War against *NRAS*-Mutant Melanoma Using Targeted Therapies Remains Challenging

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SUMMARY

In the search for targeting MAPK plus other pathways in *NRAS*-mutant melanoma, a phase Ib/II trial tested binimetinib plus ribociclib in metastatic melanoma. The response rate in the phase II trial was 19.5%, and the median progression-free survival was 3.7 months.

See related article by Schuler et al., p. 3002

In this issue of *Clinical Cancer Research*, Schuler and colleagues report a phase Ib/II multicenter study in patients with *NRAS*-mutant metastatic melanoma using binimetinib, an MEK inhibitor, in combination with ribociclib, a CDK4/6 inhibitor (1). 102 patients with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 were accrued between June 2013 and November 2016; almost all ($n = 101$) had elevated serum lactate dehydrogenase (LDH) at baseline and had not previously received a MEK inhibitor ($n = 99$). Approximately 55% and 85% of patients had previously received immunotherapy in the dose-escalation and dose-expansion phases, respectively. During the dose-escalation phase ($n = 62$), two different schedules were tested in which a 7-day ribociclib break was included; a more dose-dense, 28-day schedule and a less intense, 21-day schedule. The recommended phase II dose was the 28-day schedule of continuous administration of binimetinib, 45 mg twice a day, plus ribociclib, 200 mg every day, 21-days-on/7-days-off based on the numerically higher clinical endpoints of the 28-day as opposed to the 21-day schedule [disease control rate 69% vs. 56%, respectively; median progression-free survival (PFS) 6.7 vs. 4.1 months, respectively) and the comparable tolerability of both schedules. Although the disease control rate in the dose-expansion phase remained similar to that in the dose-escalating phase, the median PFS was shorter (3.7 months). Across the entire study, 73.5% and 25.5% of patients developed adverse events requiring dose interruption or discontinuation, respectively. Pharmacokinetic analysis suggested that the exposure to ribociclib at the recommended phase II dose (200 mg every day), as measured by the area-under-plasma, concentration-time curve over dosing interval (AUC_{tau}), was approximately 10% that of the FDA-approved label dose (200 mg three times a day). Pharmacodynamic analysis regarding the activation status of distinct MAPK pathway components as measured by single-color immunohistochemistry in baseline and on-treatment tumor samples revealed variable and nonsignificant suppression of activated phospho-ERK (pERK) but not activated phospho-MEK (pMEK).

Hotspot *NRAS* mutations, much like hotspot mutations in the *KRAS* gene, remain an elusive pharmacologic target due to the lack of *bona fide* druggable pockets on the RAS surface. Nevertheless, this decades-long pessimistic outlook about the feasibility of direct RAS targeting was recently challenged by the recent and unexpected discovery of at least two pockets on the surface of the RAS proteins amenable to small-molecule drug discovery. This breakthrough research led to the ultimate FDA approval of sotorasib, a direct *KRASG12C* inhibitor in patients with non–small cell lung cancer (2). An emerging lesson from developing direct KRAS inhibitors is that there will not probably be a one drug-fits-all-*KRASG12*/*G13* mutations approach. The potential for *RAS* mutation-specific direct inhibitors is essential to consider for the hotspot *NRAS* mutations in melanoma because there are considerable differences in oncogenic potential and target stoichiometry not only between *NRASG12*/*G13* versus the more aggressive *NRASQ61* variants (**Fig. 1**) but also among the *NRASQ61* variants themselves (*K*, *R*, and *L*; ref. 3).

The second formidable challenge with hotspot *NRAS* mutations is the large number of RAS-associated downstream effector proteins. Unlike hotspot *BRAFV600* mutations, hotspot *NRAS* mutations not only signal through the Raf—MEK–ERK and the PI3K–Akt pathways but also via several other pathways with variable oncogenic potential (**Fig. 1**). Since these downstream RAS effectors are almost always wild-type proteins with essential physiologic functions for normal cells, including immune cells, off-target toxicity consistently becomes the dose-limiting factor, like in the Schuler and colleagues study. Despite the variety of RAS's downstream effector proteins, the Raf—MEK–ERK signaling pathway remains NRAS's dominant downstream effector (**Fig. 1**). In fact, pERK (but not pMEK) was significantly higher in *RAS*-mutant than *BRAFV600*-mutant cutaneous melanoma (4). The importance of the MAPK pathway for NRAS signaling was clinically established by the (modest) clinical benefit of binimetinib over dacarbazine as part of a randomized clinical trial in *NRAS*-mutant metastatic melanoma (5). Currently, the challenge is to identify the optimal level (i.e., Raf, Ras, ERK) and/or degree of inhibition (single vs. dual blockade) of the MAPK pathway that would balance efficacy over toxicity (**Fig. 1**). High priority, in particular, is given to the development of pan-RAF kinase inhibitors, especially those that target BRAF and CRAF but spare ARAF (e.g., belvarafenib, LXH254), given the critical dependence of BRAF-CRAF dimerization to mediate NRAS signaling through the MAPK pathway (**Fig. 1**). These pan-RAF kinase inhibitors are currently being combined with MEK inhibitors, ERK inhibitors, and/or PD-L1 inhibitors in patients with *NRAS*-mutant melanoma (clinicaltrials.gov NCT04835805, NCT04417621).

