

Immune Checkpoint Inhibition for Locally Advanced NSCLC: Time to Ask New Questions?



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For those of us whose involvement in cancer clinical trials dates back well into the past millennium, imagining (relatively) recent scientific progress and advances in the treatment of lung cancer at the start of our careers would have been nearly impossible. Therapeutic nihilism frequently encountered in the 1980s was slowly replaced with guarded optimism and encouragement for patients as the outcomes of clinical trials defined step-wise progress in treating locally advanced disease. Starting with finding that neoadjuvant cisplatin-based chemotherapy followed sequentially by thoracic radiotherapy confers a modest survival benefit compared with local radiation alone¹ (though this was initially met with skepticism resulting in confirmatory trials) to further significant improvement in survival by delivering radiation and chemotherapy concurrently² and to the current era marked by integration of adjuvant immune checkpoint inhibitors (ICIs) with the landmark PACIFIC trial.³

The phase 2, randomized PACIFIC 6 (PAC-6) trial adds to rapidly expanding number of studies evaluating ICIs with local therapy, with or without systemic therapy, for localized NSCLC.⁴ It seems that the intent of PAC-6 was to open up the opportunity for a new population of patients to receive the benefit of ICIs. Indeed, there are still a substantial number of patients with stage III disease receiving sequential radiation and chemotherapy therapy for which the study provides great value, suggesting adjuvant ICI treatment is tolerable with favorable overall survival (OS) in this setting. Nevertheless, it is not clear how well the trial delivers on the goal of addressing the management of “high-risk” or frail patients with locally advanced disease.

The challenge of interpreting the effect of PAC-6 relates in large part to understanding which patients can be treated with concurrent therapy as opposed to which patients actually receive concurrent therapy. Although survival data are still preliminary, if mature outcomes in PAC-6 are less favorable than PACIFIC, it would not be clear whether this is attributable to sequential therapy or to the underlying patient population. Beyond patient-related factors, the decision to proceed with sequential

as opposed to concurrent therapy may be influenced by access to services and regional and institutional practices. Our philosophy has been to default toward concurrent therapy, and most patients in our practice with (unresectable) locally advanced disease receive weekly sensitizing doses of carboplatin and paclitaxel during thoracic radiotherapy, albeit poor-risk patients are monitored closely for toxicity.

That said, there is a relative paucity of prospective data for patients with poor performance status, so it is possible that the OS benefit with concurrent therapy in standard-risk patients does not translate to the population with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2. Although high-quality randomized trials are lacking for these patients, phase 2 trials conducted in the 1990s by SWOG suggested that the concurrent radiation and carboplatin-based chemotherapy is reasonably well tolerated in a poor-risk population.⁵ These trials enrolled patients not eligible for SWOG cisplatin-based trials, with somewhat broad eligibility criteria, though up to 40% of patients were ECOG PS 2. Other prospective trials have revealed feasibility of studying targeted agents in a backbone of sequential chemotherapy and radiotherapy in predominantly poor-risk patients.⁶ The importance of systemic therapy in this population was recently highlighted in a trial comparing modern hypofractionated and conventionally fractionated radiotherapy, in which the median OS was poor in both cohorts, ranging from 8.2 and 10.6

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months, and significantly improved OS was found in the cohort receiving optional sequential chemotherapy.⁷

The authors should be congratulated for designing a trial for an ostensibly frail population, but on the surface, the patient population enrolled in PAC-6 is not easy to differentiate from concurrent therapy trials. Enrollment does not seem to be dependent on well-defined “poor-risk” criteria, as patients with certain comorbidities were excluded and fewer than 3% of patients enrolled were ECOG PS 2. The high frequency of medical comorbidity is noted for the PAC-6 population, but it is hard to tell how this compares to other trials as similar details are generally not provided. Nevertheless, there may have been a bit of a missed opportunity given the number of patients with lung cancer with severe underlying comorbid illness that does render them as having poor performance status. The difficulty in recruiting PS 2 patients is acknowledged, but given the potential favorable therapeutic ratio of ICIs, compared with cytotoxic chemotherapy, additional data for ICIs in this population are of great interest.

