Human papillomavirus type 16 (HPV16) is a major HPV type causing anogenital cancers and the predominant HPV type causing oropharyngeal cancers. Studies in healthy individuals and patients have assigned a major role for HPV16 E6/E7 oncoprotein-specific type 1 T cell immunity in the protection against progressive premalignant disease and a better response to standard therapy at the stage of cancer (*7*, *8*). Despite all patients with progressive disease being infected with HPV16, such an immune response is usually not demonstrable or insufficient to have clinical impact (*7*–*10*). Raising the numbers of HPV-specific T cells by therapeutic vaccine several chemotherapeutics and demonstrated synergistic effects with HPV16 synthetic long peptide (SLP) vaccination in two mouse models of HPV-induced cancer (*16*, *17*). Careful analysis of the immunomodulatory effects of chemotherapy revealed that the combination of carboplatin and paclitaxel elicited a systemic and local reduction in the cancer-driven abnormal numbers of immunosuppressive myeloid cells (*18*). A pilot experiment in patients with late-stage cervical cancer showed the optimal time point to start vaccination with the therapeutic HPV16-SLP vaccine ISA101 to be 2 weeks after the second cycle of carboplatin/paclitaxel. At that time point, the

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systemic abnormally high numbers of immunosuppressive myeloid cells had declined to the numbers seen in healthy donors. This coincided with decreased immunosuppression and a stronger T cell response to a single timed ISA101 vaccine injection (*18*).

These findings led to the design of the current study, in which patients with late-stage HPV16-positive cervical cancer were vaccinated with ISA101 in a timed manner during chemotherapy. Successive patient cohorts were vaccinated with increasing ISA101 doses, and half of the patients in each cohort also received pegylated type 1 interferon (IFN) (PegIntron). This was tried because IFNα is a strong promoter of cross-presentation of proteins by dendritic cells (DCs) (*19*) and is responsible for the up-regulation of costimulatory molecule expression and costimulatory cytokine production by DCs (*20*) and also promotes more efficient processing and presentation of

vaccination (n = 72), there were 63 (87.5%) patients with TEAEs, 16 (22.2%) patients with treatment-emergent serious AEs (SAEs), 20 (27.8%) patients with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade 3 or 4 TEAEs, and 4 (5.7%) patients with TEAEs that led to withdrawal (table S4). From a comparison of tables S3 and S4, it follows that most of the serious TEAEs in the current study were expected toxicities related to chemotherapy or to complications associated with progression of cervical cancer. Previous trials documented treatment-emergent injection site reactions (TEISRs, defined as vaccination site or ISRs) and treatment-emergent systemic allergic reactions (TESARs, defined as drug hypersensitivity, hypersensitivity, injection-related reaction, systemic inflammatory response syndrome, vaccination complication, or cytokine release syndrome) as TEAEs that are likely