·综　述·

*NRAS*突变型晚期黑色素瘤的治疗进展

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［**摘要**］黑色素瘤的发生、发展与多种癌基因的激活密切相关。15%~20%的黑色素瘤患者存在*NRAS*基因的激活突变，携带该突变基因的黑色素瘤具有更强的侵袭性，治疗难度大。由于RAS蛋白突变位点属于弱药物靶标，目前尚缺乏有效的靶向抑制剂，因此临床上多以免疫检查点抑制剂作为*NRAS*突变型晚期黑色素瘤的一线治疗方案，然而治疗反应率较低。近年来，在*NRAS*突变亚型中靶向治疗方案的探索主要集中在*NRAS*下游丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）通路，但结果不一：新型MEK1/2抑制剂tunlametinib，在晚期*NRAS*突变患者中总体客观缓解率（objective response rate，ORR）达到34.7%，较既往的binimetinib显著提高；然而泛RAF抑制剂belvarafenib和ERK抑制剂ulixertinib的Ⅰ期临床试验却未能展示出该药明显的优势。此外，以MEK抑制剂为基础的联合治疗也取得一定进展，现有证据表明，分子抑制剂类药物较免疫检查点抑制剂显示出更多的优势：选择性BRAF/CRAF抑制剂naporafenib（LXH254）与MEK抑制剂trametinib联合治疗*NRAS*突变型黑色素瘤的Ⅰb期临床试验中ORR达到46.7%；细胞周期蛋白依赖性激酶4/6（cyclin-dependent kinase4/6，CDK4/6）抑制剂ribociclib和binimetinib联合治疗在携带*NRAS*突变同时合并细胞周期蛋白基因异常的人群中可达32.5%；黏着斑激酶（focal adhesion kinase，FAK）抑制剂IN10018联合cobimetinib的研究结果也表现出较好的ORR（38.5%）；但免疫检查点抑制剂程序性死亡［蛋白］配体-1（programmed death ligand-1，PD-L1）单抗durvalumab联合trametinib方案仅使27.2%的患者达到部分缓解（3/11）。与此同时，部分临床前研究结果也显示出一些转化潜质：如热激蛋白90（heat shock protein 90，HSP90）抑制剂XL888和丝氨酸/苏氨酸蛋白激酶19（serine/threonine protein kinase 19，STK19）抑制剂均在动物模型中表现出显著抑制*NRAS*突变型黑色素瘤细胞生长的能力。本文综述了*NRAS*突变型黑色素瘤的致癌机制及近年来治疗领域的研究进展，旨在展示该亚型患者的治疗现状，对多种新型治疗方法的临床研究结果进行总结和归纳，为当前临床实践和未来联合治疗方案提供依据。

［**关键词**］*NRAS*基因突变；黑色素瘤；致癌机制；靶向治疗

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Advances in the treatment of advanced melanoma with *NRAS* gene mutation

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［**Abstract**］Oncogenic mutations are responsible for a majority of the malignancy of melanoma. Activating mutations of *NRAS* gene are found in 15%-20% melanoma cases, endowing the tumor cells with more aggressive phenotypes and greater difficulty to treat. The development of targeted inhibitor of mutant *NRAS* remains a big challenge since the mutation sites could hardly be druggable. Therefore, immune checkpoint inhibitors are currently recommended as the first-line therapy for *NRAS* mutant advanced melanoma albeit the response rate is still far from satisfaction. In recent years, the exploration of targeted therapy regimens has focused on the downstream pathway of *NRAS*, the mitogen-activated protein kinase (MAPK) pathway. A novel MEK1/2 inhibitor tunlametinib was reported to achieve an objective response rate (ORR) of 34.7% which is higher than the ORR of binimetinib in previous report. However, the phase Ⅰ trial of the pan-RAF inhibitor belvarafenib and the ERK inhibitor ulixertinib failed to show

