TPS870

2018 Gastrointestinal Cancers Symposium
(ASCO-GI)
January 18–20, 2018
San Francisco, CA

Phase 1b/2 Study of Binimetinib in Combination With Nivolumab (NIVO) or NIVO Plus Ipilimumab in Patients With Previously Treated Microsatellite-Stable Metastatic Colorectal Cancer With *RAS* Mutation

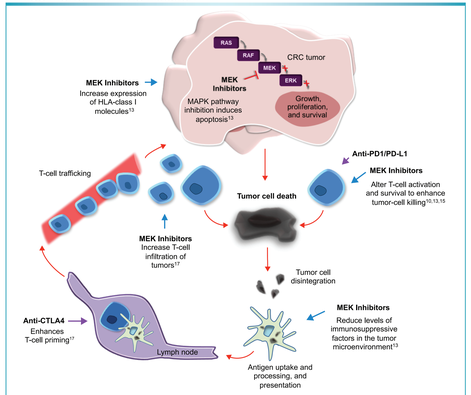
Johanna Bendell,[1] Scott Koptez,[2] Mark R. Middleton,[3] P. Taylor Eves,[4] Adam Boyd,[4] Susan Perrine,[4] Jan H. M. Schellens[5]

[1]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [2]Scott Kopetz, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]University of Oxford, Oxford, UK; [4]Array BioPharma Inc., Boulder, CO, USA; taylor.eves@arraybiopharma.com; susan.perrine@arraybiopharma.com; [5]Netherlands Cancer Institute, Amsterdam, Netherlands

INTRODUCTION

- Approximately 85% of all patients with colorectal cancer (CRC) and 96% with advanced CRC have microsatellite-stable (MSS) disease.[1,2] Single-agent programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors have not shown significant efficacy in MSS.[3,4]
- *RAS* oncogene mutations are present in 36%–43% of patients with MSS CRC.[5,6]
  - *RAS* mutation reduces immune cell infiltration and inflammatory mediators in the tumor microenvironment.[7-9]
  - *RAS* mutation may also contribute to immune escape mechanisms by downregulating MHC class I molecules required for antigen processing in tumor cells; pharmacologic inhibition of MAPK signaling can improve peptide/MHC target recognition and killing by T cells.[10-12]
- Preclinical and clinical data recently indicate that combining MEK inhibition with immunotherapy produces greater activity than either modality alone, with remarkable tumor regression observed even where either agent alone was only modestly effective.
  - MEK inhibition increases tumor responsiveness to immunotherapy through multiple mechanisms.[13]
    - Increases intratumoral CD8+ T cells
    - Upregulation of HLA molecules and induction of apoptosis markers
    - Reduction of immunosuppressive factors from tumors
  - In a colorectal allograft tumor model, the MEK inhibitor binimetinib (BINI) in combination with a PD-1 inhibitor demonstrated greater tumor growth inhibition compared with either agent alone (Array BioPharma, Data on file).
  - Clinical data recently demonstrated increased and durable responses with a combination of a MEK inhibitor and an anti–PD-L1 antibody in *RAS*-mutant MSS CRC patients compared with immunotherapy alone.[14]
  - PD-1 inhibition with nivolumab (NIVO) has higher activity when combined with cytotoxic T-lymphocyte-4 (CTLA-4) blockade than NVO alone.[15-16]
- These findings together provide a strong rationale for the phase 1b/2 study described here, which investigates combination of BINI plus NIVO with or without ipilimumab (IPI) in previously treated MSS metastatic CRC (mCRC) with *RAS* mutation (**Figure 1**; ClinicalTrials.gov Identifier: NCT03271047).

Figure 1. Contribution of MEK Inhibition to T-Cell Activation and Tumor Cell Death in MSS mCRC With *RAS* Mutation



CTLA-4=cytotoxic T-cell lymphoma-4 antigen; mCRC=metastatic colorectal cancer; PD-1=programmed death 1; PD-L1=programmed death ligand 1.

STUDY OVERVIEW

Objectives

- Phase 1b: Determine the maximum tolerated dose and recommended phase 2 dose of BINI + NIVO ± IPI
- Phase 2: Assess the antitumor activity, safety, and pharmacokinetics (PK) of BINI + NIVO ± IPI

