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Monica M. Bertagnolli, MD
Alliance Group Chair

MEMORANDUM

Date: 15 January 2019

To: Alliance Principal Investigators and Lead CRAs

From: Monica M. Bertagnolli, MD, Alliance Group Chair

Re: Alliance Data and Safety Monitoring Board (DSMB) Report

The Alliance Data and Safety Monitoring Board (DSMB) met on November 2, 2018. Attached please find a listing of each study reviewed, the DSMB recommendation, and the action taken in response to the recommendation.

These statements may be submitted to your IRB per local IRB guidelines.

Questions may be directed to Michael Kelly, MA, Director of Protocol Operations (mkelly1@uchicago.edu)

Breast Committee

A011104 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A011104, Effect of preoperative breast MRI on surgical outcomes, costs and quality of life of women with breast cancer, during a meeting on November 2, 2018. The DSMB reviewed the curent adverse event and efficacy data, and no issues requiring intervention were identified. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

A011106 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A011106, Alternate approaches for clinical stage II or III estrogen receptor, positive breast cancer neoadjuvant treatment (ALTERNATE) in postmenopausal women: A phase III study, during a meeting on November 2, 2018. The DSMB reviewed the adverse event and efficacy data, and no issues requiring intervention were identified. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

A011202 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A011202, A randomized phase III Trial evaluating the role of axillary lymph node dissection in breast cancer patients (cT1-3 N1) who have positive sentinel lymph node disease after neoadjuvant chemotherapy, during a meeting on November 2, 2018. The DSMB reviewed the adverse event and efficacy data, and no issues requiring intervention were identified. The DSMB wanted clarification on the slow event rate observed in the trial and requested the study team to provide details on the trial assumptions, and estimates of the observed hazard rate at the next meeting. The DSMB requested that the statistician be present for this discussion at the May 2019 meeting. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

A011203 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A011203, A randomized phase ii trial of tamoxifen versus Z-endoxifen HCL in postmenopausal women with metastatic estrogen receptor positive, HER2 negative breast cancer, during a meeting on November 2, 2018. The DSMB reviewed the adverse event and efficacy data, and no issues requiring intervention were identified. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

A011401 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A011401, Randomized phase III trial evaluating the role of weight loss in adjuvant treatment of overweight and obese women with early breast cancer, during a meeting on November 2, 2018. The DSMB reviewed the adverse event and efficacy data, and no issues requiring intervention were identified. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

A011502 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A011502, A randomized phase III double blinded placebo controlled trial of aspirin as adjuvant therapy for node positive HER2 negative breast cancer: The ABC trial, during a meeting on November 2, 2018. The DSMB noted the study team efforts to improve accrual. The DSMB reviewed the current adverse event and efficacy data, and no issues requiring intervention were identified. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

Z11102 The Alliance Data and Safety Monitoring Board (DSMB) reviewed Z11102, Impact of breast conservation surgery on surgical outcomes and cosmesis in patients with multiple ipsilateral breast cancers, during a meeting on November 2, 2018. The DSMB reviewed current adverse events and efficacy data, and no issues reqiring intervention were identified. The DSMB reviewed the data release request by the study team and voted to

approve the release of the radiation data to the study team for the development of abstracts and manuscripts. The DSMB recommended unanimously to continue per protocol.

Action: Recommendation Accepted

Cancer Care Delivery Research Committee

A191402CD The Alliance Data and Safety Monitoring Board (DSMB) reviewed A191402, Testing decision aids to improve prostate cancer decisions for minority men, during a meeting on November 2, 2018. The DSMB reviewed the current study data, and no issues requiring intervention were identified. The DSMB requested more information on the number of sites who were invited to participate in the study, the number currently enrolling, and how many enrolled within each site. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

Experimental Therapeutics Committee

A091304 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A091304, A phase I/randomized phase II study of MLN0128 (TAK-228) vs. pazopanib in patients with locally advanced/unresectable and/or metastatic sarcoma, during a meeting on November 2, 2018. The DSMB noted the crossing of the stopping rule in the cross-over cohort and that the study team is currently reviewing the events closely, and requested the study team to keep the DSMB informed of the study team/CTEP decision. The DSMB reviewed the current adverse event data, and no issues requring intervention were identified. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

