Research Article Open Acces

# *NNVOP 5IFSBQZ JO -VOH $BODFS )PX %PFT $BODFS $IBOHF 1BUJFOUT’ 7JTJPO

Tshetiz Dahal*

General Physician, Lugansk State Medical University, Luhansk Oblast, 93000 Luhansk, Ukraine

## Abstract

Survival rates of metastatic lung cancer including non-small cell lung cancer (NSCLC) and poor lung cell cancer (SCLC) are poor with a survival rate of less than 5%. The use of cell-oriented therapies has improved the overall survival of the median (OS) in a limited group of NSCLC patients whose tumors undergo certain genetic mutations. However in a large group of NSCLC and SCLC cell mutations are not available to lead to targeted treatment. Recent positive results from new medical research and checkpoint inhibitors have proven against the common belief that lung cancer is not immune. In particular, checkpoint inhibitors targeting the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the proposed death-1 pathway (PD-1) have shown long-term clinical responses with controlled toxicity.

6HYHUDO SKDVH ,, DQG ,,, FOLQLFDO WULDOV H[DPLQLQJ WKH FRPELQDWLRQ LPPXQR WKHUDS\ RU LPPXQR WKHUDS\ DORQH FRQWLQXH ZLWK OXQJ FDQFHU DO near future. However, further research is needed to understand the appropriate combination of immuno-therapeutic agents with chemotherapy and radiation therapy for NSCLC and SCLC.

*Corresponding author: Tshetiz Dahal, General Physician, Lugansk State Medical University, Luhansk Oblast, 93000 Luhansk, Ukraine, Tel: +380506266617; E-mail: dahaltshetiz21@gmail.com

Received: 31-Jan-2022, Manuscript No: JCD-22-52992, Editor assigned: 02-Feb-2022, PreQC No: JCD-22-52992 (PQ), Reviewed: 16-Feb-2022, QC No: JCD-22-52992, Revised: 21-Feb-2022, Manuscript No: JCD-22-52992(R), Published: 3-Mar-2022, DOI: 10.4172/2476-2253.1000140

Citation: Dahal T (2022) Immuno-Therapy in Lung Cancer - How Does Immuno-Therapy For Lung Cancer Change Patients’ Vision? J Cancer Diagn 6: 140.

advanced lung cancer screening. Fortunately; antibody-based cancer treatment helps improve the chances of a longer life for patients with lung cancer. Until recently; the most common treatments for lung cancer included surgery; chemotherapy; and radiation. Since most patients with lung cancer are diagnosed with advanced disease (stage 3b / 4); these treatments are likely not to result in complete treatment; although they can signi cantly improve survival and provide symptom relief.

In 2015; the US FDA approved the  rst immuno-therapy to treat a subset of patients with lung cancer. Immuno-therapy is a medical class that helps the human immune system to  ght or control cancer. Recent clinical research that treats patients with immuno-therapy; either alone or in combination with other therapies; has shown signi cant patient improvement; which has led to FDA approval for a few alternative therapies for many lung cancer patients; including authorization to treat patients with immuno-therapy as a  rst line. Treatment instead of conventional treatment.

## Target Antibodies

Amivantamab (Rybrevant ™): a bi-speci c antibody that regulates EGFR and MET receptors in tumor cells; authorized categories of patients with non-small cell lung cancer for non-small cell lung cancer.

Bevacizumab (Avastin®): a monoclonal antibody that regulates the VEGF / VEGFR pathway and inhibits the growth of tumor blood vessels; authorized categories of patients with non-small cell lung cancer for non-small cell lung cancer; including  rst-line treatment.

Necitumumab (Portrazza®): a monoclonal antibody that regulates the EGFR pathway; authorized categories of patients with non-small cell lung cancer non-small cell lung cancer; including  rst-line treatment.

Ramucirumab (Cyramza®): a monoclonal antibody that regulates the VEGF / VEGFR2 pathway and inhibits the growth of tumor blood vessels; authorized categories of patients with non-small cell lung cancer for non-small cell lung cancer; including  rst-line treatment.

