OHRS Information Sheet
Implementing Dose Escalation Changes at DF/HCC

(This information sheet replaces the February 2021 OHRS Information Sheet on "Implementing Dose Escalation Changes at DF/HCC").

All types of dose escalation, dose expansion, and study phase transitions should be submitted as either an *Amendment* or *Dose/Cohort Open/Closure Form*. An amendment should be submitted if the dose escalation, dose expansion, opening of a cohort, or phase transition has not already been approved by the SRC and IRB of record. The approval status of these transitions is determined by the SRC and IRB and is based upon the information provided in the protocol and New Protocol Application (NPA) form.

Effective February 2021, the Outcome Letters provided by the SRC and IRB include the phrase "in its entirety" to indicate that all transitions *within* and *between* phases submitted as part of the NPA are approved. Otherwise, if the convened committee did not approve the protocol in its entirety at its initial review, the SRC or IRB Outcome Letters will indicate that only Phase 1 of a Phase 1/2 study or only portions of a Phase 1 study were approved.

Prior to February 2021, the Outcome Letter (or IRB Minutes for approvals prior to the use of iRIS) may not specify "in its entirety" and may be silent regarding phases or portions of the Phase 1. Those approvals reflect the SRC and IRB's understanding that the approval includes the entire Phase 1 portion, unless otherwise noted. Those approvals should not be interpreted to include approval of Phase 2. An amendment form should be submitted for approval of the Phase 2 portion unless the Outcome Letter/IRB Minutes from the initial review specifically indicate approval of Phase 2. If you have any concerns or questions regarding approval of Phase 1 and Phase 2 transitions or interpretation of this policy, please contact OHRS.

DFCI IRB Studies:

Dose/Cohort Open/Closure Form:
The Dose/Cohort Form should be used:

- To open a newly declared dose for an existing dose/cohort within the approved protocol.
- To close an existing dose/cohort.
- To open a new dose, treatment schedule, or cohort that is part of the DF/HCC SRC and DFCI IRB approved adaptive or Bayesian protocol design (this includes the expansion phase of a Phase 1 as submitted and approved by the IRB).

Note that the Dose/Cohort Open/Closure Form **should not** be used if there are any associated changes to the protocol, consent, or any other documents requiring SRC or IRB review.

Therapy Amendment:
Therapy Amendments should be used instead of the Dose/Cohort Form:

- To transition from dose escalation to dose expansion when the DFCI IRB and/or DF/HCC SRC approval memos explicitly state that the protocol does not include the dose expansion within a Phase 1 trial.
- To transition from one study phase to the next (e.g., transitioning from Phase 1 to Phase 2) unless the Outcome letter specifies "in its entirety" and the NPA and protocol included Phase 2.
- When the protocol and/or consent forms are being revised.

Please note:

- A therapy amendment is required If the change in the doses are inconsistent with the dosing plan approved by the IRB.

Studies Relying on an External IRB (non-DFCI IRB):

When a study relies on an external IRB, the IRB approval letters will usually not contain any specific language identifying which arms of the study are approved. Therefore, for studies relying on an external IRB it is only necessary to include the DF/HCC SRC approval letter with the Dose/Cohort Form where applicable.

Please note:

- Studies relying on an external IRB that do not require SRC review are exempt from this requirement.
- The Dose/Cohort Open/Closure Form can NOT be used if there are any associated changes to any protocol or consent documents. If the DF/HCC SRC approval letter is not available, or does not contain the appropriate language, a Therapy Amendment must be submitted.
- When the protocol and/or consent forms are being revised an amendment form must be used.

Studies Relying on the NCI CIRB:

Dose/Cohort Open/Closure Form:
The Dose/Cohort Form should be used:

- To open a newly declared dose for an existing dose/cohort within the approved protocol.
- To close an existing dose/cohort.
- To open a new dose, treatment schedule, or cohort that is part of the approved adaptive or Bayesian protocol design.
- To transition from dose escalation to expansion.
- To transition from one study phase to the next (e.g., a Phase 1/2 study transitioning from Phase 1 to Phase 2).

Note that the Dose/Cohort Open/Closure Form can **NOT** be used if there are any associated changes to any protocol or consent documents. Also note that for studies relying on the NCI CIRB, **there is no requirement to provide IRB or DF/HCC SRC approval memos**. However, sponsor correspondence confirming the dose/cohort change is still required.

Therapy Amendments should be used instead of the Dose/Cohort Form:

- When the protocol and/or consent forms are being revised.

Please contact OHRS at OHRS@dfci.harvard.edu if you have any additional questions.