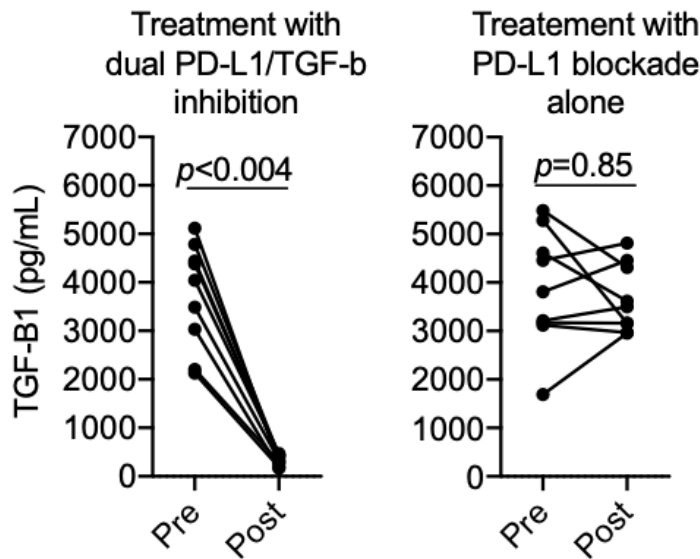


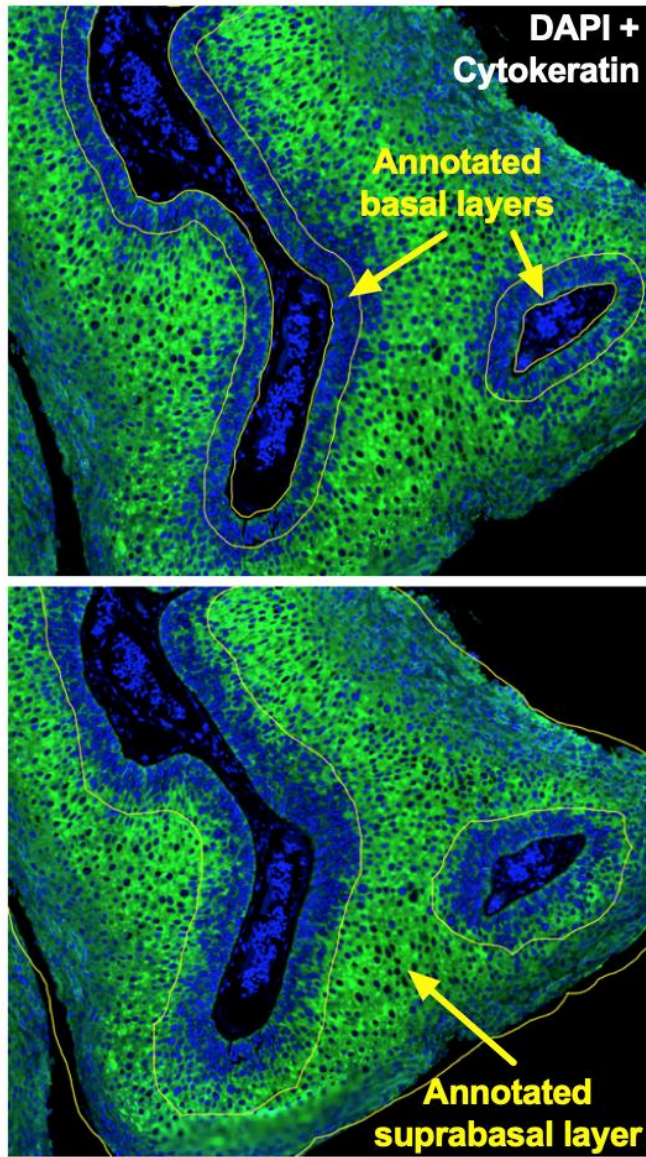
**Supplementary Figure S1 – Comparative rates of papilloma growth before and after dual PD-L1/TGF- $\beta$  inhibition.**

The percent change in the Derkay score from the four weeks prior to treatment with dual PD-L1/TGF- $\beta$  inhibition compared to the percentage change in Derkay score from two to four or six weeks after treatment.



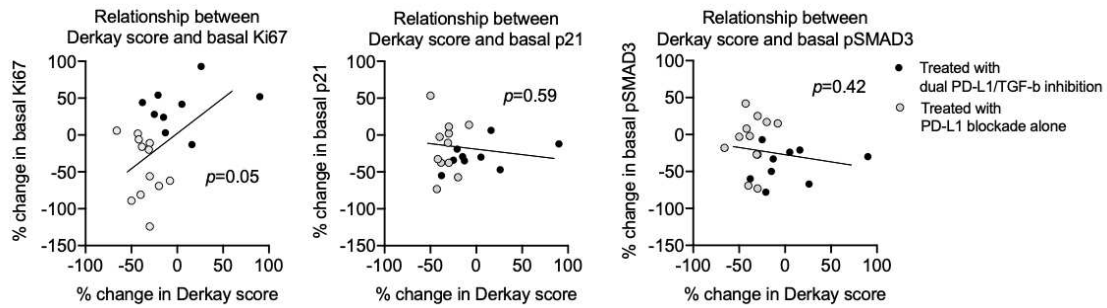
### Supplemental Figure S2 –Systemic TGF- $\beta$ levels

Spider plots of serum TGF- $\beta$  levels following treatment with dual PD-L1/TGF-b inhibition or PD-L1 blockade alone are shown. Pre-treatment serum was obtained within one week prior to initiation of treatment and post-treatment serum was obtained within one week following completion of treatment.  $p$ -value determined by Wilcoxon matched-pairs signed rank test.



