A Practical Review of Encorafenib and Binimetinib Therapy Management in Patients With BRAF V600E-Mutant Metastatic Non-Small Cell Lung Cancer

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Supplementary Tables

Table S1. Key inclusion and exclusion criteria for PHAROS study [1,2]

Key inclusion criteria
Aged ≥18 years
Histologically confirmed NSCLC stage IV or metastatic disease
Presence of measurable disease per RECIST v1.1
ECOG performance status of 0 or 1
Presence of *BRAF* V600 mutation[a]
Adequate tumor tissue for confirmation of mutation status via central laboratory
Treatment-naïve or Previously treated with one of the following: • First-line platinum-based chemotherapy • First-line anti-PD-1/PD-L1 inhibitor alone or in combination with platinum-based chemotherapy, or in combination with immunotherapy with or without platinum-based chemotherapy
Key exclusion criteria
Presence of *EGFR* mutation, *ALK* fusion, or *ROS1* rearrangement
Symptomatic brain metastasis, leptomeningeal disease, or other active CNS metastases
Prior treatment with any BRAF inhibitor or MEK inhibitor
Evidence of active noninfectious pneumonitis or history of interstitial lung disease
Impaired cardiovascular function or clinically significant cardiovascular diseases
History or current evidence of RVO or current risk factors for RVO (eg, uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes); history of retinal degenerative disease
History of thromboembolic or cerebrovascular events ≤12 weeks prior to the first dose of study treatment[b]
Concurrent neuromuscular disorder that is associated with the potential of elevated CK (eg, inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy)
Evidence of active noninfectious pneumonitis or history of interstitial lung disease
Other severe, acute, or chronic medical or psychiatric condition(s) or laboratory abnormality that may increase the risk associated with study participation or study treatment administration or that may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient an inappropriate candidate for the study

CK, creatine kinase; CNS, central nervous system; ECOG, Eastern Cooperation Oncology Group; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; RVO, retinal vein occlusion.

[a]*BRAF* V600E mutation; other less common Class I *BRAF* V600 mutations (eg, K or D) were permitted with prior discussion with the study team.

[b]Examples include transient ischemic attacks, cerebrovascular accidents, hemodynamically significant deep vein thrombosis or pulmonary emboli. For all countries except Korea, patients with either deep vein thrombosis or pulmonary emboli that did not result in hemodynamic instability were allowed to enroll if they were stable, asymptomatic and on stable anticoagulants for at least 2 weeks. Patients with thromboembolic events related to indwelling catheters or other procedures were allowed to enroll.

Table S2. ARs and treatment-emergent laboratory abnormalities reported in ≥20% of patients with BRAF V600E-mutant NSCLC treated with dabrafenib plus trametinib [3,4]

AR or laboratory abnormality (n=93)	All grade[a]	Grade 3/4[a]
General		
Pyrexia	55	5
Fatigue[b]	51	5
Edema[c]	28	0
Chills	23	1
Gastrointestinal		
Nausea	45	0
Vomiting	33	3
Diarrhea	32	2
Decreased appetite	29	0
Skin and subcutaneous tissue		
Dry skin	31	1
Rash[d]	28	3
Vascular		
Hemorrhage[e]	23	3
Respiratory system		
Cough	22	0
Dyspnea	20	5
Laboratory abnormalities		
Hyperglycemia[f]	71	9
ALP increased[f]	64	0
AST increased[f]	61	4
Hyponatremia[f]	57	17
Leukopenia[g]	48	8
Anemia[g]	46	10
Neutropenia[g]	44	8
Lymphopenia[g]	42	14
Hypophosphatemia[f]	36	7

ALT increased[f]	32	6
Increased creatinine[f]	21	1

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AR, adverse reaction; AST, aspartate aminotransferase; CTCAE, common terminology criteria for adverse events; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer
[a]Grades per NCI CTCAE v4.0.
[b]Includes fatigue, malaise, and asthenia.
[c]Includes peripheral edema, edema, and generalized edema.
[d]Includes rash, rash generalized, rash papular, rash macular, rash maculo-papular, and rash pustular.
[e]Includes hemoptysis, hematoma, epistaxis, purpura, hematuria, subarachnoid hemorrhage, gastric hemorrhage, urinary bladder hemorrhage, contusion, hematochezia, injection site hemorrhage, pulmonary hemorrhage, and retroperitoneal hemorrhage.
[f]For these laboratory tests, the denominator is 90.
[g]For these laboratory tests, the denominator is 91.

