SUPPLEMENTARY APPENDIX

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1. Supplementary Table S1: HPV characterization

HPV Positive	**Overall population n=60**	**Arm A n=30**	**Arm B n=30**
Yes	51 (91%)	25 (89%)	26 (93%)
No	5 (9%)	3 (11%)	2 (7%)
Not evaluable*	*4*	*2*	*2*
HPV type on HPV-positive patients			
HPV Type	**Overall HPV-positive population n=51**	**Arm A HPV-positive patients n=25**	**Arm B HPV-positive patients n=26**
16	34 (95%)	13 (93%)	21 (95%)
Others†	2 (5%)	1 (7%)	1 (5%)
Not evaluable*	*15*	*11*	*4*

*Missing data were not included in the denominator for better comparison between groups with data
†1 HPV39-positive tumour in arm A and 1 HPV6-positive tumour in arm B

2. Supplementary Table S2: Further treatments after PD

	Arm A **Avelumab** **N of patients with PD=28**	**Arm B** **Avelumab + Cetuximab** **N of patients with PD=28**
Further treatments received		
Yes	11 (39%)	11 (39%)
No	17 (61%)	17 (61%)
Type of treatments received		
Chemotherapy	9 (32%)	9 (32%)
Locoregional treatments or surgery	1 (4%)	0 (0%)
Chemotherapy and other treatments* (i.e. biological agents, surgery, locoregional treatments)	1 (4%)	2 (7%)

* (i.e. biological agents, surgery, locoregional treatments)

3. Supplementary Table S3: Treatment-related adverse events

* AE occurring in more than 5% of the patients in at least one arm have been detailed

	Any grade*		**G3 - G4**	
	Arm A Avelumab N=30	**Arm B Avelumab + Cetuximab N=30**	**Arm A Avelumab N=30**	**Arm B Avelumab + Cetuximab N=30**
	n of patients developing AE		***n of patients developing AE***	
Skin and subcutaneous disorders	3 (10%)	26 (87%)	-	2 (6%)
Conjunctivitis	1 (3%)	6 (20%)	-	-
Hypomagnesemia	1 (3%)	10 (33%)	-	2 (6%)
Anaemia	1 (3%)	3 (10%)	-	1 (3%)
Fever	3 (10%)	2 (6%)	-	-
Fatigue	5 (17%)	6 (20%)	-	1 (3%)
Anorexia	-	2 (6%)	-	-
Diarrhea	1 (3%)	6 (20%)	-	-
Nausea/vomiting	2 (6%)	3 (10%)	-	-
AST/ALT increase	-	2 (6%)	-	2 (6%)
Creatinine increase	-	2 (6%)	-	-
Thyroid disfunctions	3 (10%)	4 (13%)	-	-
Infusion related adverse reactions	2 (6%)	2 (6%)	-	-
Blood bilirubin increase	-	-	-	1 (3%)

4. Supplementary Table S4: Patient exposure and disposition

	Arm A Avelumab N=30	**Arm B Avelumab + Cetuximab N=30**
Total number of administrations		
Avelumab	277	315
Cetuximab	NA	319
Median number of doses (range)		
Avelumab	6·0 (2·0 – 35·0)	8·0 (1·0 – 36·0)
Cetuximab	NA	8·0 (2·0 – 36·0)
N of delayed administrations due to AE, n (% of total administrations)		
Avelumab	5 (2%)	17 (5%)
Cetuximab	NA	17 (5%)
Dose modifications due to AE, n (% of total administrations)		
Avelumab	0 (0%)	5 (2%)
Cetuximab	NA	15 (5%)
Reasons for treatment discontinuation		
Disease progression	26 (93%)	26 (93%)
AE related to study drug	0 (0%)	2 (7%)
Other*	2 (7%)	0 (0%)
Median duration of therapy (IQR), months	3·5 (1·8 – 6·0)	4·6 (1·8 – 6·4)
Continuing treatment	2 (7%)	2 (7%)

*In Arm A, one patient discontinued the treatment due to surgery; in another case in Arm A, the treatment was discontinued for patient's decision.