DNA Immunotherapy (INO-3107) Demonstrates a Durable Response for Treatment of HPV-6 and -11 Recurrent Respiratory Papillomatosis

Skolnik JM, Slog SA, Welsh C*, Sumner MJ
Inovio Pharmaceuticals, Plymouth Meeting, PA

Introduction & Methods

Recurrent Respiratory Papillomatosis (RRP) is a debilitating disease of the airway caused by an insufficient immune response to a chronic infection from Human Papillomavirus (HPV)-6 and -11. It is characterized by recurrent benign tumor growths with the potential for malignant transformation. Current standard of care is repeated surgical removal of papillomas for symptomatic management, which leads to an increased risk of laryngeal injury with each surgery. INO-3107, a DNA immunotherapy designed to elicit targeted T-cell responses against HPV-6 and -11 in adult RRP patients, has been evaluated during a 52-week Phase I/II study (RRP-001, ClinicalTrials.gov identifier: NCT04398433) and a retrospective, observational follow-up study (RRP-002). Here we present long-term safety and clinical efficacy results.

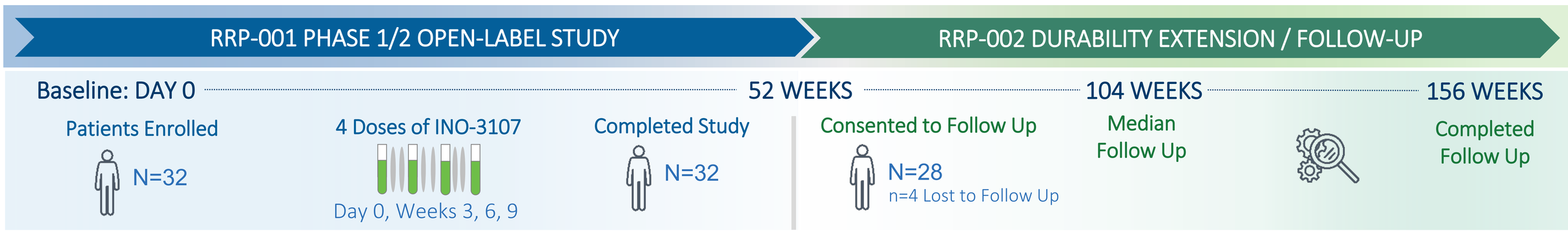

Fig 1. RRP-001 & RRP-002 study designs.

RRP-001: In a Phase I/II, single-arm, open-label study conducted at 8 US centers, eligibility included HPV-6 and/or -11 confirmed disease, requiring ≥2 RRP surgeries in the year preceding enrollment (Year -1). Patients underwent surgical debulking within 14 days prior to Dose 1, then received INO-3107 administered by intramuscular injection followed by electroporation on Day 0, and Weeks 3, 6, and 9. There was no requirement for additional surgeries to maintain minimal residual disease during the administration phase. The primary endpoint was safety and tolerability assessed by treatment-emergent adverse events (TEAEs). Secondary endpoints included post-INO-3107 surgical frequency and cellular immune responses.

RRP-002: Retrospective, observational follow-up study based on medical record review of 28 of 32 patients (4 lost to follow-up) enrolled in RRP-001 for at least 52 additional weeks. RRP-002 assessments included surgical frequency and serious adverse events (SAEs).

Patient Baseline Characteristics (RRP-001 & RRP-002)

Characteristic	RRP-001 (N=32)	RRP-002 (N=28)
Median age (range), years	46.5 (25-82)	47.5 (27-84)
Male, n (%)	24 (75.0)	20 (71.4)
Race, n (%)		
Asian	1 (3.1)	1 (3.6)
Black or African American	4 (12.5)	4 (14.3)
White	26 (81.3)	22 (78.5)
Other	1 (3.1)	1 (3.6)
Ethnicity, n (%)		
Hispanic or Latino	3 (9.4)	3 (10.7)
Not Hispanic or Latino	29 (90.6)	25 (89.3)
Median (range) number of surgeries in year prior to dosing	4 (2-8)	3 (2-8)
HPV genotype at screening, n (%)		
6	16 (50.0)	13 (46.4)
11	10 (31.3)	9 (32.1)
6 and 11	2 (6.3)	2 (7.1)
6 and/or 11[a]	4 (12.5)	4 (14.3)

a: Of the 32 subjects, three (3) subjects did not have papilloma tissue collected at Baseline and one (1) subject had the HPV genotyping assay failed. HPV-6 and/or 11 was confirmed prior to study based on documentation provided by the clinical site for these four (4) subjects, but genotype was not specified.

Table 1. RRP-001 & RRP-002 patient baseline characteristics.

A total of 32 patients were enrolled in RRP-001. Twenty-eight (28) of 32 participants from RRP-001 were enrolled in RRP-002. Four patients were either lost to follow-up or not consented.