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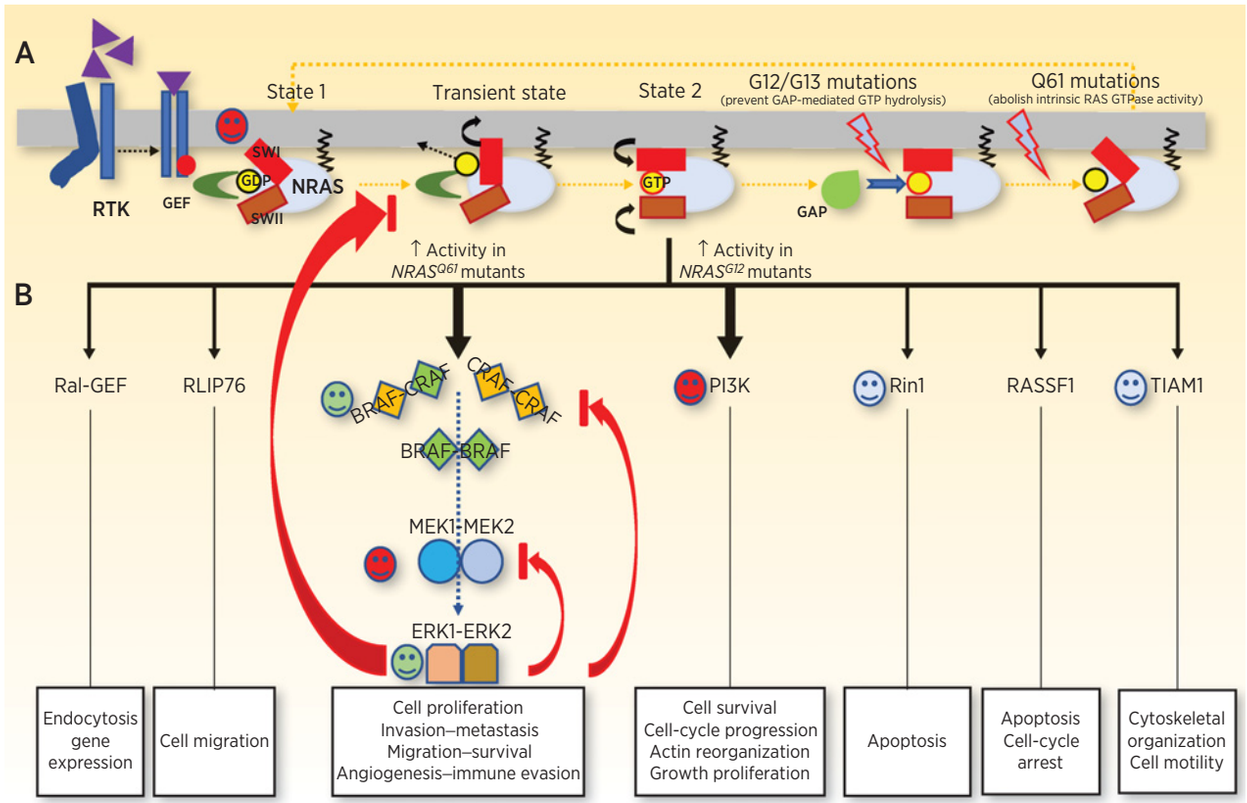

Figure 1.