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marked benefits. In the meanwhile, MEK inhibitor-based combination therapy has also achieved some progress: it was reported in the phase Ⅰb trial of the selective BRAF/CRAF inhibitor naporafenib (LXH254) combined with Trametinib in *NRAS* mutant melanoma that the ORR was 46.7%. The ORR of binetinib plus the cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, ribociclib, was 32.5% in patients with NRAS mutation with concurrent alterations of CDKN2A, CDK4, or CCND1. The response rate of the combination of focal adhesion kinase (FAK) inhibitor, IN10018, and cobimetinib was 38.5%. On the other hand, only 27.2% of patients carrying NRAS mutation responded partially to the combined regimen of immune checkpoint inhibitor programmed death ligand-1 (PD-L1) monoclonal antibody durvalumab+trametinib. In addition, some preclinical findings have also shown translational potentials: for example, heat shock protein 90 (HSP90) inhibitor XL888 and serine/threonine protein kinase 19 (STK19) inhibitors were found to inhibit the growth of NRAS mutant melanoma in animal models. This article reviewed the oncogenic roles of NRAS mutation in melanoma and the cutting-edge clinical trials for the treatment of NRAS mutant melanoma, aiming to provide alterative treatment options for clinical practice and inspire novel combination regimen.

［**Key words**］*NRAS* mutation; Melanoma; Carcinogenesis; Targeted therapy

*NRAS*和*BRAF*是人类黑色素瘤中突变率最高的两个驱动基因，其中，针对*BRAF*V600位点突变的靶向抑制剂已获得较高的治疗反应率，但携带*NRAS*突变的病例治疗仍十分困难。*RAS*基因家族作为一类原癌基因，在进化中较为保守，参与细胞增殖、凋亡、分化和骨架构建等多种重要生物学过程，本文就*NRAS*突变型黑色素瘤治疗的新进展予以综述。

1 *NRAS*基因在黑色素瘤中的促癌机制

*RAS*基因家族包含3种功能性基因：*NRAS*、*KRAS*和*HRAS*，分别位于1号、11号、12号染色体短臂上[1]，编码产物为相对分子质量均为21×10^3的G蛋白，属于一种小GTP酶，经鸟嘌呤核苷酸交换因子（guanine nucleotide-exchange factor，GEF）介导活化，再由GTP酶活化蛋白（GTPase-activating protein，GAP）催化水解还原为无活性形式，以两种状态循环的方式进行活性调节[2]，被称为细胞的“分子开关”。

高加索人群和中国人群的黑色素瘤*NRAS*突变率相近，分别为15.0%~20.0%[3]和10.9%~20.0%[4]，多发生于第61位密码子，并以Q61R为主，突变后的细胞中*NRAS*处于持续激活状态，相比于*BRAF*/*NRAS*双野生甚至*BRAF*突变型病例，携带*NRAS*突变的黑色素瘤侵袭性更强[5-7]。在正常细胞中，*RAS*活化促进BRAF/CRAF形成二聚体，二聚后的*RAF*兄弟蛋白才被激活，与野生型细胞（由*BRAF*负责信号转导）不同，在*NRAS*突变的黑色素瘤细胞中，信号主要由CRAF转导[8]。

活化的*RAS*蛋白主要通过3条信号转导通路发挥对黑色素瘤的促癌作用[9]（图1）。① MAPK信号转导通路：GTP结合的RAS变构激活RAF，随后依次级联激活丝裂原活化蛋白激酶激酶（MAPKK）家族（MEK1、MEK2）及MAPK家族（ERK1、ERK2），推动细胞周期、促进增殖[10-14]。② 磷脂酰肌醇3激酶（phosphatidylinositide3-kinases，PI3K）/丝氨酸-苏氨酸激酶（serine/threonine kinase proteins，AKT）（PI3K-AKT）信号转导通路[15]：PI3K由RAS激活后磷酸化磷脂酰肌醇-4,5-二磷酸［phosphatidylinositol(4,5)bisphosphate，PIP2］分子生成磷酸化磷脂酰肌醇-3,4,5-三磷酸［phosphatidylinositol(3,4,5)trisphosphate，PIP3］，后者招募激活AKT。AKT可以通过磷酸化底物抑制TP53降解并抑制多种促凋亡蛋白活性[16]，阻断凋亡。此外，AKT触发级联反应，导致哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）的激活，通过促进细胞代谢、推动细胞周期及抑制自噬等方式促进肿瘤增殖[17]。③ RAL信号转导通路[18]：RAL（RAS-like）GTPases属于RAS小GTP酶，包括Ral-鸟嘌呤核苷酸交换因子（Ral-GEF），例如Ral-GDS、RalA和RalB等，在活性GTP和非活性GDP结合构象之间循环。RalGEF的激活促进黑色素瘤的增殖[18]和锚定性生长[19-20]；Ral还可以通过与Ral相互作用蛋白RLIP76（也称RalBP1）的结合，促进黑色素瘤血管的生成[22-22]。