A091401 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A091401, Randomized phase II study of nivolumab with or without ipilimumab in patients with metastatic or unresectable sarcoma, during a meeting on November 2, 2018. The DSMB concurred with the study team recommendation to terminate DSMB monitoring of the initial cohort. The DSMB noted that the study team followed the recommendation from the September 2018 meeting, with the GIST cohorts temporarily closed to accrual and the statistical team closely monitoring the status of the patients enrolled on the trial. The DSMB noted that the toxicity stopping rule was crossed, and that it will be modified if the trial were to re-open to accrual following the planned interim analysis. The DSMB reviewed the current study data and identified no issues requiring intervention. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

A091605 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A091605, A randomized phase II study of anti-PD1 antibody [MK-3475 (pembrolizumab)] alone versus anti-PD1 antibody plus stereotactic body radiation therapy in advanced Merkel cell carcinoma, during a meeting on November 2, 2018. The DSMB reviewed the current adverse events, and efficacy data and no issues requiring intervention were identified. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

GI Committee

A021202 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A021202, Prospective randomized phase II Trial of Pazopanib versus Placebo in Patients with Progressive Carcinoid Tumors, during a meeting on November 2, 2018. The DSMB noted that the study has been closed to accrual for two years, and still awaiting the clean up of the primary endpoint. They acknowledged that the SDC, in conjunction with Data Management and the ICL, is performing an extensive data clean-up, submission of outstanding images, and the completion of the reviews by the ICL. The DSMB urged the study team to signficantly step up the data clean up efforts with a goal of presenting the primary results to the DSMB at the May 2019 meeting. The DSMB reviewed the current

adverse events and efficacy data, and no issues requiring intervention were identified. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

A021501 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A021501, Preoperative extended chemotherapy vs. chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas, during a meeting on November 2, 2018. The DSMB reviewed the current adverse events and efficacy data, and no issues requiring intervention were identified. The DSMB noted that the study is now a single arm trial, and thus voted unanimously to terminate further DSMB monitoring, and continue to follow the patients on study per protocol.

Action: Recommendation Accepted

A021502 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A021502, Randomized trial of standard chemotherapy alone or combined with atezolizumab as adjuvant therapy for patients with stage III colon cancer and deficient DNA mismatch repair, during a meeting on November 2, 2018. The DSMB reviewed the current adverse events, and no issues requiring intervention were identified. The DSMB noted that the study team is keeping a close watch on the adverse event profile and recommended that the monthly report summarzing the adverse event profile to Drs. Kirshner and Mandrekar be discontinued. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

C80702 The Alliance Data and Safety Monitoring Board (DSMB) reviewed C80702, A phase III trial of 6 versus 12 treatments of adjuvant FOLFOX plus celecoxib or placebo for patients with resected stage III colon cancer, during a meeting on November 2, 2018. The DSMB reviewed the adverse events and efficacy data, and no issues requiring intervention were identified. The DSMB noted that the data delinquency rates are continuing to improve and requested the study team to continue to keep abreast of the data clean up efforts. The DSMB noted that the reasons for the withdraw of consent for follow-up was not collected in the trial. The DSMB disapproved the request for data release on adverse events noting that there are still patients on active treatment, and adverse event data are continuing to be cleaned. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

N1048 The Alliance Data and Safety Monitoring Board (DSMB) reviewed N1048, A phase II/III trial of neoadjuvant FOLFOX with selective use of combined modality chemoradiation versus preoperative combined modality chemoradiation for locally advanced rectal cancer patients undergoing low anterior resection with total mesorectal excision, during a meeting on November 2, 2018. The DSMB reviewed the current adverse events and efficacy data, and no issues requiring intervention were identified. The DSMB requested information on follow-up for patients who refused to continue on the trial prior to starting treatment in the next report. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

GU Committee

A031102 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A031102, A randomized phase III trial comparing conventional-dose chemotherapy using paclitaxel, ifosfamide, and cisplatin (TIP) with high-dose chemotherapy using mobilizing paclitaxel plus ifosfamide followed by high-dose carboplatin and etoposide (TI-CE) as first salvage treatment in relapsed or refractory germ cell tumors (TIGER), during a meeting on November 2, 2018. The DSMB noted the steady improvement in accrual and the addition of international sites, and noted the study team's efforts to increase accrual. The DSMB reviewed the current adverse events and efficacy data, and no issues requring intervention were identified. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