## Immuno-modulators

Atezolizumab (Tecentriq®): a checkpoint inhibitor that directs the path of PD-1 / PD-L1; approved for patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC); which includes as a  rst-line treatment combined with chemotherapy.

Cemiplimab (Libtayo®): a checkpoint inhibitor that directs the path of PD-1 / PD-L1; authorized set of patients with non-small cell lung cancer (NSCLC)

Dostarlimab (Jemperli): a checkpoint inhibitor that directs the path of PD-1 / PD-L1; authorized categories of patients with advanced lung cancer with a de ciency of DNA modi cation (dMMR)

Durvalumab (In uence®): a checkpoint inhibitor that directs the path of PD-1 / PD-L1; authorized for patients with non-stage stage III lung cancer (NSCLC) who have completed chemo-radiation treatment; and for patients with advanced stage cancer (SCLC) who have been treated with chemotherapy.

A checkpoint inhibitor that directs the CTLA-4 route; approved; in combination with nivolumab; as a  rst-line treatment; both with or without chemotherapy; in patients with non-small cell lung cancer .097 Tw -1ed with
or withoe with withoebtientsa6nO( apyObgient directs the )Tj 0.023[(stage IaC) wh )Tj 0.1495 -1.2 Td (p Ed5r(N((o)d-1.2 Td (pTj  line1wamb

completed enrollment of more than 500 patients during 2012. e results of this study are awaited.

## EGF vaccine

e EGFR pathway is critical to the growth and development of NSCLC. High EGFR expression is common in NSCLC and EGFR mutation is associated with a response to EGFR tyrosine kinase inhibitors of the inner part of this receptor [28, 29]. e EGF vaccine (CIMAvax EGF) was developed in Cuba and contains human regenerated EGF mixed with network protein found in Neisseria Meningitides and immuno-adjuvant [30]. In a phase II study; 80 patients with phase III B-IV NSCLC previously treated with rst-line plasma chemotherapy were randomly assigned to 1: 1 to receive EGF vaccine and BSC or BSC alone [9]. A er cyclophosphamide treatment (200 mg / m2); patients in the vaccination group received the vaccine on days 1; 7; 14; 28 and monthly therea er [9]. e tendency to increase survival was observed in all vaccinated patients compared with controls; and the di erence was statistically signi cant (P = 0.0124) in the subgroup at <60 years of age (an average OS of 11.5 months of vaccinated patients compared to 5.3 months of control). e vaccine was well tolerated; with less than 25% of patients experiencing adverse events and no grade 3 or 4 episodes were noted. e analysis of the subgroup indicates the predictable number of humeral immune reaction. Patients with anti-EGF antibody titers 1: 4000 and at least four times their pre-vaccinated doses have an average OS of 11.7 months compared to 3.6 months for those with no immune response.

Building on these results; a phase III international study completed the enrollment of 579 patients with advanced NSCLC who had stable or responsive disease a er the start of platinum doublet chemotherapy [31]. Based on the evaluation analysis from a phase II study that suggests that younger patients may receive additional bene ts from EGF vaccination; enrollment in phase III studies is limited to patients aged 20-65 years. E ective results from this study are expected in late 2013. is policy is currently licensed in Cuba for use in phase IIIB / IV NSCLC.