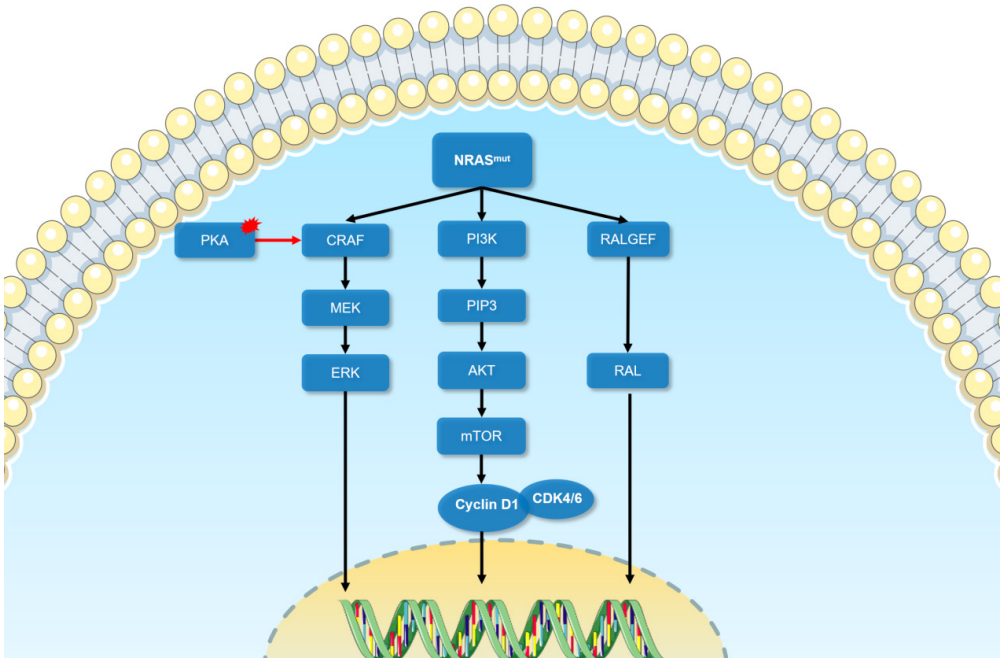

图1 *NRAS*突变的信号转导示意图

Fig. 1 The schematic diagram of signal transduction of *NRAS* mutation

Oncogenic signal transduction following NRAS mutation causes melanoma development mainly through MAPK signaling, PI3K-AKT signaling pathway and RAS-RAL signaling pathway. Black arrow: Conducted; Red arrow: Enhanced; Red area: Abnormal activation.

