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# Combination of nivolumab with radiotherapy for non-small cell lung cancer

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Συνδυασμός νιβολουμάμπης με ακτινοθεραπεία  
σε μη μικροκυτταρικό καρκίνο του πνεύμονα

Περίληψη στο τέλος του άρθρου

**Key words:** Nivolumab, Non-small cell lung cancer, Radiotherapy

Cancer is an individual disease, although more than 100 types of cancers are known, and standardized approaches to certain types of cancers are applied whenever possible. It is not surprising that, since the DNA of any human being on earth resembles that of no other, people show different responses to similar treatments. With the advancement of technology, new treatment methods are being developed in addition to the current established forms of treatment. Acceptable standard chemotherapy, radiotherapy (RT) and surgery are applied, and in addition to vaccines, immunotherapy has been used in an increasing number of gene and molecular targeted therapies. Newly developed targeted treatment approaches focus on inhibiting critical molecular pathways in tumor growth and development, and immunotherapy targeting the programmed cell death 1/programmed death-ligand 1 [PD1/PD-L1] pathway acts by blocking the recognition by the immune system of tumor cells.<sup>1-3</sup>

Nivolumab (Opdivo), an immunotherapy drug, is a recombinant humanized monoclonal IgG4 antibody. Cytotoxic T is an immune checkpoint inhibitor that is developed against

PD-1, which prevents T cells from affecting cancer cells by suppressing the activation and proliferation of T lymphocytes. It has become part of the clinical routine in diseases such as unresectable or metastatic melanoma, non-small cell lung cancer (NSCLC), metastatic renal cell carcinoma, recurrent or metastatic squamous cell head and neck cancers with progressive progression following platinum-based chemotherapy, and lymphoma. Nivolumab treatment provides patients with increased life expectancy and better prognosis regarding the most common side effects, such as fatigue, nausea, itching, diarrhea and loss of appetite.<sup>1-5</sup>

Lung cancer is the main cause of cancer mortality. Even aggressive treatment with surgery, RT and chemotherapy offers a low chance of long survival, and there is a need to develop new therapeutic strategies, including anti-tumor immunotherapy. Significant advances have been made in immunotherapy for lung cancer, where a large number of mutations play a role in its etiopathogenesis. Combined therapies with nivolumab have been started to be investigated in trials with standard forms of treatment. In a study examining the use of nivolumab and docetaxel in patients with NSCLC, the mean survival was 9.2 months with nivolumab and 6.0 months with docetaxel; disease-free survival was 3.5 months and 2.8 months, respectively. The treatment-related rate of side effects was 7% in the nivolumab and 55% in the docetaxel group. In addition, the risk of death in the nivolumab group was 41% lower than in the docetaxel group.<sup>3</sup> In another study, patients who were given nivolumab for advanced or postoperative recurrent NSCLC were analyzed. The rates of response to treatment and disease control were found to be 20% and 60%, respectively. Mean disease-free survival and survival time were 115 days and 126 days, respectively. Concerning side effects, two patients had dermatitis, general fatigue and drug-induced pneumonia. The authors stated that nivolumab is effective and safe in the treatment of lung cancer.<sup>4</sup>

In NSCLC, a combination of nivolumab with RT has started to be tested, but the interaction of radiation with

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the immune system is unclear. There are promising results from case reports and preclinical studies investigating the combination of immunotherapy and thoracic RT, but there is only a limited number of studies available to guide us in the safety of combination therapy.<sup>5-8</sup> Investigation was conducted of pneumonia and non-hematological toxicity in patients with stage 4 NSCLC who received nivolumab and stereotactic RT. While partial and complete response was observed in three patients, grade 3 pneumonia was observed in one patient. Combined use has been reported to be safe.<sup>5</sup> In another study evaluating combined use, 1-year overall survival rates were 57.8% in patients treated with RT-nivolumab and 27.4% in patients treated with nivolumab only ( $p=0.043$ ) and 1-year progression-free survival was 57.8% and 20.6%, respectively ( $p=0.040$ ). There was no difference in the rate of acute toxicity, and it was reported that combined use increases overall survival and disease-free survival.<sup>6</sup> In another study examining the combined use of nivolumab in patients with lung cancer who required palliative RT, serious or unexpected side effects that may occur due to nivolumab and any irradiation method (hypofractionated stereotactic RT, stereotactic radiosurgery, intensity-modulated RT, or three-dimensional conformal RT) were reported to be unrelated.<sup>7</sup> No difference was reported in the rate of side effects (pneumonitis, esophagitis and dermatitis) of grade 2 and above in simultaneous or sequential use of thoracic RT and immunotherapy, and concurrent immunotherapy and thoracic RT were considered to be safe.<sup>8</sup>

As a result of the above review, it appears that many studies show that nivolumab, which is an immunotherapy drug, is highly effective in the treatment of NSCLC, significantly prolonging both overall survival and disease-free survival when combined with RT/chemotherapy. When the advantages and disadvantages of RT and immunotherapy are evaluated, it can be seen that combined therapy may be more beneficial, but extensive studies on this subject are needed.

## ΠΕΡΙΛΗΨΗ

### Συνδυασμός νιβολουμάμπης με ακτινοθεραπεία σε μη μικροκυτταρικό καρκίνο του πνεύμονα

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Μελέτες δείχνουν ότι το ανοσοθεραπευτικό φάρμακο νιβο-

λουμάμπη (nivolumab) είναι εξαιρετικά αποτελεσματικό στη θεραπεία του μη μικροκυτταρικού καρκίνου του πνεύμονα και ότι παρατείνει σημαντικά τόσο τη συνολική επιβίωση όσο και την επιβίωση χωρίς νόσο όταν συνδυάζεται με παράγοντες ακτινοθεραπείας/χημειοθεραπείας. Όταν αξιολογηθούν τα πλεονεκτήματα και τα μειονεκτήματα της ακτινοθεραπείας και της ανοσοθεραπείας, μπορεί να φανεί ότι η συνδυασμένη θεραπεία ενδέχεται να είναι περισσότερο ωφέλιμη, αλλά απαιτούνται μεγαλύτερες μελέτες.

**Λέξεις ευρητηρίου:** Ακτινοθεραπεία, Μη μικροκυτταρικός καρκίνος πνεύμονα, Νιβολουμάμπη

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