Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

or how previous approvals will affect its adoption. When balancing the observed survival outcomes with adverse events across the IMpower133,[2] CASPIAN,[3] and CAPSTONE-1 trials,[4] it appears that four cycles of triplet induction therapy might suffice. Even though all three trials have improved survival outcomes, and patients with extended survival suggest that there might even be a survival tail in extensive-stage small-cell lung cancer, there is still much work to be done to improve outcomes for patients with extensive-stage small-cell lung cancer.[9] It is possible that the new transcriptome classifiers for small-cell lung cancer will intensify efforts to develop targeted therapies or improve selection of patients for immunotherapy.[10] One thing is for certain, we are slowly making progress against a recalcitrant disease.

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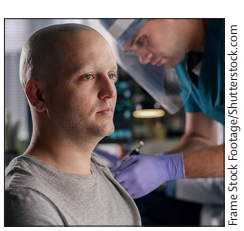
COVID-19 vaccine effectiveness in patients with cancer: remaining vulnerabilities and uncertainties

Patients with cancer are at an increased risk of serious complications and death from COVID-19, which is heightened by being aged 40 years or older, major medical comorbidities, poor performance status, the presence of haematological malignancies, and the receipt of immunosuppressive cancer therapies.[1–3] Early pivotal randomised trials of COVID-19 vaccines showed their high level of safety and efficacy, but excluded individuals on immunosuppressive therapies, which includes most patients with cancer, leaving uncertainty about vaccine efficacy and safety in this setting. Reduced humoral or cellular immune vaccine responses have been observed in patients receiving cancer chemotherapy or other immunosuppressive treatments, most notably in patients with multiple myeloma or other B-cell malignancies and in those receiving B-cell-depleting or cellular therapies.[4]

Evidence for a waning of antibody responses to COVID-19 vaccination with time and subsequent breakthrough infections has been reported in people with and without cancer.[4] Waning of humoral immunity in patients with cancer varies with cancer type and treatment, appearing greatest in patients with haematological malignancies or major comorbidities and in those receiving immunosuppressive therapies.[4]

A large, retrospective study of adults with solid tumours or haematological malignancies compared rates of SARS-CoV-2 infection between vaccinated and unvaccinated patients from Dec 15, 2020, to May 4, 2021, in the USA.[5] Starting 14 days after the second vaccine dose, vaccine effectiveness was 57% (95% CI –23 to 90) for patients who received chemotherapy within 3 months of the first vaccine dose, 76% (50 to 91) for those receiving endocrine therapy, and 85% (29 to 100) for those who had not received systemic therapy for at least 6 months, with mortality being around 10% in both vaccinated and unvaccinated individuals with breakthrough infections.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More recently, the National COVID Cohort Collaborative reported that vaccinated patients with cancer were more likely to have SARS-CoV-2 breakthrough infections resulting in more severe outcomes than vaccinated individuals without cancer.[6] Breakthrough infections were most common among patients with haematological malignancies or those receiving immunosuppressive therapies or stem-cell transplantation. An electronic health record cohort study of vaccinated participants from 66 US academic health centres found that patients with cancer, and especially those receiving active cancer care, were at a significantly greater risk of breakthrough infections than were propensity-matched control participants without cancer, with variation across cancer types.[7] Among patients with cancer, breakthrough infections resulted in hospitalisation in 31·6% and death in 6·7%.[7]

In *The Lancet Oncology*, the UK Coronavirus Cancer Evaluation Project (UKCCEP) reports a population-based, test-negative case-control study.[8] Participants' unique National Health Service identification numbers were used to link SARS-CoV-2 PCR results from the Second Generation Surveillance System to vaccination records in the National Immunisation Management Service and cancer diagnoses and interventions from Public Health England's Rapid Cancer Registration Dataset. Among 377 194 patients with cancer, 42 882 PCR-confirmed SARS-CoV-2 breakthrough infections were identified following a second vaccine dose. Vaccine effectiveness was compared between a cohort of patients with cancer and a control cohort of participants without cancer. Although initially similar between the cohorts, vaccine effectiveness waned more rapidly in the cancer cohort, falling to 47·0% (95% CI 46·3–47·6) at 3–6 months, than in the control cohort, in which it decreased to 61·4% (61·4–61·5). Waning of vaccine effectiveness was greatest in patients with leukaemia or lymphoma or a recent cancer diagnosis and in those who had received systemic anticancer therapy or radiotherapy within the preceding 12 months. A post-hoc analysis estimated that vaccine effectiveness was 74·6% (72·8–76·3) against COVID-19-related hospitalisation and 90·3% (89·3–91·2) against COVID-19-related death at 3–6 months after the second dose in the cancer cohort; other studies have reported a more severe disease course and higher mortality associated with SARS-CoV-2 breakthrough infections in patients with cancer versus those without.[4,5,7]

