Prolonged complete response to the pan-RAF inhibitor DAY101 in a patient with an *NRAS*-mutated acral lentiginous melanoma

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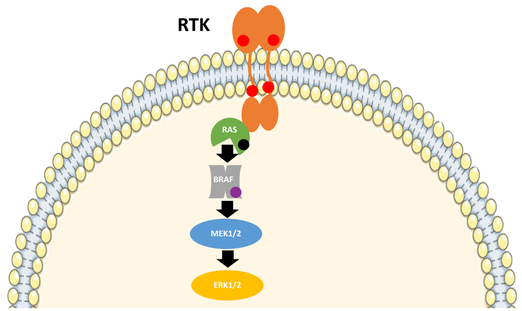
Poster #125

Background

- Genomic alterations resulting in deregulation of the MAPK pathway occur in many adult and pediatric malignancies, especially in melanoma (**Figure 1**)[1]
- The RTK–NRAS–BRAF–MEK–ERK signaling cascade appears to be activated in nearly all melanomas (**Figure 1**)[1]
- DAY101 (TAK-580, MLN2480, or BIIB-024) is an oral, selective, central nervous system-penetrant, type II pan-RAF inhibitor that is undergoing clinical development in patients with cancers harboring an activating *BRAF* alteration
- Preclinical data show that DAY101 inhibits BRAF V600E mutation, wild-type BRAF or CRAF, and both monomeric and dimeric forms of RAF:[2]
  - In contrast to clinically approved type I RAF inhibitors, DAY101 does not induce paradoxical activation of MAPK signaling, as has been shown in tumor models driven by a specific *BRAF* gene fusion[2]
- To date, >200 patients have been treated across 3 phase 1 trials (NCT01425008, NCT02327169 and NCT03429803) in adults and children with RAF alteration-driven cancers
  - Patients with BRAF-altered melanoma demonstrated an objective response rate of 50%[3]
- DAY101 was granted **breakthrough therapy designation** by the U.S. Food and Drug Administration (FDA) for the treatment of pediatric patients with an advanced low-grade glioma harboring an activating *RAF* alteration
- DAY101 has also received **orphan drug designation** from the FDA and the European Commission for the treatment of glioma
- Here, we report a >8-year complete response (CR) to monotherapy with DAY101 in a heavily pretreated patient with *NRAS*-mutant melanoma

Figure 1. Key genetic alterations in the MAPK signaling pathway components in melanoma



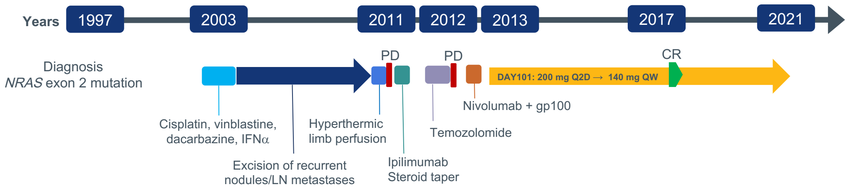
- *KIT* mutations/amplifications: ~40% of acral and mucosal melanomas[1]
- *NRAS* mutations: ~20% of cutaneous melanomas[1]
- *BRAF* mutations: ~50%–60% of cutaneous melanomas[1]

RTK, receptor tyrosine kinase.

Case description

- A female patient aged 81 years was initially diagnosed with an acral lentiginous melanoma at 57 years of age (**Figure 2**)
- The genetic testing of melanoma lesions identified an *NRAS* exon 2 mutation, but no *BRAF* and *KIT* mutations were found

Figure 2. Treatment summary



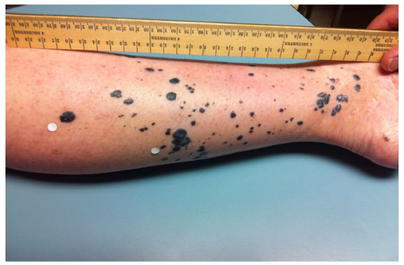
Data cutoff, 20 July 2021

CR, complete response; gp100, glycoprotein 100; IFNα, interferon α; LN, lymph node; PD, progressive disease; Q2D, every second day; QW, once weekly.