The NRAS pathway in melanoma and implications for targeted intervention. **A,** Under physiologic conditions, extracellular signals (purple triangles) activate membrane-bound receptor tyrosine kinases (RTK), which in turn activate various guanine nucleotide exchange factors (GEF; e.g., SOS, PLCE1). GEFs, in turn, mediate exchange of GDP for GTP. Breakthrough nuclear magnetic resonance (NMR) studies have recently deciphered the different conformation states that RAS adopts during the complex GDP-to-GTP exchange, the critical role of RAS's switch I (SWI) and switch II (SWII) regions in binding GDP (or GTP), and the existence of swallow pockets—one between SWI and SWII (SI/II) and the other above the SWII region (SII)—that are amenable to drug targeting (red smiling faces). More specifically, in state 1, the SW1 region adopts an open conformation that favors nucleotide exchange and inhibits binding of downstream RAS effectors. In state 2, SW1 adopts a closed conformation over GTP that promotes effector binding and subsequent GTP hydrolysis. Different oncogenic mutations in RAS impair GTP hydrolysis, via different mechanisms; *G12/G13* mutations prevent guanine activating protein (GAP; e.g., NF1)-mediated GTP hydrolysis, whereas *Q61* mutations abolish intrinsic RAS GTPase activity. The end result leads to stabilization of the activated GTP-RAS form and subsequently enhanced RAS signaling. **B,** RAS/MEK/ERK signaling remains the most crucial downstream pathway in *NRAS*-mutant melanoma. RAS-GTP dimers recruit RAF homo-/hetero-dimers and, in turn, activate/recruit MEK dimers to the plasma membranes. Activated MEK phosphorylates ERK, which mediates various cellular effects. Activated ERK, however, also mediates complex negative feedback loops within at least the same MAPK pathway; the complexity of this feedback has complicated clinical efforts to effectively target NRAS signaling in *NRAS*-mutant melanoma (see main text of this commentary). Nevertheless, there are multiple downstream NRAS effectors with broad cellular effects other than the MAPK pathway, an unpleasant reality that challenges clinical efforts to indirectly target downstream RAS signaling with efficiency and minimal side effects. For the majority of these downstream RAS effectors, there are no available drugs in clinical development (no green or red smiling faces). Interestingly, different *NRAS* mutations may preferentially signal via one over another pathway. Red smiling faces, FDA-approved drugs; green smiling faces, drugs in clinical development; blue-smiling faces, drugs in preclinical development.

To further complicate matters, however, patients with *NRAS*-mutant melanoma have a variable degree of MAPK activation, as measured by pERK and pMEK levels in tumor tissue (Supplementary Fig. S2 of the Schuler and colleagues paper; **Fig. 1**; ref. 4). Therefore, not all *NRAS*-mutant tumors are addicted to MAPK activation, which may account for the moderate clinical benefit of MAPK inhibitors in *NRAS*-mutant melanoma. However, the most exciting finding in the Schuler and colleagues study was targeting a pathway other than the MAPK in *NRAS*-mutant melanoma. In particular, a higher overall response rate was seen in patients bearing melanomas with genetic aberrations in the G1 phase cell-cycle checkpoint genes (e.g., *CDK4*, *CCND1*, *RB1*, and *CDKN2A* locus). The difference in response rate (32.5% vs. 10%) is remarkable–and perhaps unexpected–given that the phase II recommended dose for ribocyclib was significantly lower than its FDA-approved dose for breast cancer. Targeting *NRAS*-mutant melanoma with CDK4/6 inhibitors is highly clinically relevant because approximately 50% of *NRAS*-mutant melanomas also bear genetic aberrations in cell-cycle–associated genes (Supplementary Fig. S3 of the Schuler and colleagues paper; ref. 4). Therefore, the combined targeting of the MAPK pathway with CDK4/6 inhibitors in *NRAS*-mutant melanoma may be a preferred strategy for patients with additional genetic aberrations in cell-cycle–associated genes.

The optimal sequence of targeted therapies for *NRAS*-mutant melanoma and immunotherapies would be the next logical question to address. Interestingly, the median PFS in the dose-expansion study was lower than the corresponding median PFS in the 28-day schedule

cohort from the dose-escalation portion of the study. Given that the Schuler and colleagues study was conducted during the years before and after the approval of PD-1 inhibitors, we must reasonably assume that more patients in the dose-expansion portion of the study may have previously received PD-1 inhibitors than the patients in the dose-escalation part of the study, which may have negatively affected clinical benefit. Thus, if the clinical benefit from combined MEK plus CDK4/6 inhibition is limited following immunotherapies, then the upfront administration of targeted therapies with immunotherapies may result in a better outcome. This clinical question is actively being pursued in a clinical trial (clinicaltrials.gov NCT04835805).

The inability to directly target hotspot *NRAS* mutations in metastatic melanoma remains the holy grail treatment for these patients: the "elephant in the room." Interestingly, nearly all *NRAS*-mutant patients in the Schuler and colleagues study had high baseline serum LDH, suggesting that these are poor-prognosis patients. Until the day that we can target a subset of these *NRAS* hotspot mutations directly, indirect targeting may require combination MAPK inhibitor-based approaches that aim to balance safety with efficacy.

Author's Disclosures

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