## TG4010

TG4010 is a recombinant viral vector that combines the genetically modi ed Ankara virus that has been genetically modi ed to produce MUC1 and interleukin-2 (IL-2) [32]. IL-2 has been implicated in immuno-adjuvant because it is able to reverse the suppression of the MUC1 [33] cancer-associated T-cell response. In a phase II study; cisplatin / gemcitabine chemotherapy rst-line was randomly assigned with or without TG4010 to 148 untreated advanced NSCLC patients with tumors expressing MUC1 by immunohistochemistry [10]. e vaccine was given under the skin each week for 6 weeks and then every 3 weeks until the disease progressed to the main end of the six-month PFS with a target of 40% or more in the experimental group. e addition of TG4010 appears to enhance the e ect of chemotherapy with a survival rate of no more than six months of 43% (95% CI: 33-54%) in TG4010 and a group of chemotherapy and 35% (95% CI: 26-45 %) in the chemotherapy group only. e Median OS was not statistically di erent between the groups. Speci c analysis of cellular immune response to MUC1 did not show signi cant di erences between vaccinated and non-vaccinated patients. However; experimental analyzes have suggested that elevated levels of activated cells that kill the environment (anNK) may prevent the vaccine response. In fact; the median OS was 18 months in patients with normal levels of aNK cells; while it was 11.3 months in those with high levels of aNK cell (P = 0.02). e authors speculate that in addition to their role in tumor e cell death; NK cells also inhibit an autoimmune immune response if present at very high levels. In January 2012; a phase IIB / III study of TG4010 was initiated; comparing dual chemical treatment of platinum with TG4010 and only chemotherapy with the primary end-stage OS phase III [34]. In the IIB section; the predictive role of aNK will be assessed based on the PFS terminal. Patients enrolled in this study wi receive weekly subcutaneous injection or placebo within the rst six weeks of chemotherapy followed by injections once every three weeks until the disease progresses [34].

Obstruction of the immune system: ere are many experimental molecules that reduce the T-cell's immune response to antigen expressed by tumor cells [35]. Monoclonal antibodies interacting with two of these molecular mechanisms; PD-1 and CTLA-4; demonstrated activity in the enhanced NSCLC. Obstruction of the immune system is of great interest because some patients with advanced tumors appear to receive unusually long-term bene ts; this has been clearly demonstrated in metastatic melanoma; in which approximately 5-8% of patients will live for many years with stable or responsive disease a er anti-CTLA-4 antibody treatment [36, 37].

## Anti-CTLA-4

Monoclonal antibodies against CTLA-4 are designed to block interactions between CTLA-4 and its ligands (CD80 / CD86) resulting in blockade of the CTLA-4 inhibitory signal and enhanced activation and proliferation of speci c tumor T-cells ; thus allowing an e ective immune response against the tumor [38]. A comprehensive study of Ipilimumab for advanced melanoma has led to controlled authorization demonstrating survival bene ts in phase III clinical trials [36, 37]. For ung cancer; a large blind phase II study assigned 204 patients with advanced NSCLC and randomized SCLC patients 1: 1: 1 in one arm: three standard carboplatin / paclitaxel chemotherapy and placebo; Ipilimumab at a time. One (four doses of Ipilimumab and paclitaxel and carboplatin followed by two doses of placebo and paclitaxel and carboplatin); or Ipilimumab divided into doses (two doses of placebo plus paclitaxel and carboplatin followed by doses four of Ipilimumab plus paclitaxel and carboplatin) [11]. Treatment was done by injection every 3 to 18 weeks. Patients with stable disease or tumor respons er four cycles of chemotherapy continued receiving Ipilimumab or placebo injections every three months until the disease progressed. e dose of Ipilimumab used in this study was higher than that allowed for melanoma (10 vs. 3 mg / kg).

NSCLC results are reported separately in the SCLC collection. e results of SCLC patients are reported in the SCLC section of this review paper. is study was new to the rst reported phase II study to accept the immune-related PFS (irPFS) as its primary endpoint; de ned as the time from random allocation to immunity-related progression or death. In fact; observations made in clinical trials of melanoma indicate di erences in the pattern of responses in immuno-therapies compared with those in cytotoxic agents [39]. With the prevention of immune checkpoint; a number of patients initially showed progressive illness with the Traditional Solid Tumors Response Policy (RECIST) followed by delayed immuno-therapy response and in some cases long-term survival [40]. e second conclusions of the phase II study of Ipilimumab in NSCLC included a modi ed World Health Organization response module; PFS; OS; and other immune-related response mechanisms. In the NSCLC; the study met its main objective of the enhanced irPFS of the divided Ipilimumab (HR: 0.72; P= 0.05) compared with controls; whereas interestingly this was not the case compared with the same Ipilimumab (HR: 0.81; P = 0.13) and

