8.9 Health Economics

Not applicable.

8.10 Immunogenicity Assessments

Whole blood samples of approximately 5 mL will be collected for the detection of antibodies against bintrafusp alfa in serum, as specified in the bintrafusp alfa Pharmacokinetic, Immunogenicity Sampling (Table 2). Samples will be collected prior to any bintrafusp alfa administration on the same study day. Collection times are specified in the SoA.

The detection of antibodies to bintrafusp alfa will be performed using a validated immunoassay assay method with tiered testing of Screening, confirmatory, and titration. Confirmed positive antibodies may be tested for the presence of neutralizing antibodies and may be further characterized.

Remaining samples collected for analysis of anti-bintrafusp alfa antibodies may also be used to evaluate bintrafusp alfa concentration or exploratory biomarkers during or after the study.

Details on processes for collection and handling of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

9 Statistical Considerations

9.1 Statistical Hypotheses

The study aims to estimate the ORR with a sufficient level of precision and that the associated 95% confidence interval is above a minimal threshold of 15%.

9.2 Sample Size Determination

The planned total sample size is 135 participants for addressing the primary objective, and further efficacy and safety assessments. If the target number of 15% of China participants is not met when global enrollment of 135 participants is finalized, enrollment will continue in China only to achieve 15% of Chinese participants as per local requirement.

Assuming a true ORR of 25%, the probability to observe a lower bound of the exact 95% CI above 15% would be 80% when analyzing 135 participants.

Based on 81 participants, the probability to observe a lower bound of the exact 95% CI above 15% would be 57%.

The 2-sided 95% Clopper-Pearson CIs for different observed values for the ORR are provided in Table 9 and Table 10.

Table 9 Confidence Intervals for Different Objective Response Rates at the Interim Analysis

Sample Size N	Number of Participants with CR or PR	ORR (%)	95% CI	
			Lower bound (%)	Upper bound (%)
81	19	23.5%	14.8%	34.2%
81	20	24.7%	15.8%	35.5%
81	21	25.9%	16.8%	36.9%
81	22	27.2%	17.9%	38.2%
81	24	29.6%	20.0%	40.8%
81	25	30.9%	21.0%	42.1%
81	29	35.8%	25.4%	47.2%

CI=confidence interval, CR=complete response, N=number of participants, PR=partial response, ORR=objective response rate.

Table 10 Confidence Intervals for Different Objective Response Rates at the Primary Analysis

Sample Size N	Number of Participants with CR or PR	ORR (%)	95% CI	
			Lower bound (%)	Upper bound (%)
135	22	16.3%	10.5%	23.6%
135	29	21.5%	14.9%	29.4%
135	30	22.2%	15.5%	30.2%
135	31	23.0%	16.2%	31.0%
135	32	23.7%	16.8%	31.8%
135	38	28.1%	20.8%	36.5%
135	45	33.3%	25.5%	42.0%

CI=confidence interval, CR=complete response, N=number of participants, PR=partial response, ORR=objective response rate.

Justification for the Assumption of a Confirmed ORR of 25%

Bintrafusp alfa, as a monotherapy, has demonstrated promising clinical efficacy signal in recurrent or persistent cervical cancer. In the Phase I study, a total of 25 patients with recurrent or persistent cervical cancer following standard of care treatment with systemic therapy for advanced disease were treated with bintrafusp alfa for a median duration of 9.6 (range 2.0 to 72.0) weeks with the following results:

- ORR of 24.0% (95% CI: 9.4, 45.1) with 6 confirmed responses per RECIST 1.1; 5/6 responses were ongoing at data cutoff (median DOR not reached; range 2.3+ to 24.9+ months).
- One additional patient developed a PR after initial confirmed disease progression ("delayed PR") bringing the total clinical response rate to 28.0% (95% CI: 12.1, 49.4), delayed PR was ongoing for 8.7 months at data cutoff, with 73.3% disease shrinkage after initial PD.

Therefore, it is reasonable to assume that the confirmed ORR of bintrafusp alfa is 25% or higher in patients with advanced unresectable cervical cancer who experienced disease progression during or after platinum-containing chemotherapy.

Justification for the Assumption of a Benchmark ORR of 15% to Define the Study Sample Size

The benchmark ORR for platinum-experienced patients is based on a literature review of published clinical studies reporting efficacy outcomes for systemic anticancer treatments (excluding studies with immune checkpoint inhibitors) in platinum-experienced patients with locally advanced or metastatic cervical cancer.

A total of 59 relevant publications were identified reporting results on 1,943 platinum-experienced patients (either as systemic therapy or in the context of chemoradiation). Due to significant heterogeneity across settings, treatments and outcomes, a random-effect analysis was conducted to define the ORR benchmark. Based on this analysis the benchmark ORR was estimated at 15% (95% CI: 12.4%, 18.2%).

Additionally, this benchmark of 15% was also selected based upon review of the results of the Phase II KEYNOTE-158 study of pembrolizumab in advanced cervical cancer (Chung 2019). Among the 98 patients with previously treated advanced cervical cancer, the ORR was 12.2% (95% CI: 6.5, 20.4). Among the 77 patients with PD-L1 positive, chemotherapy refractory cervical cancer, the ORR was 14.3% (95% CI: 7.4, 24.1). At the time of the publication, median DOR was not reached (range 4.1 to 18.6+ months) and median OS was 11 months (95% CI: 9.1, 14.1).

9.3 Populations for Analyses

The analyses populations are specified below. The final decision to exclude participants from any analysis population will be made and documented during a data review meeting prior to database lock.

The analysis will be performed on approximately 135 patients globally. China participants (whether enrolled before or after the completion of the global enrollment) may be analyzed separately per local regulatory requirements, and follow the same definition as Section 4.1.

For purposes of analysis, the analysis populations are defined in Table 11.