2 *NRAS*突变型黑色素瘤的治疗现状

由于缺乏有效的靶向抑制剂，目前美国国家综合癌症网络（National Comprehensive Cancer Network，NCCN）和欧洲肿瘤内科学会（European Society for Medical Oncology，ESMO）指南[23-24]中均推荐以免疫治疗作为*NRAS*突变型晚期黑色素瘤的一线治疗，但*NRAS*突变状态对免疫疗效的影响报道并不一致：Jaeger等[25]对16项临床研究进行系统评价发现*NRAS*突变的黑色素瘤病例比野生型对免疫检查点抑制剂具有更高的客观缓解率（objective response rate，ORR）（RR=1.28，95% CI：1.01~1.64）。然而在亚洲人群[26]，接受程序性死亡［蛋白］-1（programmed death-1，PD-1）单抗治疗的*NRAS*突变型亚组疗效却显著差于野生型亚组：在皮肤型患者中，两亚组ORR分别为9.5%和23.9%；在非皮肤型患者中，两亚组ORR分别为0.0%和13.7%。少部分*NRAS*突变病例也可获益于MEK抑制剂：比美替尼（binimetinib）在*NRAS*突变型晚期患者的Ⅲ期临床试验（NEMO研究）证实，binimetinib组中位无进展生存期（median progression-free survival，mPFS）长于达卡巴嗪组（2.8个月 *vs* 1.5个月），但ORR仅为15%[27]。另一MEK抑制剂匹马赛替尼（pimasertib）在*NRAS*突变型患者中达到27%的ORR，虽高于达卡巴嗪对照组（14%），但中位总生存期（median overall survival，mOS）差异无统计学意义（HR=0.89，95% CI：0.61~1.30）[28]。由于临床获益有限，目前MEK抑制剂仅作为免疫治疗进展后的二线选择。

3 *NRAS*突变型黑色素瘤的治疗进展

3.1 单药治疗

由于突变位点已经明确，既往研究曾尝试针对突变位点的靶向治疗，然而不同于*BRAF* V600突变位点，RAS蛋白突变位点属于弱药物靶标，因为在核苷酸结合位点之外缺乏药物分子的结合口袋，GTP分子与RAS蛋白的亲和力达到皮摩级别，针对GTP本身的竞争性抑制药物已被证实无

效[29]。其他的单药治疗策略包括以下几种：

3.1.1 RAS抑制剂

法尼基转移酶抑制剂（farnesyl transferase inhibitor，FTI）：FTI的作用机制是通过抑制法尼基转移酶将法尼基结合到p21RAS羧基端的半胱氨酸（cysteine，Cys）残基，使其不能被羧甲基化，p21RAS就不能定位在细胞膜上，从而阻滞RAS的激活。但目前FTI阻断RAS翻译后修饰和细胞膜定位只能在理论上实现，一项FTI的Ⅱ期临床试验入组的14例黑色素瘤患者均无治疗反应，已提前终止[30]。此外，此类药物显著的毒性也限制了其进一步开发及临床转化[31-32]。

新近公布KRAS抑制剂索托拉西布（sotorasib，*KRAS G12C*靶向抑制剂，NCT03600883）可明显延长*KRAS* G12C突变实体瘤患者的mPFS[33-34]，这一结果提示该药或将给携带*NRAS* G12C突变的黑色素瘤患者带来获益，但仍需临床数据验证。

3.1.2 RAF-MAPK通路抑制剂

由于针对*NRAS*突变位点的靶向抑制剂开发进展缓慢，因此*NRAS*突变型黑色素瘤的治疗策略主要是通过抑制其活化后的下游效应，目前主要集中在RAF-MAPK通路抑制剂。

3.1.2.1 RAF抑制剂

经shRNA同时敲低BRAF和CRAF可显著抑制*NRAS*突变型黑色素瘤的生长[35]，因此，泛RAF抑制剂或可有效地阻断*NRAS*信号向MEK的传递。在泛RAF抑制剂belvarafenib（又称RG6185或HM95573）的Ⅰ期临床试验中其ORR为11%，mPFS为25周[36]。

3.1.2.2 MEK1/2抑制剂

2023年美国临床肿瘤学会（American Society of Clinical Oncology，ASCO）会议上公布新型MEK1/2选择性抑制剂妥拉美替尼（tunlametinib、HL-085）在晚期*NRAS*突变型黑色素瘤的疗效数据显示总体ORR为34.7%，即使在免疫治疗失败的患者中，ORR也高达39.1%[37]，较既往binimetinib的疗效有明显提高[27]。