control.  e reason why one dose of Ipilimumab administration has caused signi cant statistical di erences; while the other is unclear and annoying. Hypotheses suggest that a phased state regime allows for a signi cant short-term sequence of chemical antigen release before Ipilimumab treatment or the fact that simultaneous chemotherapy can reduce lymphocyte counts and thus reduce Ipilimumab activity at a critical time. Separated ipilimumab; compliant Ipilimumab; and control arms were associated with irPFS intervals of 5.7; 5.5 and 4.6 months; and an intermediate OS of 12.2; 9.7 and 8.3 months; respectively. Subset

a di erent e ect and found that former / current smokers had an ORR of 26% (n = 43) compared with 10% of non-smokers (n = 10) [51, 53]. Currently a multi-arm phase I trial is continuing to test nivolumab in combination with cisplatin / gemcitabine; cisplatin / pemetrexed; carboplatin / paclitaxel; erlotinib (EGFR in patients with poor NSCLC mutations); or Ipilimumab as mono-therapy for patients receiving treatment. -naïve class IIIB or IV NSCLC as a post-chemical nutritional therapy combined with bevacizumab [54].

## Immuno-therapy in SCLC

Few immuno-therapy trials were performed at SCLC. e BEC2 / BCG vaccine (Bacillus Chalmette-Guerin) was extensively studied in SCLC over the past decade based on the fact that BEC2 is a monoclonal antibody that mimics GD3; a glycosphingolipid antigen that is highly expressed in SCLC but rarely in normal tissue [55]. When BSG was combined with GD3 three out of fourteen patients developed antibodies against GD3 [56]. BEC2 / BCG showed promising results in the rst clinical trial in SCLC [57]; however; a large European trial by Giacco et al. [55] showed no statistically signi cant di erence in the average OS in 515 patients with moderate SCLC (16.4 months with BSC and 14.3 months with BEC2 / BCG; HR = 1.12; 95% CI: 0.91-1.371) (Table 2).

e combined Ipilimumab schedule (two cycles of chemotherapy and placebo followed by four cycles with Ipilimumab) but not the Ipilimumab schedule (four cycles of chemotherapy and Ipilimumab followed by two cycles with placebo) improved irPFS against and control over the wider phase of the SCLC phase II team. Randomized double-blind randomized controlled trials associated with carboplatin / paclitaxel chemotherapy (HR: 0.64; P = 0.03) [56]. Ipilimumab combined with platinum-topside chemotherapy against platinum-topside alone is currently being evaluated in a phase III clinical trial in patients with a broad stage of SCLC in order to improve T cell responses and increase OS [58]. Clinical trials of phase I / II of Nivolumab alone or combined with Ipilimumab are currently concentrating in patients with solid tumors that include SCLC for a broader stage a er the rst line of chemotherapy [59]. ere are many challenges to improving immunode ciency treatment in SCLC which includes a signi cant burden of disease and a lack of speci c goal-based treatment. In addition; the response to immuno-therapy takes time. In extended SCLC infections patients have severe clinical deterioration with a rapidly developing disease that may not allow time to incorporate the proper immune response. erefore; the timing and timing of immuno-therapy in relation to other therapies; in particular chemotherapy represents an important tool for facilitating disease control and improving immune response.

