MEK Inhibitor-Based Combination Strategies in Selected Molecular Subsets of Non-Small Cell Lung Cancer (NSCLC): Rationale for the Design of Phase I Clinical Trials

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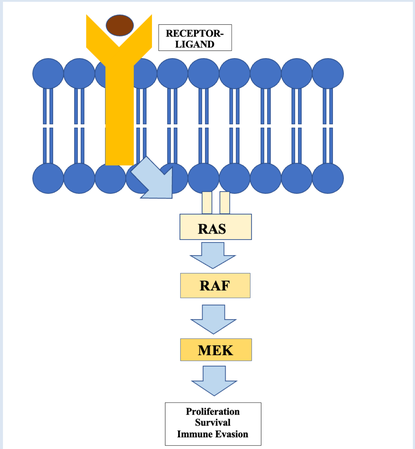
Background

- Lung cancer is the leading cause of both cancer and cancer-related mortality in the United States. Targeting different receptor tyrosine kinase pathways has proven to be a potent therapeutic strategy for such cancers.
- The mitogen-activated protein kinase (MAPK or MEK) represents one such pathway that promotes tumor growth and resistance to therapy.

Methods

- Our objective was to review relevant literature on MEK treatment strategies, specifically in the context of various combinations with other molecular targeted therapies.
- Articles were selected via Pubmed using keywords such as MEK-BRAF-, MET-, and ALK-inhibition, among others.
- Results were used to inform the design and/or development of clinical trials of MEK inhibition-based combination therapies in oncogene-driven NSCLC.



MEK Inhibitor Monotherapy

- Clinical trial results have showed that MEK inhibitor monotherapy possessed minimal clinical efficacy and may even be more toxic than traditional chemotherapy.
- Common side effects included rash, diarrhea, nausea, vomiting, and fatigue.

Selected Paper	Author(s)	Finding
A phase II, open-label, randomized study to assess the efficacy and safety of AZD6244 versus pemetrexed	Hainsworth JD, Cebotaru CL, Kanarev V, Ciuleanu TE, Damyanov D, Stella P, Ganchev H, Pover G, Morris C, Tzekova V.	No significant difference in median progression free survival in a cohort of 84 patients
A phase II study of PD-0325901, an oral MEK inhibitor, in previously treated patients with advanced non-small cell lung cancer.	Haura EB, Ricart AD, Larson TG, Stella PJ, Bazhenova L, Miller VA, Cohen RB, Eisenberg PD, Selaru P, Wilner KD, Gadgeel SM	Showed no appreciable tumor response in a cohort of 34 patients
A randomized phase II study of the MEK1/MEK2 inhibitor trametinib compared with docetaxel in KRAS-mutant advanced NSCLC.	Blumenschein GR Jr, Smit EF, Planchard D, Kim DW, Cadranel J, De Pas T, Dunphy F, Udud K, Ahn MJ, Hanna NH, Kim JH, Mazieres J, Kim SW, Baas P, Rappold E, Redhu S, Puski A, Wu FS, Jänne PA	No significant difference in PFS and median overall survival between patients treated with trametinib versus docetaxel

Dual BRAF + MEK Inhibition

The combination of MEK and BRAF inhibitors appears to have more impressive clinical results than MEK monotherapy. Common side effects included neutropenia, anemia, and hyponatremia.

Selected Paper	Author(s)	Finding
Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic NSCLC	Planchard D, Besse B, Groen HJM, Souquet PJ, Quoix E, Baik CS, Barlesi F, Kim TM, Mazieres J, Novello S, Rigas JR, Upalawanna A, D'Amelio AM Jr, Zhang P, Mookerjee B, Johnson BE.	Overall response rate was 63.2% and median progression free survival was 9.7 months.
Phase 2 Study of Dabrafenib Plus Trametinib in Patients With BRAF V600E-Mutant Metastatic NSCLC	Planchard D, Besse B, Groen HJM, Hashemi SMS, Mazieres J, Kim TM, Quoix E, Souquet PJ, Barlesi F, Baik C, Villaruz LC, Kelly RJ, Zhang S, Tan M, Gasal E, Santarpia L, Johnson BE.	Showed no appreciable tumor response in a cohort of 34 patients
Dabrafenib and trametinib in patients with tumors with BRAF(V600E) mutations: results of the NCI-MATCH trial subprotocol H	Salama AKS, Li S, Macrae ER, Park JI, Mitchell EP, Zwiebel JA, Chen HX, Gray RJ, McShane LM, Rubinstein LV, Patton D, Williams PM, Hamilton SR, Armstrong DK, Conley BA, Arteaga CL, Harris LN, O'Dwyer PJ, Chen AP, Flaherty KT	No significant difference in PFS and median overall survival between patients treated with trametinib versus docetaxel

Inhibition of ALK/ROS1 + MEK

The combination of ALK/ROS1 targeted therapy with MEK inhibitors has shown promising preclinical efficacy

