MINIREVIEWS

729 Hyperprogression under treatment with immune-checkpoint inhibitors in patients with gastrointestinal cancer: A natural process of advanced tumor progression?
Wang MX, Gao SY, Yang F, Fan RJ, Yang QN, Zhang TL, Qian NS, Dai GH

ORIGINAL ARTICLE

Retrospective Study
738 Whipple’s pancreaticoduodenectomy at a resource-poor, low-volume center in Trinidad and Tobago
Cawich SO, Thomas DA, Pearce NW, Naraynsingh V

Observational Study
748 Factors predicting upstaging from clinical N0 to pN2a/N3a in breast cancer patients

LETTER TO THE EDITOR

758 Neoadjuvant immunotherapy in non-small-cell lung cancer: Times are changing—and fast
Aguado C, Maestre UJ, Mielgo-Rubio X
### AIMS AND SCOPE

The primary aim of *World Journal of Clinical Oncology* (WJCO, *World J Clin Oncol*) is to provide scholars and readers from various fields of oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJCO* mainly publishes articles reporting research results and findings obtained in the field of oncology and covering a wide range of topics including art of oncology, biology of neoplasia, breast cancer, cancer prevention and control, cancer-related complications, diagnosis in oncology, gastrointestinal cancer, genetic testing for cancer, gynecologic cancer, head and neck cancer, hematologic malignancy, lung cancer, melanoma, molecular oncology, neurooncology, palliative and supportive care, pediatric oncology, surgical oncology, translational oncology, and urologic oncology.

### INDEXING/ABSTRACTING

The *WJCO* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 Journal Citation Indicator (JCI) for *WJCO* as 0.35.

### RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Xiang-Di Zhang; Production Department Director: Xu Guo; Editorial Office Director: Yu-Jie Ma.

### NAME OF JOURNAL

*World Journal of Clinical Oncology*

### ISSN

ISSN 2218-4333 (online)

### LAUNCH DATE

November 10, 2010

### FREQUENCY

Monthly

### EDITORS-IN-CHIEF

Hiten RH Patel, Stephen Safe, Jian-Hua Mao, Ken H Young

### EDITORIAL BOARD MEMBERS

https://www.wjgnet.com/2218-4333/editorialboard.htm

### PUBLICATION DATE

September 24, 2022

### COPYRIGHT

© 2022 Baishideng Publishing Group Inc

### INSTRUCTIONS TO AUTHORS

https://www.wjgnet.com/bpg/gerinfo/204

### GUIDELINES FOR ETHICS DOCUMENTS

https://www.wjgnet.com/bpg/gerinfo/287

### GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

https://www.wjgnet.com/bpg/gerinfo/240

### PUBLICATION ETHICS

https://www.wjgnet.com/bpg/gerinfo/288

### PUBLICATION MISCONDUCT

https://www.wjgnet.com/bpg/gerinfo/208

### ARTICLE PROCESSING CHARGE

https://www.wjgnet.com/bpg/gerinfo/242

### STEPS FOR SUBMITTING MANUSCRIPTS

https://www.wjgnet.com/bpg/gerinfo/239

### ONLINE SUBMISSION

https://www.ffpublishing.com
Neoadjuvant immunotherapy in non-small-cell lung cancer: Times are changing—and fast

Carlos Aguado, Unai Jiménez Maestre, Xabier Mielgo-Rubio

Abstract
Recent data from a phase 3 trial have shown that the addition of immunotherapy to neoadjuvant chemotherapy improves event-free survival in patients with non-small-cell lung cancer (NSCLC). This is the first positive phase 3 trial in this setting, although several phase 3 trials are currently investigating the efficacy of neoadjuvant and adjuvant immunotherapy in resectable NSCLC.

Key Words: Neoadjuvant; Immunotherapy; NSCLC; Perioperative; Checkmate-816; nivolumab; Chemo-immunotherapy

Core Tip: Recent data from a phase 3 trial show that the addition of immunotherapy to neoadjuvant chemotherapy in patients with non-small-cell lung cancer (NSCLC) improves pathologic complete response and event-free survival. This is the first positive phase 3 trial in this setting, although several other phase 3 studies are currently investigating the efficacy of neoadjuvant and adjuvant immunotherapy in resectable NSCLC. We describe the results of the CheckMate-816 phase 3 trial, which found that neoadjuvant chemoinmunotherapy was superior to chemotherapy alone. We also briefly review the main phase 3 studies currently underway to evaluate the role of immunotherapy in the perioperative setting of NSCLC.
TO THE EDITOR

The management of localized non-small-cell lung cancer (NSCLC) is set to undergo an important change in the first few months of this year (2022) due to the recent publication of the second primary endpoint—event-free survival (EFS)—from the Checkmate-816 trial. The data show that the combination of chemotherapy + nivolumab yielded a mean disease-free survival of 31.6 m in the experimental arm vs 20.8 m [hazard ratio (HR): 0.63] in the control arm (chemotherapy alone), with a 2 year-EFS rate of 64% vs 45%, respectively [1]. These results, in addition to previously reported results showing an improvement in pathological complete response (pCR) of 24% vs 2%, confirm the combination of three cycles of chemotherapy + neoadjuvant nivolumab as the new standard of care in resectable NSCLC [2].

