**SUMMARY OF CHANGES – Initial Protocol going to CIRB**

NCI Protocol #:

Local Protocol #:

NCI Version Date:

Protocol Date:

*I. Comments Requiring a Response (and discussed in the event of a teleconference) – Major Issues*

| **#** | **Section** | **Change** |
| --- | --- | --- |
| 1. |  | This area will contain the response to CTEP reviews plus any additional changes by the study team that have been approved by CTEP as it appeared when submitted to PIO. Examples below |
| 2. | 10.4 | For consented patients, 10 FFPE tumor tissue sections of 5µm is recommended instead of three 2 mm punches constituting 6mm tumor tissue which may leave the block unusable, depending on the size of the tissue, for future studies.**PI Response**:**We agree and have changed the protocol to reflect this recommendation.** |
| 3. | 11.1 | The background section is inadequate. It describes what will be done but provides no information regarding why neurocognitive and QOL are being measured. Please provide justification including what is known and how the QOL correlative study will inform the parent trial. **PI Response**:**A review of our current understanding of the adverse neurologic, QOL, and potentially neurocognitive, side effects of nivolumab/ipilimumab as well as the limited mechanistic work in this area was added to 11.1.1. Including neurocognitive testing and QOL measures will allow us to evaluate if enhanced disease control through this therapeutic approach is also associated with maintained or improved neurocognitive function or if is improved disease control comes at a cost to neurocognitive function due to increased neurotoxicity.** |
| 4. | 2.3 | Please use 4-OHT as the acronym for 4-hydroxytamoxifen), include data from the published DCIS study and mention why bexarotene gel may be different in terms of toxicity. **PI Response:****This has been added to the protocol\** |

1. **Recommendations (no response required):**

| **#** | **Section** | **Comments** |
| --- | --- | --- |
| 1.
 | [Cover Page](#_NRG-BN007) | Please consider contacting the NCTN Groups for a Study Champion. **PI Response**:**We are in the process of confirming study champions. We will update the protocol cover page when champions are final.**  |
|  | 3.B |  Please consider if a dose expansion cohort would be warranted for both understanding safety and increasing the potential number of subjects that have tissue available for analysis at the dose of interest. **PI Response:** **A dose expansion cohort has been added to the study to better understand safety and penetration of bexarotene into the breast tissue. We will plan for a dose expansion cohort at the maximum tolerated dose level and will plan to accrue an additional 10 patients. Participants in this cohort will be required to have breast biopsies before and after treatment.** |

**SUMMARY OF CHANGES – Response to CIRB stipulations of initial CIRB review (prior to activation)**

NCI Protocol #:

Local Protocol #:

NCI Version Date:

Protocol Date:

**SUMMARY OF CHANGES – Protocol**

1. **CIRB Stipulations Requiring a Response:**

| **#** | **Section** | **Change** |
| --- | --- | --- |
| 1. |  | The change memo that accompanied the initial review should be removed. Only keep in new changes such as response to stipulations plus any additional changes by the study team. These should also be in track changes in the document and hyperlinked. Do not track change the deletion of the old summary of changes. (Note: DCP studies do not require hyperlinks and do not allow additional changes by the study team)Example below: |
| 2. |  | Agent Diaries:1. Change “tablet” to “capsule”. Tablets are stated 5 times on each diary.
2. Add the following to the diary instructions; “Capsules should not be crushed, chewed or opened”.

**PI Response:** We have made the requested changes to the medication diaries. |

**SUMMARY OF CHANGES – Pre and post activation amendments (after there is a CIRB approved protocol)**

NCI Protocol #:

Local Protocol #:

NCI Version Date:

Protocol Date:

| **#** | **Section** | **Change** |
| --- | --- | --- |
| 1. |  | Only keep in new changes since the last approved version of the protocol. These should also be in track changes in the document and hyperlinked. Do not track change the deletion of the old summary of changes. (Note: DCP studies do not require hyperlinks) |
| 2. |  | If there are stipulations from the CIRB, place them in a separate section of the change memo but keep the changes from the PIO submitted version and keep track changes in place throughout the document. Remember to hyperlink the new changes in the protocol.(Note: DCP studies do not require hyperlinks) |

1. **Changes by Study Team (Approved by CTEP and sent to CIRB):**

| **#** | **Section** | **Comments** |
| --- | --- | --- |
|  | All | Updated Version Date in Header |
|  | [Title Page](#Title_page_Lead_Clinical_Project_Manager) | Added email address for Lead Clinical Project Manager |
|  | [Title Page](#face_page_version) | Updated Protocol Type / Version # / Version Date |
|  | [2.5](#Section_2_5) | Updated Correlative Studies Background section with new exploratory metabolomic correlative studies |

1. **CIRB Stipulations Requiring a Response:**

| **#** | **Section** | **Comments** |
| --- | --- | --- |
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