A031201 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A031201, Phase III trial of enzalutamide (NSC#766085) versus enzalutamide, abiraterone and prednisone for castration resistant metastatic prostate cancer, during a meeting on November 2, 2018. The DSMB reviewed the final analysis on overall survival, and concurred with the study team that there was no statistically significant difference in overall survival time between the two treatment arms. The DSMB reviewed the current adverse events data and no issues requiring intervention were identified. The DSMB voted unanimously to release these data to the study team. With evaluation of the primary endpoint completed, the DSMB recommended termination of future DSMB monitoring and continuing follow-up of patients per protocol.

Action: Recommendation Accepted

A031501 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A031501, Phase III randomized adjuvant study of MK-3475 (Pembrolizumab) in muscle invasive and locally advanced urothelial carcinoma (AMBASSADOR) vs. observation, during a meeting on November 2, 2018. The DSMB reviewed the current adverse events data, and no issues requring intervention were identified. The DSMB noted that the accrual to the trial has been slower than expected and urged the study team to enhance their accrual efforts. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

C90203 The Alliance Data and Safety Monitoring Board (DSMB) reviewed C90203, A randomized phase III study of neo-adjuvant docetaxel and androgen deprivation prior to radical prostatectomy versus immediate radical prostatectomy in patients with high-risk, clinically localized prostate cancer, during a meeting on November 2, 2018. The DSMB reviewed the final analysis on 3-year biochemical PFS rates. Applying the censoring rules per the FDA guidance document, the trial did not meet the efficacy boundary for superiority. Therefore, the DSMB concurred with the study team that LHRH + Docetaxel + surgery arm is not superior to the surgery alone arm in this trial. The DSMB noted that all patients have been followed for 3 years, and the PSA reporting delinquency is low with only 1.0% of patients being considered delinquent. The DSMB reviewed the current adverse events data and no issues requiring intervention were identified. The DSMB voted unanimously to release these data to the study team. With evaluation of the primary endpoint completed, the DSMB recommended termination of future DSMB monitoring and continuing follow-up of patients per protocol.

Action: Recommendation Accepted

C90601 The Alliance Data and Safety Monitoring Board (DSMB) reviewed C90601, A randomized double-blind phase III study comparing gemcitabine, cisplatin, and bevacizumab to gemcitabine, cisplatin, and placebo in patients with advanced transitional cell carcinoma, during a meeting on November 2, 2018. The DSMB noted that number of events over the last two years has essentially plateaued, and that the data are sufficiently mature for analysis (the primary endpoint being up to date on 97% of the patients). Based on the primary and sensitivity analyses presented, the DSMB concurred with the study team that trial did not meet the efficacy boundary for superiority, and there was no statistically significant difference in overall survival time between the two treatment arms. The DSMB reviewed the current adverse events data and no issues requiring intervention were identified. The DSMB voted unanimously to release these data to the study team. With evaluation of the primary endpoint completed, the DSMB recommended termination of future DSMB monitoring and continuing follow-up of patients per protocol.

Action: Recommendation Accepted

Leukemia Committee

A041501 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A041501, A phase III trial to evaluate the efficacy of the addition of inotuzumab ozogamicin (a conjugated anti-CD22 monoclonal antibody) to frontline therapy in young adults (ages 16-39 years) with newly diagnosed precursor B-Cell ALL, during a meeting on November 2, 2018. The DSMB noted that the trial recently reopened after completing the safety assessment. The DSMB reviewed the current adverse events, and no issues requiring intervention were identified. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

Lymphoma Committee

A051301 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A051301, A randomized double-blind phase III study of ibrutinib during and following autologous stem cell transplantation versus placebo in patients with relapsed or refractory diffuse large B-cell lymphoma of the activated B-Cell subtype, during a meeting on November 2, 2018. The DSMB noted the submitted protocol amendment. The DSMB reviewed the current adverse events, and efficacy data and no issues requiring intervention were identified. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

Myeloma Committee

A061202 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A061202, A phase I/II study of pomalidomide, dexamethasone, and ixazomib vs. pomalidomide and dexamethasone for patients with multiple myeloma refractory to lenalidomide and proteasome inhibitor-based therapy, during a meeting on November 2, 2018. The DSMB reviewed the adverse event data and no issues requiring intervention were identified. The DSMB noted the revised study design. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