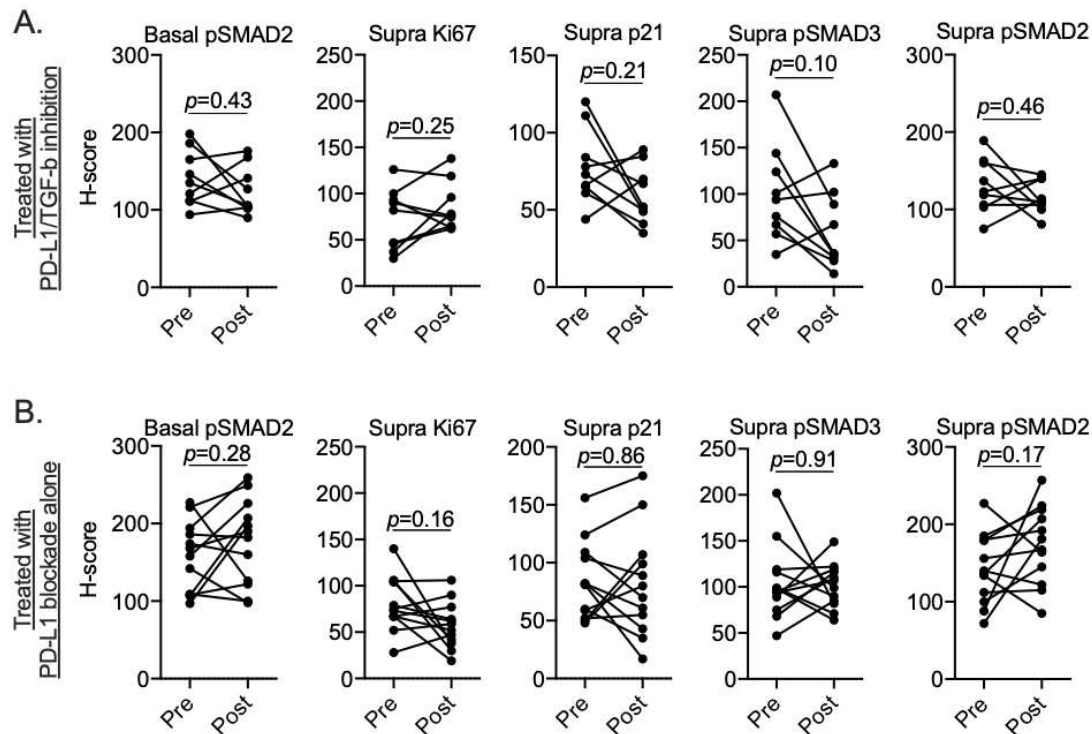
**Supplemental Figure S3 – Representative basal and suprabasal layer annotations.**

Photomicrographs of papillomas stained with a pan-cytokeratin antibody (green) and DAPI (blue) with representative basal (top) and suprabasal (bottom) annotations. The entire section was annotated and scored for each pre- and post-treatment biopsy.



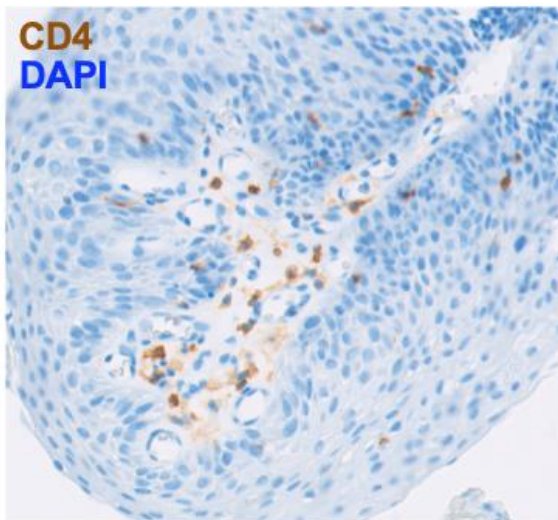
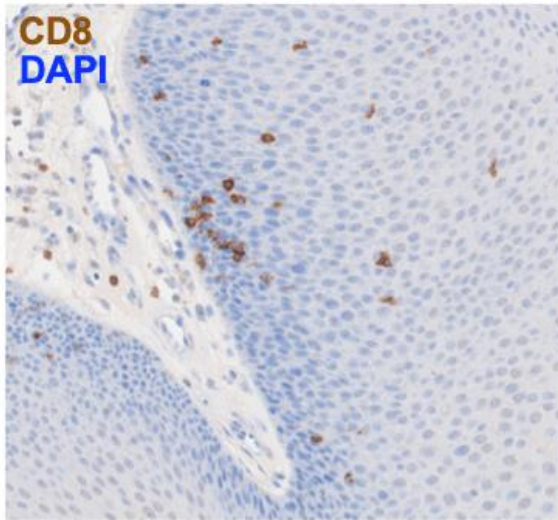
#### Supplemental Figure S4 – Correlation between immunofluorescence and Derkay scores

The correlation between TGF- $\beta$  signaling pathway protein expression or phosphorylation and clinical response in patients treated with dual PD-L1/TGF- $\beta$  inhibition or PD-L1 blockade alone is shown. Significance of correlation was tested by linear regression analysis.