Table S3. ARs and treatment-emergent laboratory abnormalities reported in ≥10% of patients with BRAF V600E/K-mutant melanoma treated with encorafenib plus binimetinib [5,6]

AR or laboratory abnormality (n=192)	All grade[a]	Grade 3/4[a,b]
General		
Fatigue[c]	43	3
Pyrexia[c]	18	4
Gastrointestinal		
Nausea	41	2
Vomiting[c]	30	2
Abdominal pain[c]	28	4
Constipation	22	0
Musculoskeletal and connective tissue disorders		
Arthralgia[c]	26	1
Myopathy[c]	23	0
Pain in extremity	11	1
Skin and subcutaneous tissue disorders		
Hyperkeratosis[c]	23	1
Rash[c]	22	1
Dry skin[c]	16	0
Alopecia[c]	14	0
Pruritus[c]	13	1
Nervous system disorders		
Headache[c]	22	2
Dizziness[c]	15	3
Peripheral neuropathy[c]	12	1
Vascular disorders		
Hemorrhage[c]	19	3
Laboratory abnormalities		
Increased creatinine	93	4
Increased gamma glutamyl transferase	45	11
Anemia	36	4

ALT increased	29	6
AST increased	27	3
Hyperglycemia	28	5
ALP increased	21	1
Hyponatremia	18	4
Neutropenia	13	3
Lymphopenia	13	2
Leukopenia	13	0
Hypermagnesemia	10	1

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AR, adverse reaction; AST, aspartate aminotransferase; CTCAE, common terminology criteria for adverse events; NCI, National Cancer Institute.
[a]Grades per NCI CTCAE v4.03.
[b]Grade 4 ARs limited to one event each of fatigue, pruritus, and rash.
[c]Represents a composite of multiple, related preferred terms.

References

1. Riely GJ, Ahn MJ, Felip E, Ramalingam SS, Smit EF, Tsao AS, et al. Encorafenib plus binimetinib in patients with *BRAF*^{V600}-mutant non-small cell lung cancer: phase II PHAROS study design. Future Oncol. 2022;18(7):781-791.
2. Riely GJ, Smit EF, Ahn MJ, Felip E, Ramalingam SS, Tsao A, et al. Phase II, open-label study of encorafenib plus binimetinib in patients with BRAF^{V600}-mutant metastatic non-small-cell lung cancer. J Clin Oncol. 2023; 41(21):3700-11.
3. Novartis Pharmaceuticals Corporation. Tafinlar (dabrafenib). Package insert. Available online at https://www.accessdata.fda.gov/spl/data/23689dc5-f2a5-4475-bbc1-bd73107e51ba/23689dc5-f2a5-4475-bbc1-bd73107e51ba.xml. Accessed Jan 25 2024.
4. Novartis Pharmaceuticals Corporation. Mekinist (trametinib). Package insert. Available online at https://www.accessdata.fda.gov/spl/data/26a4b56c-c10d-4b34-97d2-e46d150f2043/26a4b56c-c10d-4b34-97d2-e46d150f2043.xml. Accessed Jan 29 2024.
5. Array BioPharma Inc. Braftovi (encorafenib). Package insert. Available online at https://www.accessdata.fda.gov/spl/data/c2eedf4c-59b6-43ed-9820-a5621fa3e18f/c2eedf4c-59b6-43ed-9820-a5621fa3e18f.xml. Accessed Nov 20 2023.
6. Array BioPharma Inc. Mektovi (binimetinib). Package insert. Available online at https://www.accessdata.fda.gov/spl/data/4e0f2551-01a9-46c6-8019-bd5535c09ee6/4e0f2551-01a9-46c6-8019-bd5535c09ee6.xml. Accessed Nov 20 2023.