## Radiation and immuno-therapy

e abs copal e ect is mediated by the immune system where radiation provides the release of antigen that stimulates immune cells to cause tumor cell death outside the radiation site [60]. ese impressive system responses have become increasingly evident amon

e ects of anti-CTLA-4; PD-1; and PDL-1 drugs to improve abs copal e ects when used in combination with limited radiation; where the radiation can be used to give antigen. Reactivate and assist in initiating the immune response; which may improve the response rate in remote areas of non-radioactive disease. ere are many ongoing trials examining the role of immuno-therapy in the treatment of lung cancer. Recent studies of novel agents; particularly checkpoint inhibitors; have shown the rst promising results in achieving sensible and robust therapeutic responses that are toxic. To identify patient communities that can bene t the most from treatment with immuno-therapeutic agents and to determine the best duration of patient immuno-therapy treatment; at present; are the most important challenging questions that need to be answered. e combination of chemotherapy and / or radiation therapy with immuno-therapy and duration of treatment needs to be further investigated. Immuno-therapy trials a er stereotactic ablative radiation therapy have recently revealed encouraging responses that will need to be re-evaluated in clinical trials. Finally a combination of two major groups of immuno-therapy; antigen-speci c vaccines and immuno modulatory agents; may have synergistic e ects in increasing the anti-tumor immune response.

## Conclusion

e use of cell-oriented therapies has improved the overall survival of the median (OS) in a limited group of NSCLC patients whose tumors undergo certain genetic mutations, have shown a positive results. New medical research and checkpoint inhibitors have proven against the common belief that lung cancer is not immune. In particular, checkpoint inhibitors targeting the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the proposed death-1 pathway (PD-1) have shown long-term clinical responses with controlled toxicity.

References


1. Siegel R, Naishadham D, Jemal A (2013) Cancer statistics 2013. CA Cancer J Clin 63:11-30.
2. Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, et al. (2005) Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst 97:339-346.
3. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, et al. (2010) Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 363:1693-1703.
4. Holt GE, Podack ER, Raez LE (2011) Immunotherapy as a strategy for the treatment of non-small-cell lung cancer. Therapy 8:43-54.
5. Vansteenkiste J, Zielinski M, Linder A, Dahabreh J, Gonzalez EE, et al. (2013) Adjuvant MAGE-A3 immunotherapy in resected non-small-cell lung cancer: phase II randomized study results. J Clin Oncol 31:2396-2403.
6. Butts C, Murray N, Maksymiuk A, Goss G, Marshall E, et al. (2005) Randomized

phase IIB trial of BLP25 liposome vaccine in stage IIIB and IV non-small-cell lung cancer. J Clin Oncol 23:6674-6681.

7. Butts C, Maksymiuk A, Goss G, Soulières D, Marshall E, et al. (2011) Updated survival analysis in patients with stage IIIB or IV non-small-cell lung cancer receiving BLP25 liposome vaccine (L-BLP25): phase IIB randomized, multicenter, open-label trial. J Cancer Res Clin Oncol 137:1337-1342.

8. Nemunaitis J, Dillman RO, Schwarzenberger PO, Senzer N, Cunningham C, et al. (2006) MPhase II study of belagenpumatucel-L, a transforming growth factor EHWD DQWLVHQVH JHQH PRGL¿HG DOORJHQHLF WXPRU FHOO YDFFLQH LQ QRQ VPDOO FHOO lung cancer. J Clin Oncol 24:4721-30.

9. Vinageras EN, de-la-Torre A, Rodriguez MO, Ferrer MC, Bravo I, et al. (2008) Phase II randomized controlled trial of an epidermal growth factor vaccine in advanced non-small-cell lung cancer. J Clin Oncol 26:1452-1458.

10. Quoix E, Ramlau R, Westeel V, Papai Z, Madroszyk A, et al. (2011) Therapeutic YDFFLQDWLRQ ZLWK 7* DQG ¿UVW OLQH FKHPRWKHUDS\ LQ DGYDQFHG QRQ VPDOO cell lung cancer: a controlled phase 2B trial. Lancet Oncol 12:1125-1133.

11. Lynch TJ, Bondarenko I, Luft A, Serwatowski P, Barlesi F, et al. (2012) [illegible]

49. ClinicalTrials.gov Study of BMS-936558 compared to docetaxel in previously treated advanced or metastatic squamouscell non-small cell lung cancer (NSCLC) (Checkmate 017).

50. Grosso J, Horak CE, Inzunza D, et al. (2013) Association of tumor PD-L1