Continued Reduction in Annual Surgeries

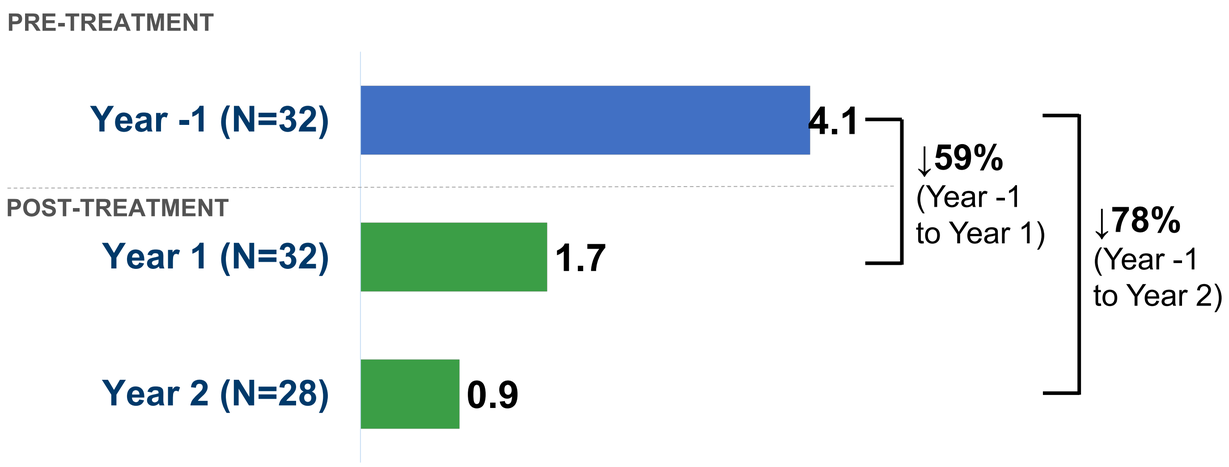

Fig 2. Mean number of surgeries per year before and after INO-3107 immunotherapy. Prior to INO-3107 treatment, patients enrolled in RRP-001 underwent an average of 4.1 surgeries annually (blue bar). In the years following treatment, average annual surgeries reduced from 1.7 at Year 1 to 0.9 at Year 2 (green bars).

Durable Response Observed Through Year 2

PARAMETERS
(during the year compared to baseline)

CR **Complete Response:** No surgeries

PR **Partial Response:** A 50-99% reduction in surgeries

OCR **Overall Clinical Response:** Reduction of ≥1 surgery

NR **Non-Responders:** No reduction in surgeries

Four patients (I, W, Z, FF) were lost to follow-up or not consented from RRP-001 to RRP-002.

Alternative treatment use:
†: intravenous bevacizumab
‡: intralesional bevacizumab
#: intravenous pembrolizumab

	RRP-001 (*N*=32)		RRP-002 (*N*=28)
Patient ID	**Year -1 Pre-Treatment**	**Year 1 Post-Treatment**	**Year 2 Post-Treatment**
A	2	0	0
B	3	0	0
C	3	0	0
D	2	0	0
E	3	0	0
F	3	0	0
G	6	0	0
H	3	0	1†
I	4	0	
J	8	1	0
K	6	2	0
L	5	2	0
M	6	2	0
N	4	1†	0#
O	3	1	1
P	5	1	2
Q	5	2	2†
R	6	3	2
S	6	3	1
T	2	1	1
U	4	1	2
V	2	1	2‡
W	5	1	
X	6	4	3
Y	5	3	3
Z	7	5	
AA	3	3	0†
BB	3	3	0
CC	3	3	1
DD	2	3	2
EE	2	3	2
FF	4	4	
Mean Annual Surgeries	**4.1**	**1.7**	**0.9**

Fig 3. Number of surgical interventions 2 years post-baseline compared with 1 year prior to Day 0 (RRP-001 & RRP-002).

Patients receiving INO-3107 demonstrated a durable response to treatment, along with continued clinical improvement over time.

At Year 1, 81% of patients (26/32) experienced a reduction of at least 1 surgery (OCR, overall clinical response) compared to the year prior to treatment. This was maintained in 91% (21/23) of those not lost to follow-up at Year 2. Of the 9 patients experiencing no surgeries post-INO-3107 at Year 1 (CR, complete response), 7 maintained their response through Year 2. As a result of clinical response improving over time, patients experiencing a CR increased from 28% (9/32) in Year 1 to 50% (14/28) in Year 2.

Conclusions

DNA immunotherapy INO-3107 for recurrent respiratory papillomatosis demonstrates a durable response through post-treatment Year 2 with 91% of patients continuing to experience clinical effect of surgery reduction compared to the year prior to treatment initiation. Patients also demonstrated improvement in clinical response over time, with 50% experiencing no surgeries in Year 2, compared to 28% in Year 1. This supports INO-3107's ability to provide long-term immunologic and clinical effects.