This is the first time that pCR has been validated as a surrogate marker for survival in a randomized trial. In the experimental arm, the median EFS was 26.6 m in patients without pCR and not reached in those with pCR (HR: 0.13). Although the results in terms of overall survival are still immature, a trend towards better survival was observed in the experimental arm, in which 12% more patients were alive at 2 years (HR: 0.57).

This new change in clinical practice comes with several questions that need be resolved in the next few years, including the following: The role of adjuvant therapy; the selection of the most suitable candidates; comparison with adjuvant chemoimmunotherapy; the optimal approach in stage I-II disease; standardization of pathological response assessment; and changes in the preoperative algorithm.

The perioperative management of NSCLC will undoubtedly undergo a major transformation in the coming years due to the arrival of targeted therapy in this clinical setting, mainly the incorporation of pre- or post-operative immunotherapy [3]. The CheckMate 816 study was the first phase 3 trial to report positive results for the addition of immunotherapy to neoadjuvant chemotherapy [1]. However, other ongoing phase 3 trials evaluating other PD-1 axis inhibitors are expected to report results soon, such as the Impower-030 trial [atezolizumab] [4], KeyNote-671 trial (pembrolizumab) [5], and the Aegean trial (durvalumab) [6] (Table 1). Likewise, atezolizumab has already obtained FDA approval for use in the adjuvant setting in patients with resected PD-L1 positive stage II-III A NSCLC [7], and positive results have also been reported from an interim analysis of the KeyNote-091 trial, showing the benefits of pembrolizumab in resected stage IB-IIIA NSCLC [8]. Nivolumab and durvalumab are also being evaluated in the adjuvant setting in several other phase 3 trials (ANVIL, NADIM-Adjuvant, Mermaid-1) [9-11] (Table 2). As a result, the panorama for the treatment of early-stage NSCLC is becoming increasingly interesting, and the data suggest that it will be crucial to personalize treatment to offer the best treatment scheme for each individual patient.

These new options bring hope of a cure to a greater number of patients, but also new challenges for the multidisciplinary team and other professionals involved in the treatment of these patients. Once again, coordinated multidisciplinary work will be essential, especially among medical oncology, thoracic surgery, and radiation oncology.

### Table 1 Main phase 3 trials evaluating neoadjuvant chemoimmunotherapy in non-small-cell lung cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>IO agent</th>
<th>Strategy</th>
<th>Objective</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate-816 [1]</td>
<td>Nivolumab (anti-PD1)</td>
<td>ChT + IO</td>
<td>EFS and pCR</td>
<td>FDA approved</td>
</tr>
<tr>
<td>KeyNote-671 [5]</td>
<td>Pembrolizumab (anti-PD1)</td>
<td>ChT + IO</td>
<td>EFS and OS</td>
<td>Active, not recruiting</td>
</tr>
</tbody>
</table>

IO: Immunotherapy; ChT: Chemotherapy; EFS: Event-free survival; pCR: Pathologic complete response; PFS: Progression-free survival; OS: Overall survival; FDA, Food and Drug Administration; NSCLC: Non-small-cell lung cancer.
Table 2 Main phase 3 trials evaluating adjuvant immunotherapy in non-small-cell lung cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>IO agent</th>
<th>Strategy</th>
<th>Objective</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>KeyNote-091 (PEARLS)[8]</td>
<td>Pembrolizumab (anti-PD-L1)</td>
<td>IO mono</td>
<td>DFS</td>
<td>Interim analysis: positive in IB-IIIA NSCLC all corners</td>
</tr>
<tr>
<td>ANVIL[9]</td>
<td>Nivolumab (anti-PD1)</td>
<td>IO mono</td>
<td>OS and DFS</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>NADIM-Adjuvant[10]</td>
<td>Nivolumab (anti-PD1)</td>
<td>ChT + IO</td>
<td>DFS</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

IO: immunotherapy; mono: monotherapy; OS: overall survival; NSCLC: non-small-cell lung cancer; DFS: disease-free survival; ChT: chemotherapy; MRD: minimal residual disease; FDA, Food and Drug Administration; NSCLC: Non-small-cell lung cancer.

FOOTNOTES

Author contributions: Aguado C, Maestre UJ, and Mielgo-Rubio X wrote and revised the letter.

Conflict-of-interest statement: All authors declare no conflict of interests related to this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Spain

ORCID number: Carlos Aguado 0000-0002-5624-8035; Unai Jiménez Maestre 0000-0001-5034-4723; Xabier Mielgo-Rubio 0000-0002-0985-6150.

REFERENCES


6 Heymach JV, Mitsudomi T, Harpole D, Aperghis M, Jones S, Mann H, Foud TM, Reck M. Design and Rationale for a Phase III, Double-Blind, Placebo-Controlled Study of Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant...