Older patients have likewise been greatly underrepresented in clinical trials, with limited high-quality data in part because many trials used an (arbitrary) upper age limit for enrollment. The median age of patients on the PAC-6 trial is 68 years, compared with 64 years on the PACIFIC trial, though the greatest population of interest may be the cohort (approximately 18%) of patients aged 75 years or greater. There is a growing body of data suggesting that treatment decisions should not be based solely on age, and older patients should not be lumped in with the poor-risk population. In fact, though several phase 3 trials have revealed better OS with concurrent versus sequential therapy, older patients in the landmark Radiation Therapy Oncology Group 9410 trial derived an outsize benefit for concurrent therapy compared with younger patients. Median OS was 22.4 months with concurrent therapy and 10.5 months with sequential therapy in patients aged greater than or equal to 70 years.² At the same time, older patients are at higher risk for treatment-related toxicity meriting more frequent monitoring as compared with the younger population. There is a need to increase accrual of older patients who more and more represent the real-world population. Standardization of a validated geriatric assessment tool, which incorporates measures of physical and cognitive function, comorbid disease burden, in addition to factors such as social support, would help in that regard.⁸

Given the overwhelming evidence for ICIs in NSCLC, the suggestion of improved outcomes in PAC-6 is not surprising. Perhaps it is time to accelerate the move away from questions relating to whether ICIs should be given and toward addressing the following core questions regarding optimal integration of these agents.

Duration of Therapy

Although it may be counterintuitive to use a longer treatment course in a poor-risk population, perhaps it makes sense to continue ICI therapy longer if less intensive chemoradiotherapy is given. Furthermore, although most patients do not complete 2 years of therapy, the pertinent question may be whether to continue immune oncology in patients with responsive disease who are tolerating the therapy well.

Sequencing of Therapy

The optimal sequencing of therapy remains to be clearly defined. The ongoing ECOG-ACRIN EA5181 trial randomizes patients to start durvalumab with chemoradiotherapy, with both arms receiving consolidative durvalumab.⁹ Nevertheless, it would be of great interest to formally address whether ICIs should be given before chemoradiotherapy for stage III disease and a recent phase 2 study of induction atezolizumab which reported progression-free survival of almost 24 months.¹⁰ Given the recent approval of induction chemotherapy plus nivolumab for the neoadjuvant treatment of select patients with resectable lung cancer, addressing the role of chemoimmunotherapy versus ICIs alone may also be a fertile ground in appropriate patients.

Challenging Currently Accepted Tenets for Treating Locally Advanced NSCLC

Perhaps the integration of ICIs should make us rethink of the lessons learned during the past 30 years for treating locally advanced disease?

1. Do ICIs obviate the need for systemic chemotherapy in (select) patients with locally advanced NSCLC? The NRG LU-004 pilot trial evaluated durvalumab with either standard or accelerated radiotherapy in programmed death-ligand 1-high (>50% expression) tumors,¹¹ and this approach may be particularly attractive for subsets of poor-risk patients.
2. Radiotherapy has immunomodulatory effects that may potentiate the effects of ICIs. Though the optimal regimen in this setting is not known, moderately or marked hypofractionated regimens may be more synergistic with ICIs or even render tumors with low programmed death-ligand 1 expression more susceptible to immunotherapy.¹²
3. It is also conceivable that the inclusion of ICIs in the overall treatment regimen might reduce the difference in outcomes between sequential and concurrent chemoradiotherapies, allowing more patients to avoid the toxicity of concurrent therapy without sacrificing efficacy. Mature results from the PAC-6 trial may provide impetus for further study.

- Given the major response rate observed in surgical trials of induction ICI in localized disease, perhaps the current treatment paradigm for locally advanced NSCLC can be more radically challenged.¹³ This could result in the design of response-adaptive studies evaluating whether local therapy and/or cytotoxic chemotherapy might be delayed or even avoided in select patients with exceptionally responsive disease after initial immunotherapy.

There is a tremendous opportunity and responsibility in the near future to continue to design and complete trials that challenge the status quo and help define and refine the treatment paradigm for localized NSCLC in the ICI era. Further personalization of therapy through biomarker-driven studies and trials geared to special populations, including older patients and those with poor performance status, will be critical to achieving this goal.

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