A061402 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A061402, Solitary plasmacytoma of bone: randomized phase III trial to evaluate treatment with adjuvant systemic treatment and zoledronic acid versus zoledronic acid after definite radiation therapy, during a meeting on November 2, 2018. The DSMB reviewed the current adverse events, and efficacy data and no issues requiring intervention were identified. The DSMB nored that in February 2018, ALLIANCE leadership appealed to CTEP not to terminate enrollment to this trial due to low incidence of solitary plasmacytoma of bone, and that CTEP agreed to keep the study open for an additional 12 months with the stipulation that if 25 patients have not been enrolled by that time, the study would be permanently closed. The DSMB noted that a total of 9 patients have been enrolled to the trial, with only 4 patients accrued to the trial since February, 2018. The DSMB believes that the study is not viable, and voted unanimously to permanently close the study to accrual, effective immediately, termination of future DSMB monitoring and continuing follow-up of patients per protocol.

Action: Recommendation Accepted

Neuro Oncology Committee

A071102 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A071102, A phase II/III randomized trial of veliparib or placebo in combination with adjuvant temozolomide in newly diagnosed glioblastoma with MGMT promoter hypermethylation, during a meeting on November 2, 2018. The DSMB discussed the data release request to analyze and publish the phase II results of the trial. The DSMB reminded the study team that this is a phase 2/3 design, and that all phase II patients are part of the phase III trial, and that the phase II endpoint of PFS is a secondary efficacy endpoint of the phase III trial. The DSMB unanimously voted to disapprove this request for data release to the study team. The DSMB reviewed the current adverse events, and efficacy data and no issues requiring intervention were identified. The DSMB voted unanimously to continue the study per protocol.

Action: Recommendation Accepted

N0577 The Alliance Data and Safety Monitoring Board (DSMB) reviewed N0577, Phase III intergroup study of radiotherapy versus temozolomide alone versus radiotherapy with concomitant and adjuvant temozolomide for patients with 1p/19q codeleted anaplastic glioma, during a meeting on November 2, 2018. The DSMB was encouraged by the steady increase in accrual rate and the anticipated participation of EORTC to the trial in the

summer. The DSMB reviewed the current adverse events, and no issues requiring intervention were identified. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

Prevention Committee

A211102 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A211102, Testing for atypia in random periareolar fine needle aspiration (RPFNA) cytology after 12 months metformin (1,1-dimethylbiguanide hydrochloride) chemoprevention versus placebo control in premenopausal women, during a meeting on November 2, 2018. The DSMB reviewed the current adverse events and efficacy data, and no issues requiring intervention were identified. The DSMB voted unanimously to continue study per protocol.

Action: Recommendation Accepted

A211401 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A211401, Reducing surgical complications in newly diagnosed lung cancer patients who smoke cigarettes, during a meeting on November 2, 2018. The DSMB reviewed the adverse event and efficacy data, and no issues requiring intervention were identified. The DSMB noted that there are currently 207 sites open to accrual for this trial, with only 2 sites that have enrolled patients to the trial to date. The DSMB noted the efforts made by the study team to improve accrual.

The DSMB sent a request to the study chair to provide a detailed accrual enhancement plan for their review by November 8, 2018, as there were some outreach and education efforts planned at the November 2018 Alliance meetings. The DSMB reviewed the accrual enhancement plan provided on November 8, 2018, and noted the many efforts made by the study team to increase accrual.

The DSMB requested an updated report at the May 2019 meeting and voted unanimously to continue per protocol with the following immediate recommendations: provide a report by December 15, 2018 to the DSMB on the progress on the various accrual initiatives, summary of leadership calls, roster issues and documentation of identified surgeon champions; provide an updated accrual report and site PI responses that indicate accrual commitment by January 15, 2019; and aim for a target accrual of 1-2 patients per month, with an accrual target of 10-15 patients by the May 2019 meeting.