ARRAY-162-202 Overview

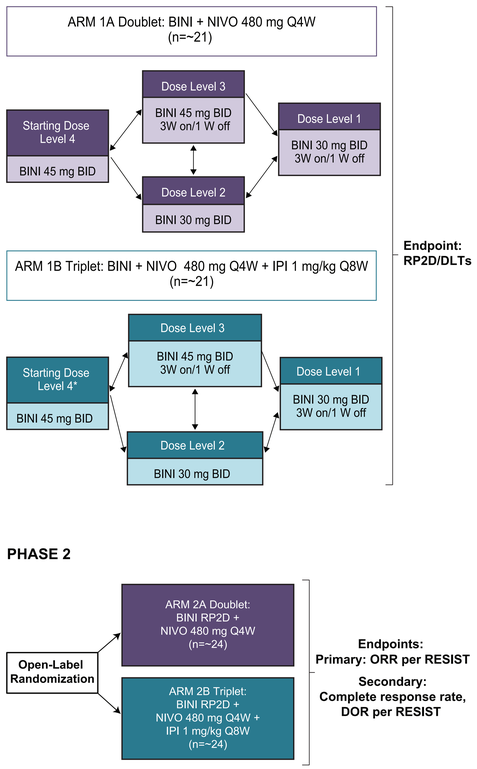
- Multicenter, open-label, phase 1b/2 study conducted in Belgium, the Netherlands, Spain, the United Kingdom, and the United States (**Figure 2, Figure 3**).
- Study start date: October 4, 2017; the study is currently recruiting participants to the phase 1b portion of the study.
- Key eligibility criteria are described in **Table 1**.
- Approximately 90 patients will be enrolled in the study.
- In the phase 1b dose-finding cohort, dose escalation and de-escalation decisions will be guided by the modified toxicity probability interval design (mTPI-2).[18]
- 1 treatment cycle is equivalent to 28 days.

Table 1. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• ≥18 years of age	• Prior MEK inhibitor, anti–PD-1, anti–PD-L1, anti–PD-L2, anti-CD137, anti–CTLA-4, or antibody or drug targeting T-cell costimulation or checkpoint pathways
• Measurable, histologically or cytologically confirmed mCRC	• Untreated CNS lesion, active autoimmune disease, known history of RVO or Gilbert syndrome
• mCRC categorized as MSS by PCR per local assay before screening or by the central laboratory*	• History of severe hypersensitivity reactions to mAbs or intolerance to study drug components
• *RAS* mutation per local or central laboratory*	• Treatment with systemic immunosuppressive medications
• Have received at least 1 prior line of systemic therapy and no more than 2 prior lines in the metastatic setting	• History of thromboembolic or cerebrovascular events, HIV, or AIDS
• ECOG PS of 0 or 1	• Residual CTCAE grade ≥2 toxicity from any prior anticancer therapy†
• Postmenopausal (≥1 year) or surgically sterile (≥6 weeks) female patients	
• Adequate renal and bone marrow, hepatic, and cardiac function	

*Patients must be able to submit sufficient tumor samples for central laboratory testing to be eligible for participation in the prescreening period. If a fresh tissue sample is provided, a blood sample is required.
†With the exception of grade 2 alopecia or grade 2 neuropathy.
CNS=central nervous system; CTCAE=Common Terminology Criteria for Adverse Events; CTLA-4=cytotoxic T-cell lymphoma-4 antigen; ECOG PS=Eastern Cooperative Oncology Group performance status; mAb=monoclonal antibody; mCRC=metastatic colorectal cancer; MEK=mitogen-activated protein kinase kinase; MSS=microsatellite stable; PCR=polymerase chain reaction; PD-1=programmed death 1; PD-L1=programmed death ligand 1; PD-L2=programmed death ligand 2; RVO=retinal vein occlusion.

Figure 2. Study Schema



BID=twice daily; BINI=binimetinib; DLT=dose-limiting toxicity; DOR=duration of response; IPI=ipilimumab; NIVO=nivolumab; ORR=objective response rate; Q4W=every 4 weeks; Q8W=every 8 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=recommended phase 2 dose; W=week.
*The starting dose level of arm 1B will be the RP2D of BINI from arm 1A. If tolerated, the RP2D of BINI from arm 1A will be considered the RP2D for arm 1B. If not tolerated, any dose level below the RP2D for arm 1B may be explored.

Study Endpoints

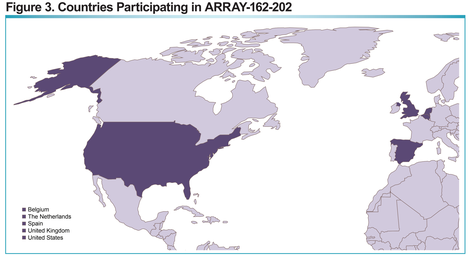
- Primary endpoints
  - Phase 1b: Incidence of dose-limiting toxicities: BINI + NIVO ± IPI
  - Phase 2: Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v.1.1)
- Secondary endpoints
  - Phase 1b: ORR per RECIST v.1.1
  - Both phases
    - Duration of response (DOR) per RECIST v.1.1
    - Rate of complete response (CR) per RECIST v.1.1
    - Incidence and severity of adverse events (AEs) per Common Terminology Criteria for Adverse Events, version 4.03
    - Plasma concentrations for BINI
- Exploratory endpoints
  - Preliminary efficacy estimates
    - Progression-free survival (PFS) per RECIST v.1.1
    - Overall survival (OS)
  - Immune response and efficacy
    - PFS per immune RECIST (iRECIST)
    - ORR per iRECIST
    - DOR per iRECIST
    - Rate of CR per iRECIST
  - Model-based correlations between BINI PK and measures of safety and efficacy
  - Status of genomic, proteomic, and immune biomarkers in blood and tissue samples at baseline
  - Change from baseline in genomic, proteomic, and immune biomarkers