3.1.2.3 ERK抑制剂

ERK是MAPK通路中的关键节点，抑制ERK活性可以提高*NRAS*突变黑色素瘤对MEK抑制剂的反应[38]。在*NRAS*突变黑色素细胞中，ERK抑制剂VX-11e对细胞增殖的抑制作用比MEK抑制剂更明显[39]。但在Ⅰ期临床试验中，应用ERK1/2抑制剂优立替尼（ulixertinib），仅13.5%的患者达到部分缓解[40]。

3.2 联合治疗

由于*NRAS*活化后激活的下游通路较多，单一通路抑制剂易产生耐药，故联合不同通路治疗也被不断尝试，主要策略是以MEK抑制剂为基础联合其他通路抑制剂或免疫治疗药物。

3.2.1 基于MEK抑制剂的联合方案

3.2.1.1 靶向抑制剂

*NRAS*突变型黑色素瘤细胞对泛RAF抑制剂的耐药与MAPK活化的相关性已被证实，故联合曲美替尼（trametinib）可增强泛RAF抑制剂的疗效[41]。目前正在进行的泛RAF抑制剂联合MEK抑制剂的临床试验有NCT02974725、NCT03284502等，NCT03284502目前公布的ORR为40%（n=9）。此外，选择性*BRAF*/*CRAF*抑制剂naporafenib(LXH254)与trametinib联合治疗KRAS/BRAF突变的非小细胞肺癌和*NRAS*突变黑色素瘤的Ⅰb期临床试验结果[42]显示，接受naporafenib 200 mg每日两次联合trametinib 1 mg每日2次治疗的患者的ORR和mPFS分别为46.7%和5.52个月。除了MAPK通路外，同时抑制PI3K-AKT通路也可产生协同作用[43]。PI3Kα抑制剂（alpelisib）联合binimetinib的Ⅰb期临床试验中ORR为20%[44]。而AKT抑制剂（GSK2141795）和trametinib的联合方案的Ⅱ期临床试验显示mPFS和mOS仅为2.3和4.0个月，ORR为0%，未能产生临床获益[45]（表1）。

3.2.1.2 CDK4/6抑制剂

CDK4/6抑制剂瑞博西尼（ribociclib）和binimetinib联合治疗的Ⅱ期队列（n=41）结果显示，mPFS为3.7个月，总体ORR为19.5%，在伴有CDKN2A、CDK4或CCND1基因表达异常的患者表现出更高的ORR（32.5%），因此，携带*NRAS*突变和细胞周期基因异常的患者从该联合方案获益的可能性更高[46]。