Action: Recommendation Accepted

Respiratory Committee

A081105 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A081105, Randomized double blind placebo controlled study of erlotinib or placebo in patients with completely resected epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC), during a meeting on November 2, 2018. The DSMB remained concerned with the low accrual rate, and urged the study team to significantly enhance their accrual efforts. The DSMB requested the study team to present an updated accrual report at the next meeting. The DSMB reviewed the current adverse event data and no issues requiring intervention were identified. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

C30610 The Alliance Data and Safety Monitoring Board (DSMB) reviewed C30610, Phase III comparison of thoracic radiotherapy regimens in patients with limited small cell lung cancer also receiving cisplatin and etoposide, during a meeting on November 2, 2018. The DSMB approved the request for data release, specifically the adverse event data from arms B and C that was used to make the decision to drop arm C. The DSMB reviewed the current adverse events and efficacy data, and no issues requiring intervention were identified. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

C140503 The Alliance Data and Safety Monitoring Board (DSMB) reviewed C140503, A phase III randomized trial of lobectomy versus sublobar resection for small (<2 cm) peripheral non-small cell lung cancer, during a meeting on November 2, 2018. The DSMB reviewed the current adverse events and efficacy data, and no issues requiring intervention were identified. While the DSMB noted the improvement in data delinquecy, it strongly urged the study team to step up the data clean up efforts signficantly with a goal to be current by the May 2019 meeting. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

Symptom Intervention Committee

A221101 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A221101, A phase III randomized, double-blind placebo controlled study of armodafinil (Nuvigil) to reduce cancer-related fatigue in patients with glioblastoma multiforme, during a meeting on November 2, 2018. The DSMB noted the various efforts made by the study team to reduce the rate of non-evaluable patients. The DSMB encourages the study team to continue its educational activities, and provide an updated report on non-evaluable patients at the May 2019 meeting. The DSMB reviewed the current adverse events and efficacy data, and no issues requiring intervention were identified. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted

A221208 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A221208, Randomized phase II study: corticosteroids + bevacizumab vs. corticosteroids + placebo (BeSt) for radionecrosis after radiosurgery for brain metastases, during a meeting on November 2, 2018. The DSMB reviewed the current adverse events and efficacy data, and no issues requiring intervention were identified. The DSMB noted that the sponsor (Genetech) has decided to discontinue drug supply by December 31, 2018, and thus the enrollment to the study will be closed on December 31, 2018. The DSMB felt it was not ethical to continue to enroll patients into the trial given the trial will be permanently closed and voted unanimously (Dr. Goulet was excused during the voting) to permanently close the study to accrual, effective immediately, termination of future DSMB monitoring and continuing follow-up of patients per protocol.

Action: Recommendation Accepted

A221502 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A221502, Pulmonary rehabilitation before lung cancer resection, during a meeting on November 2, 2018. The study opened on 03/15/2017 and has accrued 6 of 194 patients. The study is now open to accrual at all sites, and the study team is actively monitoring accrual at each site. The DSMB noted that the NCI disapproved the proposed changes to the protocol to reduce sample size and broaden eligibility criteria (which seemed to modify the original scientific question of the study), and that the study team is working on resubmitting a proposal to the NCI to help improve accrual. The DSMB reviewed the current study data and no issues requiring intervention were identified. The DSMB believes that the study is not viable, and voted unanimously to permanently close the study to accrual, effective immediately, termination of future DSMB monitoring and continuing follow-up of patients per protocol.

Action: Recommendation Accepted

A221504 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A221504, A randomized, double-blind, placebo-controlled pilot study of an oral, selective peripheral opioid receptor antagonist in advanced non-small cell lung cancer (Adenocarcinoma), during a meeting on November 2, 2018. The DSMB reviewed the current study data, and no issues requiring intervention were identified. The DSMB noted the study team's efforts to enhance accrual, and requests an updated accrual report and the accrual enhancement efforts at the next meeting. The DSMB requested the Alliance leadership to cross reference this protocol within NCORP and Alliance respiratory committee open studies list. The DSMB voted unanimously to continue per protocol..

Action: Recommendation Accepted

A221505 The Alliance Data and Safety Monitoring Board (DSMB) reviewed A221505, Phase III randomized trial of hypofractionated post mastectomy radiation with breast reconstruction, during a meeting on November 2, 2018.

The DSMB reviewed the current study data, and no issues requiring intervention were identified. The DSMB noted the study team's efforts to enhance accrual, and requests an updated accrual report and the accrual enhancement efforts at the next meeting. The DSMB voted unanimously to continue per protocol.

Action: Recommendation Accepted