NCI Protocol #: Not applicable

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TITLE: A phase II trial of all-trans retinoic acid (ATRA) in advanced adenoid cystic carcinoma

STATISTICAL PLAN

STATISTICAL CONSIDERATIONS

Original Design When Trial Opened.
The trial was originally designed as a two-stage one arm phase II trial with primary endpoint of best overall response with n=14 patients who are eligible and begin protocol treatment to be entered into the first stage. Details of the original design as follows:

The primary endpoint of this study is best overall response rate (CR+PR). A Simon two-stage design will be used to minimize the number of patients exposed to this regimen and the specific sample size and operating characteristics were chosen to be able to show that the response rate is greater than 10% (that found in prior studies) and closer to 28%. Fourteen eligible patients who start protocol treatment are to be accrued in the first stage. If there are ≤ 1 of 14 patients with disease in response, accrual to this trial will be closed with the expectation that there is little evidence that the response rate will reach 28%. The probability that the trial will close early is 58% if the true response rate is 10%. If there are >1 patients with disease in response, accrual will continue until a total of 25 eligible patients who start protocol treatment are entered. If > 4 of 25 patients who are eligible and begin protocol treatment have disease in response, then this regimen will be considered worth further study. The probability of concluding that the regimen is worth further study is 85% if the true response rate is 28%. The probability of concluding that the regimen is worth further study is 9% if the true response rate is 10%. Allowing 2 patients to be entered and then declared ineligible and/or to not start protocol treatment, the overall accrual goal is 27.

Amendment 3: Details, Rational and Design:

Fourteen patients (eligible and began protocol streatment) have been entered into stage 1 for the original design when the trial opened and now referred to as 'Cohort 1'. Due to preliminary results of low efficacy in Cohort 1, accrual to Cohort 1 is suspended and n=6 additional patients ('Cohort 2') are to be entered to assess safety and tolerability of continuous daily dosing. The choice of n=6 is due to lack of concerning SAEs in Cohort 1 as well as to keep within the constraints of original budget and its corresponding drug availability for the testing of continuous dosing. For Cohort 2, AEs plan to be continuously monitored and best overall response assessed. With n=6 eligible patients who being protocol treatment, the lower limit of one-sided 90% exact binomial confidence interval will be greater than 10% (the null hypothesis in the original design) if at least 3 patients have disease in response (CR or PR). All aspects of the AE profile and outcome of these 6 patients are to be assessed with decisions made regarding amending the trial for any further design changes and continuation or closure of accrual. The table below gives the lower limit of one-sided 90% exact binomial confidence interval based on various scenarios.

Sample size Cohort 2	# of patients with disease in response	Lower limit of one-sided 90% CI
6	2	9.2%
6	3	20.1%

Analysis and Accrual Estimates

The primary efficacy population includes all eligible patients who begin protocol treatment. Best overall response will be summarized as a proportion with a corresponding exact 95% confidence interval (CI).

For secondary objectives:

- Adverse events will be classified and graded according to the CTCAE v.5.0. Frequencies of adverse events will be summarized among patients who begin protocol therapy.

- The distributions of time-to-event endpoints will be estimated using the Kaplan-Meier method with corresponding 95% confidence intervals for the median or time-specific event time.

With an estimated monthly accrual of 2 patients, accrual to the first stage (Cohort 1) is estimated to take approximately 7-8 months to accrue n = 15 (of which n = 14 who are eligible and who begin protocol treatment). Estimated monthly accrual to Cohort 2 is estimated to be similar (1-2 patients per month). Due to possible delays in initiation of approval and/or in initiation of accrual itself, accrual could take longer. As is customary with this type of design, accrual will be suspended after the first stage (Cohort 1, n = 14 eligible patients who begin protocol therapy) in order to assess outcome; however, this suspension is also dependent on the actual observed accrual rate and the number of patients with confirmation of disease response status while the first stage of the trial is accruing. Accrual to Cohort 2 would be suspended when n=6 eligible patients who begin protocol therapy are entered.