/F	0/3	2/2	1/4	3/9
Median Age (range)	59 (50-60)	51 (38-69)	59 (57-74)	59 (38-74)
DLTs	0	0	0	0

◊ 1 patient received quaratusugene ozeplasmid in 1st cycle but was excluded from RP2D assessment for reasons not related to DLT.
^ 1 patient withdrew and 1 lost to follow up before completing 1st cycle

References: [1] PLoS ONE. 2015; 10: e0123967. [2] Cancer Immunol Research. 2018; 6: 163–177.

Adverse Events

- No DLTs occurred at any dose level
- A delayed infusion related reaction was observed
  - Included myalgia, fever, chills, diarrhea, influenza like illness, headache, and muscle spasms
  - Started approximately 3-6 hours after the quaratusugene ozeplasmid infusion
  - Resolved over approximately 2-6 hours
  - Symptoms decreased markedly with repeat cycles of treatment
  - Presumed to be reaction to lipid nanoparticles
- Based on preliminary safety data, the only Gr 3/4 AEs considered to be related were lymphopenia in 2 patients, and neutropenia in 1 patient
- Safety Review Committee recommended 0.12 mg/kg as the Recommended Phase 2 Dose (RP2D) based on the lack of DLTs

Delayed Infusion Related Reaction

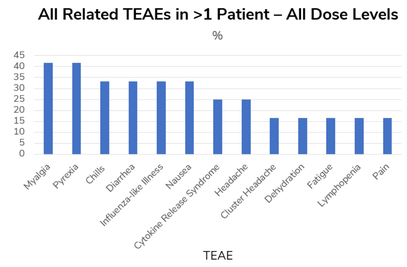
- Symptoms decrease with repeat cycles of treatment

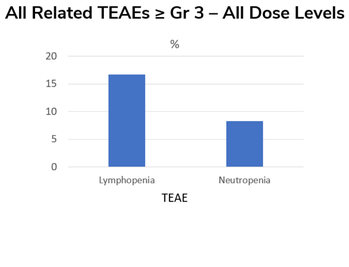
Patient	Symptom (CTCAE Grade)						
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7
009-001	Chills (2) Body ache (2) Headache (2)	-	Chills (2) Body ache (2) Headache (2)	Chills (1) Myalgia (1) Headache (1) Fatigue (1)	-	Flu-like Symptoms (1)	-
012-002	Wheezing (1)	Fever (1) Hyperten-sion (2) Chills (1)	-	-	-	-	-

All Treatment Emergent Adverse Events in >1 Patient

TEAE	0.06 mg/kg N=3 n(%)	0.09 mg/kg N =4 n(%)	0.12 mg/kg N = 5 n(%)	Total N=12 n(%)
Myalgia	2 (66.7)	2 (50.0)	1 (20.0)	5 (41.7)
Pyrexia	1 (33.3)	3 (75.0)	1 (20.0)	5 (41.7)
Chills	2 (66.7)	1 (25.0)	1 (20.0)	4 (33.3)
Diarrhea	1 (33.3)	2 (50.0)	1 (20.0)	4 (33.3)
Influenza-like Illness	1 (33.3)	1 (25.0)	2 (40.0)	4 (33.3)
Nausea	0	1 (25.0)	3 (60.0)	4 (33.3)
Cytokine Release Syndrome	0	0	3 (60.0)	3 (25.0)
Dehydration	0	0	3 (60.0)	3 (25.0)
Headache	1 (33.3)	1 (25.0)	1 (20.0)	3 (25.0)
Cluster Headache	1 (33.3)	1 (25.0)	0	2 (16.7)
Constipation	1 (33.3)	0	1 (20.0)	2 (16.7)
Fatigue	1 (33.3)	0	1 (20.0)	2 (16.7)
Lymphopenia	0	1 (25.0)	1 (20.0)	2 (16.7)
Muscle Spasms	1 (33.3)	1 (25.0)	0	2 (16.7)
Pain	1 (33.3)	1 (25.0)	0	2 (16.7)

Related Treatment Emergent Adverse Events

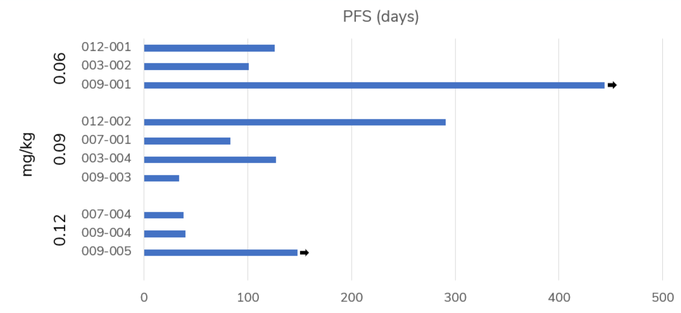




Efficacy

- 1 patient at the 0.06 mg/kg dose level had a PR after Cycle 2 and continues on treatment more than 1 year later
  - Recently received Cycle 22
  - Previously treated with carboplatin, pemetrexed, and osimertinib
- 1 patient at the 0.09 mg/kg dose level had SD for 14 cycles before progression
  - Previously treated with osimertinib
- 1 patient at the 0.12 mg/kg dose level has had SD for 8 cycles and continues on treatment
  - Previously treated with cisplatin, pemetrexed, carboplatin, and osimertinib

Progression Free Survival by Dose Group



1 patient withdrew and 1 patient was lost to follow up before completing first cycle and therefore were not evaluable for PFS
➡ = Patient's study treatment ongoing

Conclusions

- Quaratusugene ozeplasmid was generally well tolerated with no DLTs
- Quaratusugene ozeplasmid administration was associated with a delayed infusion related reaction with most common symptoms being myalgia, fever, and chills based on preliminary safety data
  - Managed with prophylactic steroids, acetaminophen and diphenhydramine and repeated treatment based on symptoms. Symptom incidence and intensity decrease with repeat cycles of treatment.
- 2/12 patients progressing on osimertinib containing regimens had prolonged PFS on quaratusugene ozeplasmid and osimertinib combination therapy
  - 1 with continuing PR after 22 cycles of treatment
  - 1 progressing after 14 cycles of treatment
- RP2D is 0.12 mg/kg based on the lack of DLTs