Statistical Analysis

- Baseline patient characteristics will be summarized by treatment group.
- Safety analysis
  - AEs, electrocardiogram, and laboratory data will be reviewed and summarized.
  - AEs will be coded by body system using the Medical Dictionary for Regulatory Activities.
- PK analysis will use a model-based approach to determine appropriate model-based PK parameters.
- Efficacy analysis
  - ORR as assessed by RECIST v.1.1 and exact 95% CIs (Clopper-Pearson) will be provided.
  - iRECIST will also be used for estimating response-related parameters.

STUDY OVERVIEW (continued)

Figure 3. Countries Participating in ARRAY-162-202



REFERENCES

1. Koopman M, et al. *Br J Cancer.* 2009;100(2): 266-273.
2. Seppala TT, et al. *Br J Cancer.* 2015;112(12): 1966-1975.
3. Angelova M, et al. *Genome Biol.* 2015;16:64.
4. Le DT, et al. *N Engl J Med.* 2015;372(26): 2509-2520.
5. Amado R, et al. *J Clin Oncol.* 2008;26(10): 1626-1634.
6. Van Cutsem E, et al. *N Engl J Med.* 2009; 360(14):1408-1417.
7. Loi S, et al. *Clin Cancer Res.* 2016;22(6): 1499-1509.
8. Zelenay S, et al. *Cell.* 2015;162(6):1257-1270.
9. Hugo W, et al. *Cell.* 2015;162:1271-1285.
10. Brea EJ, et al. *Cancer Immunol Res.* 2016; 4(11):936-947.
11. Atkins D, et al. *Int J Cancer.* 2004;109(2):265-73.
12. Seliger B, et al. *Eur J Immunol.* 1998;28(1): 122-133.
13. Liu L, et al. *Clin Cancer Res.* 2015;21(7): 1639-1651.
14. Bendell JC, et al. *Journal of Clinical Oncology.* 2016;34.
15. Ebert PJR, et al. *Immunity.* 2016;44(3):609-621.
16. Overman MJ, et al. *J Clin Oncol.* 2016;34.
17. Hughes PE, et al. *Trends Immunol.* 2016; 37(7):462-476.
18. Guo W, et al. *Contemp Clin Trials.* 2017;58:23-33.

DISCLOSURES

JB: Research funding from Gilead, Genentech, BMS, Five Prime, Lilly, Merck, MedImmune, Celgene, EMD, Serono, Taiho, MacroGenics, GSK, Novartis, OncoMed, LEAP, TG Therapeutics, AstraZeneca, BI, Daiichi Sankyo, Bayer, Incyte, Apexigen, Roche, Kolltan, SynDevRx, Forty Seven, AbbVie, StemCentrx, Array, Onyx, Sanofi, Takeda, Abbott, Eisai, Celldex, Agios, ARMO, CytomX, Nektar, Boston Biomedical, Ipsen, Merrimack, and Tarveda (all to her institution).

SK: Consulting advisory role for Amgen, Roche, Bayer, Array BioPharma, Genentech, Symphogen, Guardant Health, EMD Serono, and Merck; stock or other ownership interests in MolecularMatch and Navire; research funding from Amgen, Sanofi, Biocartis, Guardant Health, Array BioPharma, Genentech/Roche, EMD Serono, MedImmune, and Novartis (all to his institution).

MM: Consulting advisory role for Array, Bioline, CytomX, Takeda, Rigontec, GSK, BMS, Amgen, NewLink Genetics, Merck, and Roche (all compensated), Agalimmune, Medicenna, Clovis, and Immunocore (uncompensated); research funding from Array, GSK, Takeda, Rigontec, Regeneron, AZ, Eisai, Clovis, BMS, Amgen, Roche, Merck, Vertex, Immunocore, Pfizer, and MedImmune (all to his institution); honoraria from BMS; travel/accommodations/ expenses provided by Merck and BMS.

PTE, AB, SP: Employment at Array BioPharma; stock or other ownership at Array BioPharma.

JHMS: No conflicts of interest to report.

Available at: http://www.arraybiopharma.com/download_file/283/

Scan this QR code with your reader to receive a PDF file of the poster. To download a scan reader, go to www.i-nigma.mobi on your mobile device.

Acknowledgments

This study is sponsored by and conducted in collaboration between Array BioPharma Inc. and Bristol-Myers Squibb. Medical writing and editorial support was funded by Array BioPharma and provided by Shelly Lim .