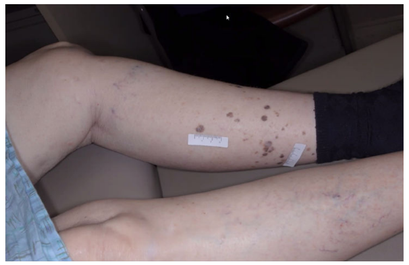
- The patient received 2 cycles of neoadjuvant chemotherapy comprising cisplatin, vinblastine, dacarbazine and IFNα in 2003
- Recurrent nodules and lymph node metastases were excised on multiple occasions between 2003 and 2011
- In 2011, the patient underwent hyperthermic limb perfusion with melphalan and eventually developed progressive disease
- Subsequently, she was treated with ipilimumab, and due to rash, oral lesions, and colitis, which developed in response to ipilimumab, the patient received a prolonged steroid taper
- In 2012, the patient started low-dose temozolomide, but progressive disease developed
- Consequently, the patient enrolled in a phase 1 trial to receive nivolumab plus glycoprotein 100 peptide vaccine, but after one dose, severe toxicity developed leading to the termination of treatment
- In 2013, the patient was enrolled in a phase 1, multicenter, nonrandomized, open-label, dose escalation study of DAY101 (NCT01425008)
- Initially, DAY101 was administered at a 200 mg dose every other day
  - Rash, thrombocytopenia, and peripheral edema developed in response to DAY101 treatment, and the dose was decreased to 140 mg weekly, which was tolerated well by the patient
- In a remarkable response, all skin lesions resolved, and a biopsy in November 2017 revealed only pigmentation, with no evidence of disease
- DAY101 treatment was maintained beyond the clinical trial under a compassionate use protocol as the patient continued to demonstrate clinical benefit
- As of 20 July 2021, she has received DAY101 for 8+ years with a sustained CR
- The only adverse event reported with the 140 mg/QW dose is a mild intermittent grade 1 rash

Figure 3. Resolution of skin lesions in response to DAY101

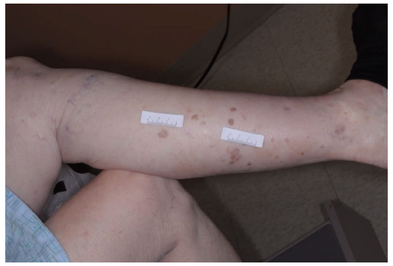
Baseline



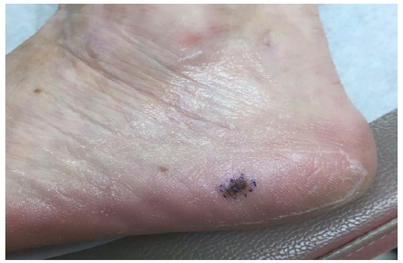
1-year treatment



2-year treatment



4-year treatment



Conclusions

- The rapid and long-term response and tolerability to monotherapy with DAY101 in a heavily pretreated patient with *NRAS*-mutated melanoma provides evidence that targeting wild-type RAF downstream of mutated *NRAS* may be an effective strategy to block tumor growth
- DAY101 may be a potentially effective treatment option for patients with melanoma harboring *NRAS* mutations
- FIRELIGHT is an open-label, phase 1/2 umbrella study (NCT04985604) investigating the efficacy and safety of DAY101 in patients ≥12 years of age, including patients with melanoma, with recurrent or progressive solid tumors with alterations in the key components of the MAPK signaling pathway:
  - Patients with a BRAF fusion are currently eligible for enrollment to receive DAY101 as monotherapy
  - A sub-study to treat patients with alterations in the MAPK pathway with DAY101 in combination with pimasertib, a MEK inhibitor, is planned for 2022

References

1. Ji Z, et al. *Trends Mol Med.* 2012;18:27-35.
2. Sun Y, et al. *Neuro Oncol.* 2017;19:774-85.
3. Olszanski AJ, et al. *Ann Oncol.* 2017;28(suppl. 5):136