# メラノーマに対する併用療法による過去最長の生存期間（Abstract: LBA9003）

## IpilimumabとnivolumabのIpilimumabの併用免疫療法は進行メラノーマの長期生存を達成する

## Combination immunotherapy with ipilimumab and nivolumab achieves long-term survival for patients with advanced melanoma

拡大第I相試験の長期追跡結果から、進行メラノーマ患者に対するipilimumabとnivolumabの同時併用療法が約3年半（40か月）という前例のない生存期間中央値を生み出した、と第50回American Society of Clinical Oncology学会のLate Breaking Clinical Trial sessionで発表された。この併用療法により、どちらかの薬剤を用いた単剤療法の過去のスタディで認められた全生存期間中央値が、ほぼ2倍になった。全体で、切除不能stage IIIまたはIVのメラノーマ患者53人中22人（41%）に奏効を認め、9人（17%）は完全寛解した。腫瘍縮小は迅速かつ広範囲であった—42%の患者が第36週までに80%超の腫瘍縮小を示した—持続的な奏効は、解析時点で22人中18人（82%）に認められた。全ての用量で、1年および2年全生存率中央値は、それぞれ85%および79%であり、生存期間中央値は39.7か月であった。臨床的奏効は*BRAF*変異やPD-L1発現の有無に関係なく認められた。副作用はほぼ全ての患者で、対処可能かつ可逆性であった。

## Full Text

Long-term follow-up results from an expanded phase I study show that concurrent treatment with ipilimumab and nivolumab produces an unprecedented median survival of roughly three and a half years (40 months) for patients with advanced melanoma. In the study, the combination treatment nearly doubled the median overall survival found in previous studies of either agent alone.

"Just a few years ago, median survival for patients diagnosed with advanced melanoma was as little as a year or less, and only approximately 20-25 percent survived two years, so it's truly remarkable that we're seeing a median survival over three years in this trial. Even in the latest era of targeted and immunotherapy agents, the median survival is on average only about 16-18 months with any new treatment alone," said lead study author Mario Sznol, M.D., a professor of medical oncology at Yale School of Medicine in New Haven, CT. "While we're encouraged by what we're seeing with the use of these two drugs together, this trial was small, so a randomized phase III trial will be important to validate our initial results."

Nivolumab and ipilimumab are antibody drugs that target and block two different "gatekeepers" or checkpoints (PD-1 and CTLA-4, respectively) on T cells, disarming the tumor's defense against the immune system and boosting the immune system's ability to fight melanoma. Ipilimumab is FDA-approved for the treatment of metastatic melanoma. Lasting antitumor effects have been observed with nivolumab as a single-agent therapy.

In the study, 94 patients with inoperable stage III or IV melanoma who had undergone up to three prior systemic therapies received concurrent treatment with ipilimumab and nivolumab. Approximately 53 percent of patients had very advanced disease (stage M1c), and 55 percent had no prior systemic treatments.

Long-term follow-up data on the 53 patients enrolled in the initial four concurrent dosing cohorts are being reported. Those patients received ipilimumab and nivolumab every three weeks for four cycles, followed by nivolumab alone every three weeks for four cycles. At week 24, patients who did not have disease progression or severe side effects could continue nivolumab plus ipilimumab every 12 weeks for eight cycles.

Overall, 22 out of 53 patients (41 percent) responded to the treatment, and nine (17 percent) had complete remissions. Tumor shrinkage was rapid and extensive — 42 percent of the patients had a greater than 80 percent tumor reduction by week 36 — and the responses were durable, with 18 of 22 responses (82 percent) ongoing at time of analysis. Across doses, the one-year and two-year median overall survival rates were 85 percent and 79 percent, respectively, and the median survival duration was 39.7 months. (At the nivolumab 1 mg/kg and ipilimumab 3 mg/kg dose being tested in an ongoing phase II/III trial, one- and two-year overall survival rates were 94 and 88 percent, respectively). The rate of side effects related to induction of immune reactivity against normal tissues was higher than previously observed for either single agent, but side effects were manageable and reversible in almost all patients.

Clinical responses were seen regardless of tumor *BRAF* mutation status or PD-L1 status, and across all dose levels. According to the authors, the activity of the combination in the PD-L1 negative subgroup was higher than observed in prior trials of nivolumab alone, and therefore supports the observation that the combination is more effective than nivolumab by itself. In addition, the authors stated, if the activity is validated in the phase III trial, patients with melanomas that test positive for a *BRAF* mutation would have an even more effective immunotherapy option in addition to targeted therapy for treatment of their disease.

Researchers will continue following patients in all cohorts of this study, including a separate cohort of 41 patients who received the combination treatment every three weeks for four cycles, followed by nivolumab alone every two weeks for up to two years. A separate, ongoing phase III study comparing nivolumab plus ipilimumab versus nivolumab or ipilimumab alone, and a phase II randomized study comparing nivolumab plus ipilimumab to ipilimumab alone, completed accrual; findings have not yet been reported.

"Anti CTLA-4 and anti PD1 single-agent therapies for metastatic melanoma have made significant contributions in recent years. This study combines the two checkpoint inhibitors concurrently in efforts to improve clinical outcomes further," said Steven O'Day, M.D., ASCO Expert. "This update on the initial group of 53 patients treated with ipilimumab and nivolumab confirm continued excitement, with remarkable clinical benefit and longer survival than we've typically seen. Phase III trials will be necessary to determine the benefit of combination checkpoint therapy versus sequential single-agent therapy and delineate the price of additional toxicities."

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