The UKCCEP represents the largest population-level study of COVID-19 vaccine effectiveness in patients with cancer assessing risk factors for breakthrough infections before the omicron (B.1.1.529) wave or the initiation of booster vaccinations. The test-negative case-control method is not without limitations, but is commonly used in large, population-based, surveillance studies and reasonably controls for health behaviour biases.[9] A major challenge of all observational studies is the presence of unrecognised or unmeasured confounding factors that can impact the assessment of medical interventions.[10] The presence and severity of major comorbidities, which are common in older patients with cancer, and the pandemic time period of exposure are known potential confounding factors that were not accounted for in this study. Likewise, COVID-19 monitoring might have differed between cohorts, as patients with cancer are followed up more closely than the general population.[4]

The UKCCEP results and those from other population studies[4,5,7] strongly support a recommendation that clinically vulnerable patients with cancer be prioritised for additional vaccine doses, early anti-COVID-19 treatments for documented infection, and COVID-19 prophylaxis when indicated. More data are needed on outcomes from breakthrough infections and adverse events, including mortality, in susceptible subgroups. Further studies of vaccine boosters are encouraged to establish valid risk thresholds of waning humoral and cellular immunity to identify the most clinically vulnerable. In the meantime, high-quality face masks and physical distancing offer important protection against any strain of SARS-CoV-2. We cannot forget that no one will be truly safe until global disparities in access to COVID-19 vaccines are finally addressed.

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Tiragolumab and atezolizumab in patients with PD-L1 positive non-small-cell lung cancer

Anti-PD-1 and anti-PD-L1 antibodies, alone or in combination with chemotherapy or anti-CTLA-4 antibodies, are standard therapeutic options for patients with advanced non-small-cell lung cancer (NSCLC). In patients with NSCLC with high PD-L1 expression (ie, with more than 50% of cancer cells staining positive for PD-L1 on immunohistochemistry), pembrolizumab or atezolizumab monotherapy can substantially improve objective response rates, progression-free survival, and overall survival compared with chemotherapy, sparing selected patients from chemotherapy.[1,2] Combining anti-PD-1 and anti-PD-L1 antibodies with chemotherapy for patients with non-squamous NSCLC with a high PD-L1 expression can push the median overall survival to 27·7–30·0 months (up from 20·2–26·3 months with pembrolizumab or atezolizumab monotherapy), although the combination can have higher adverse events.[3,4] Immunotherapy combinations such as nivolumab plus ipilimumab (with or without chemotherapy) are also standard regimens, but do not appear to add benefit versus single agents, as shown by a median overall survival of 21·2 months reported in a high-PD-L1 population.[5] Therefore, there is an unmet need to improve outcomes for patients with NSCLC with a high expression of PD-L1, by use of immunotherapy combinations that dispense with the need for upfront chemotherapy.

The immune checkpoint molecule TIGIT, a key checkpoint expressed by different lymphoid cells, mediates immunosuppression by binding to its ligand CD155 (also known as the poliovirus receptor) and can be expressed by cancer cells and tumour-infiltrating myeloid cells. TIGIT upregulation causes resistance to PD-1 blockade,[6,7] and low TIGIT expression and high PD-L1 expression correlate with improved outcomes in murine models treated with anti-PD-1 antibodies.[8] A combination of tiragolumab (anti-TIGIT) and atezolizumab (anti-PD-L1) has been reported to be safe in a phase 1 study containing preliminary data on a small number of patients with PD-L1-positive NSCLC.[9] The CITYSCAPE study, reported by Byoung Chul Cho and colleagues[10] in the *The Lancet Oncology*, is a phase 2 randomised trial comparing atezolizumab in combination with tiragolumab or placebo in untreated patients with advanced NSCLC with PD-L1 expression on at least 1% of cancer cells. Randomisation was stratified by PD-L1 expression status (1–49% *vs* ≥50%) and the coprimary endpoints were objective response rate and progression-free survival in the intention-to-treat population; key secondary endpoints were duration of response, overall survival, and safety. The statistical design was not powered to study the efficacy in key subgroups. 135 patients were included: 67 in the tiragolumab–atezolizumab group and 68 in the placebo–atezolizumab group. With a median follow-up of 30·4 months (IQR 29·4–33·0), objective response rate (38·8% [95% CI 26·4–51·2] *vs* 20·6% [10·2–30·9]; p=0·013), and progression-free survival (5·6 months [95% CI 4·2–10·4] *vs* 3·9 months [2·7–4·5]; hazard ratio [HR] 0·62 [95% CI 0·42–0·91]; p=0·013) in

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