Selected Paper	Author(s)	Finding
RAS-MAPK dependence underlies a rational polytherapy strategy in EML4-ALK-positive lung cancer.	Hrustanovic G, Olivas V, Pazarentzos E, Tulpule A, Asthana S, Blakely CM, Okimoto RA, Lin L, Neel DS, Sabnis A, Flanagan J, Chan E, Varella-Garcia M, Aisner DL, Vaishnavi A, Ou SH, Collisson EA, Ichihara E, Mack PC, Lovly CM, Karachaliou N, Rosell R, Riess JW, Doebele RC, Bivona TG.	• Constitutive activation of MAPK signaling induced tumor resistance to ALKi therapy in cancer cell lines that previously responded to crizotinib • Low dose trametinib was enough to sensitize cancer cell lines to ALKi therapy and increasing doses of MEK inhibitor induced greater levels of apoptosis • The combination of ALKi therapy with trametinib demonstrated little toxicity
Inhibition of Mitogen-Activated Protein Kinase Kinase Alone and in Combination with Anaplastic Lymphoma Kinase (ALK) Inhibition Suppresses Tumor Growth in a Mouse Model of ALK-Positive Lung Cancer.	Shrestha N, Bland AR, Bower RL, Rosengren RJ, Ashton JC.	Combination of crizotinib and the MEK inhibitor selumetinib potently inhibited the growth of both crizotinib-naive and crizotinib resistant ALK+ lung cancer
Combined effect of ALK and MEK inhibitors in EML4-ALK-positive non-small-cell lung cancer cells.	Tanizaki J, Okamoto I, Takezawa K, Sakai K, Azuma K, Kuwata K, Yamaguchi H, Hatashita E, Nishio K, Janne PA, Nakagawa K.	Experimental ALKi TAE684 was only effective in inhibiting tumor proliferation and inducing apoptosis when combined with a MEK inhibitor

Dual MET and MEK Inhibition

Preclinical data on dual MET- and MEK- inhibition has also shown initial and encouraging evidence of efficacy

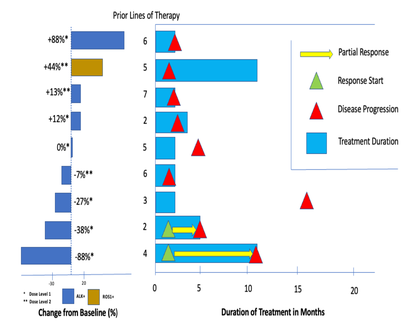
Selected Paper	Author(s)	Finding
MEK inhibitors against MET-amplified non-small cell lung cancer.	Chiba M, Togashi Y, Tomida S, Mizuuchi H, Nakamura Y, Banno E, Hayashi H, Terashima M, De Velasco MA, Sakai K, Fujita Y, Mitsudomi T, Nishio K.	• MEK inhibition showed significant effects in all MET-amplified cell lines • One cell line that demonstrated EGFR to MET driver gene alteration displayed enhanced sensitivity to MEK inhibitors
Activation of KRAS Mediates Resistance to Targeted Therapy in MET Exon 14-mutant Non-small Cell Lung Cancer	Suzawa K, Offin M, Lu D, Kurzatkowski C, Vojnic M, Smith RS, Sabari JK, Tai H, Mattar M, Khodos I, de Stanchina E, Rudin CM, Kris MG, Arcila ME, Lockwood WW, Drilon A, Ladanyi M, Somwar R.	The combination of MET TKI and trametinib had a synergistic effect and that trametinib/crizotinib combination therapy reduced cell growth in mice tumor xenografts
Genomic Status of *MET* Potentiates Sensitivity to MET and MEK Inhibition in NF1-Related Malignant Peripheral Nerve Sheath Tumors.	Peacock JD, Pridgeon MG, Tovar EA, Essenburg CJ, Bowman M, Madaj Z, Koeman J, Boguslawski EA, Grit J, Dodd RD, Khachaturov V, Cardona DM, Chen M, Kirsch DG, Maina F, Dono R, Winn ME, Graveel CR, Steensma MR.	Capmatinib/trametinib combination therapy was effective in reducing response variability and suppressing tumor growth/downstream pathway signaling in NF1-related malignant peripheral sheath tumors.

Design and Conduct of Early Phase NSCLC Trials

The results of this review in part contributed to the design and conduct of two investigator initiated clinical trials at UC Davis Comprehensive Cancer Center

Phase Ia Trial of Trametinib (MEK inhibitor) plus Ceritinib (ALK inhibitor) in Advanced NSCLC

- We reported the preliminary results of a Phase Ia dose escalation trial of the ALK inhibitor ceritinib with trametinib in heavily pretreated patients with advanced ALK+ NSCLC
- The most common adverse events were rash, diarrhea, and elevated AST/ALT; only one dose-limiting toxicity (a grade 3 rash) was observed
- The observed ORR of 22% was encouraging given the heavily pre-treated population.



Phase I Trial of Trametinib (MEK inhibitor) plus Capmatinib (MET inhibitor) in Advanced NSCLC

- We recently initiated a multicenter Phase I/Ib trial examining the combination of the MET inhibitor capmatinib plus trametinib in NSCLC patients with tumors harboring METex14 skipping mutations.
- We will employ a standard 3+3 design to determine a recommended phase 2 dose (RP2D). We will then move to a dose expansion phase to further characterize the combination's safety profile.
- We anticipate that the results of this trial will further inform the use of combination targeted therapies in this specific oncogene-driven lung cancer subtype.