表1 针对*NRAS*突变型黑色素瘤的临床试验

Tab. 1 Treatment of *NRAS* mutant melanoma in clinical trials

Identifier	Target	Study design	*NRAS*-mutant mlanoma patients	Efficacy	Time frame
NCT03013101, NCT02821000, NCT02738489, CTR20160872[25]	PD-1 antiboby	Clinical data from four clinical trials in patients with advanced melanoma treated with anti-PD-1 monoclonal antibodies between 2016 and 2019 were analyzed. The efficacy of immunotherapy in patients with cutaneous and non-cutaneous *NRAS* mutant melanoma was analyzed separately.	A total of 206 patients were assessed, including 12 patients with *NRAS*-mutated cutaneous melanoma and 21 patients with *NRAS*-mutated non-cutaneous melanoma	In cutaneous melanoma, patients with *NRAS* mutations had a lower overall response rate (ORR) than patients without *NRAS* mutations (9.5% *vs* 23.9%). In non-cutaneous melanoma, response rates were 0% and 13.7%, median progression-free survival (mPFS) was 3.6 months and 4.3 months (P=0.015), and median survival time (mOS) was 10.8 months and 15.3 months (P=0.025) in *NRAS* mutant and wild-type patients, respectively	2016-2019
NCT01763164[27]	MEKi binimetinib	Phase Ⅲ randomized, multicenter, open-label clinical trial. Patients with advanced, unresectable stage ⅢC-Ⅳ *NRAS* mutated melanoma who were previously untreated or progressed following prior immunotherapy were randomized (2:1) to receive binimetinib 45 mg orally twice daily or dacarbazine 1 000 mg/m^2 intravenously every 3 weeks.	A total of 402 patients with *NRAS*-mutated melanoma were enrolled, 269 treated with binimetinib and 233 treated with dacarbazine (1:2)	In the binimetinib arm mPFS was 2.8 months and 1.5 months in the dacarbazine arm	2013-2015
NCT01693068[28]	MEKi pmasertib	Phase Ⅱ multicenter, open-label clinical trial. Patients with unresectable stage Ⅲc/ⅣM1 *NRAS*-mutated cutaneous melanoma were randomized 2:1 to receive pmasertib (60 mg orally twice daily) or DTIC (1 000 mg/m^2 intravenously). Primary endpoint: investigator-assessed PFS; secondary endpoints: OS, ORR, quality of life (QoL), and safety.	191 patients with *NRAS* mutated cutaneous melanoma, 191 treated (pimasertib n=130, DTIC n=61)	PFS and 6-month PFS rates were significantly improved in the pimasertib arm compared with the DTIC arm: 13 weeks versus 7 weeks, 17% *vs* 9%. Investigator-assessed ORR was 27% in the pimasertib arm and 14% in the DTIC arm. However, there was no difference in OS between patients treated with pimasertib and DTIC (mOS 9 and 11 months, respectively; HR=0.89, 95% CI: 0.61-1.30)	2012-2014
NCT00060125[30]	Farnesyltransferase inhibitor (FTI)	Three-stage trial design, up to 40 patients, stopped early if first 14 patients did not respond, or first 28 patients had less than 2 responders	14 patients with *NRAS* mutated melanoma	2 patients presented with grade 3 toxicity and all patients had no clinical response and the trial was prematurely discontinued	2003-2006
Identifier	Target	Study design	*NRAS*-mutant mlanoma patients	Efficacy	Time frame
NCT03118817[36]	RAFi belvarafenib	Single-arm, open-label, multicenter, phase Ⅰ extension study	9 *NRAS* mutated melanoma patients	ORR 11%, mPFS 25 weeks	2017-2020
NCT03973151[37]	MEKi HL-085	Phase Ⅰ/Ⅱ, single-arm, dose-escalation and cohort expansion study	42 patients with *NRAS* mutated melanoma	HL-085 was published in 2023 confirming an ORR of 34.7%	2019-2023

表1（续）

Identifier	Target	Study design	*NRAS*-mutant mlanoma patients	Efficacy	Time frame
NCT02974725[42]	BRAF/CRAF protein kinases inhibitor Naporafenib(LXH254) + MEKi trametinib	Phase Ⅰb escalation/ expansion study	30 patients with *NRAS* mutated melanoma	The ORR was 46.7%, the median DOR was 3.75 and the overall median PFS was 5.52 months in patients treated with naporafenib 200 mg twice a day plus trametinib 1 mg once daily.	2017-2023
NCT01449058[44]	PI3K α inhibitor BYL719 +MEKi binimetinib	Phase Ⅰb open-label, multicenter, dose escalation and expansion study	5 *NRAS* mutated melanoma patients	ORR 20%	2011-2017
NCT01941927[45]	MEKi trametinib +AKT inhibitor GSK2141795	Phase Ⅱ non-randomized, multicenter, open-label clinical trial	Efficacy and safety of MEK inhibitors combined with AKT inhibitors in 10 patients with *NRAS*-mutated melanoma and 10 patients with *BRAF*WT/*NRAS*WT melanoma	The mPFS and mOS of the 10 *NRAS*-mutated melanoma patients were only 2.3 and 4.0 months. Median PFS and OS for the wild-type cohort were 2.8 months and 3.5 months, respectively. No objective responses were identified in either cohort. The combination of Trametinib and GSK2141795 has no significant clinical activity in *NRAS* mutants or *BRAF*WT/*NRAS*WT melanomas	2013-2020
NCT03932253	MEKi FCN-159	Phase Ⅰa/Ⅰb, open-label, dose escalation and dose expansion study	33 patients with *NRAS* mutated melanoma were enrolled	The ORR and clinical benefit rates were 19.0% and 52.4%, respectively. Median duration of response and progression-free survival were 4.8 months and 3.8 months (1.8-5.6 months), respectively.	2019-2023
NCT03284502	MEKi cobimetinib + RAFi HM95573	Phase Ⅰb, open-label, multicenter dose escalation study	9 *NRAS* mutated melanoma patients	Available data published ORR of 40%	2017-2023
NCT03979651	MEKi trametinib+autophagy inhibitor hydroxychloroquine	Phase Ⅰb/Ⅱ non-randomized, open-label clinical trial	29 *NRAS* mutated melanoma patients	Results to be further published	2019-2022
NCT04109456	MEKi cobimetinib	Phase Ⅰb open-label clinical study	Estimated enrollment is 120 patients with *NRAS* mutated melanoma	Results to be further published	2019-2023