**Supplemental Figure S5 - Assessment of additional TGF- $\beta$  signaling parameters in subjects treated with dual PD-L1/TGF- $\beta$  inhibition or PD-L1 blockade alone.**

Spider plots of changes in quantification of TGF- $\beta$  signaling pathway protein expression or phosphorylation within the basal or suprabasal layers of papillomas in patients treated with (A) dual PD-L1/TGF- $\beta$  inhibition ( $n=9$ ) or (B) PD-L1 blockade alone ( $n=12$ ) are shown. H-scores were determined by quantifying annotated basal cell fluorescence of individual cells across entire biopsy sections.  $p$ -value determined by Wilcoxon matched-pairs signed rank test.



**Supplemental Figure S6 – Representative T-lymphocyte immunohistochemistry.**

Representative photomicrographs of CD8 or CD4 immunohistochemistry.

Supplemental Table I. Demographics of patients treated with bintrafusp alpha

Patient	Age at treatment (years)	Sex	HPV type	Age at diagnosis (years)	Number of lifetime RRP surgeries	Pulmonary lesions
1	65	M	11	19	>50	Yes
2	52	F	6	23	>70	No
3	42	M	6	37	>25	No
4	37	F	6	28	>90	No
5	39	M	6	37	8	No
6	25	M	11	1	>100	Yes
7	20	M	11	1	>200	Yes
8	18	F	6	5	>90	No
9	33	F	6	1	>250	Yes

Supplemental Table II. TGF- $\beta$  superfamily genes

Gene	Protein product
<i>TGFB1</i>	Transforming growth factor beta 1
<i>TGFB2</i>	Transforming growth factor beta 2
<i>TGFB3</i>	Transforming growth factor beta 3
<i>TGFBRI (ALK5)</i>	Transforming growth factor beta receptor 1
<i>TGFBR2</i>	Transforming growth factor beta receptor 2
<i>TGFBR3</i>	Transforming growth factor beta receptor 3
<i>BMP2</i>	Bone morphogenic protein 2
<i>BMP3</i>	Bone morphogenic protein 3
<i>BMP4</i>	Bone morphogenic protein 4
<i>BMP5</i>	Bone morphogenic protein 5
<i>BMP6</i>	Bone morphogenic protein 6
<i>BMP7</i>	Bone morphogenic protein 7
<i>BMP9 or GDF2</i>	Bone morphogenic protein 9
<i>BMP10</i>	Bone morphogenic protein 10
<i>BMP15</i>	Bone morphogenic protein 15
<i>BMPRI1A (ALK3)</i>	Bone morphogenetic protein receptor type 1A
<i>BMPRI1B (ALK6)</i>	Bone morphogenetic protein receptor type 1B
<i>BMPRI2</i>	Bone morphogenetic protein receptor type 2
<i>ACVR1 (ALK2)</i>	Activin A receptor type 1
<i>ACVR1B (ALK4)</i>	Activin A receptor type 1B
<i>ACVR1C (ALK7)</i>	Activin A receptor type 1C
<i>ACVR2A</i>	Activin A receptor type 2A
<i>ACVR2B</i>	Activin A receptor type 2B
<i>ACVRL1 (ALK1)</i>	Activin A receptor like type 1
<i>Nodal</i>	Nodal
<i>GDF1</i>	Growth differentiation factor 1
<i>GDF11</i>	Growth differentiation factor 11
<i>INHA (Activin A)</i>	Inhibin alpha
<i>INHBA</i>	Inhibin subunit beta A
<i>INHBB</i>	Inhibin subunit beta B
<i>INHBC</i>	Inhibin subunit beta C
<i>INHBE</i>	Inhibin subunit beta E
<i>SMAD2</i>	Mothers against decapentaplegic homolog 2
<i>SMAD3</i>	Mothers against decapentaplegic homolog 3
<i>SMAD1</i>	Mothers against decapentaplegic homolog 1
<i>SMAD5</i>	Mothers against decapentaplegic homolog 5



<i>SMAD4</i>	Mothers against decapentaplegic homolog 4
<i>SMAD9</i>	Mothers against decapentaplegic homolog 9
<i>SMAD6</i>	Mothers against decapentaplegic homolog 6
<i>SMAD7</i>	Mothers against decapentaplegic homolog 7
<i>SPTBN1</i>	Spectrin beta chain, brain 1
<i>TGFBRAP1</i>	Transforming growth factor beta receptor associated protein 1
<i>ZFYVE9</i>	Zinc finger FYVE domain-containing protein 9