mPFS: Median progression-free survival; mOS: Median overall survival; ORR: Overall response rate. WT: Wild type.

3.2.1.3 FAK抑制剂

FAK抑制剂（IN10018）联合考比替尼（cobimetinib）在*NRAS*突变黑色素瘤患者的Ⅰ期临床试验中ORR为38.5%，mPFS为5.45个月[47]。

3.2.1.4 自噬抑制剂

已证实细胞自噬可保护肿瘤细胞免受RAS抑制剂的细胞毒性作用[48]，现有临床试验（NCT03979651）正在评估自噬抑制剂（羟氯喹）联合MEK抑制剂治疗*NRAS*突变黑色素瘤的疗效，但研究结果尚未公布。

3.2.1.5 免疫检查点抑制剂

针对PD-L1的度伐利尤单抗（durvalumab）联合trametinib（同用或序贯）方案在*NRAS*突变患者中获得27.7%的部分缓解（3/11）[49]。IMspire170研究对比了cobimetinib联合PD-L1单抗阿替利珠单抗（atelizumab）和帕博利珠单抗（pembrolizumab）一线治疗BRAF野生型患者，

发现两种治疗的mPFS（5.7个月 *vs* 5.5个月）及ORR（53% *vs* 65%）差异无统计学意义，即使在*NRAS*突变的患者中，cobimetinib联合atelizumab方案也未能显示出优势[50]。

3.2.2 基于酪氨酸激酶抑制剂的联合方案

*NRAS*突变黑色素瘤表达大量细胞表面受体酪氨酸激酶（receptor tyrosine kinase，RTK），具有驱动细胞增殖的潜力，例如Axl、ERBB2、c-MET、EGFR等[51-52]。索拉非尼（sorafenib，VEGFR抑制剂）联合MET酪氨酸激酶抑制剂（tivantinib）治疗晚期实体肿瘤的Ⅰ期临床试验中[53]，*NRAS*突变黑色素瘤患者的ORR虽然低于野生型或未知状态的患者（20.0% *vs* 33.3%），但其mPFS却更长（5.4个月 *vs* 3.3个月），初步显示出TKI联合METi的协同疗效。

4 总结与展望

本综述所阐述的临床研究的具体情况见表1。目前针对*NRAS*突变型黑色素瘤的靶向和免疫治疗方案均未能媲美BRAF抑制剂在*BRAF*突变型病例中达到的治疗反应率，但近年来基于MEK抑制剂的部分联合治疗策略已经取得喜人的进展[54]。此外，临床前研究中，热激蛋白90（heat shock protein 90，HSP90）抑制剂[55]及丝氨酸/苏氨酸蛋白激酶19（serine/threonine protein kinase 19，STK19）抑制剂[56]也显示出很强的转化潜力，有望成为未来*NRAS*突变型黑色素瘤治疗的突破口。

利益冲突声明：所有作者均声明不存在利益冲突。

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文章摘要写作需要以长摘要格式，中文摘要字数在800~1000字，一般不超过1000字。英文摘要的内容应与中文摘要一致。写作要求如下：

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