Early Treatment Failure of Consolidation Durvalumab for Unresectable Stage III NSCLC: A Real-World Canadian Cohort

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Background

The standard of care for advanced non-small cell lung cancer (NSCLC) which is not amenable to resection is concurrent chemoradiotherapy (cCRT) followed by consolidation durvalumab in patients with a minimum of stable disease following cCRT. The introduction of consolidation durvalumab was based on the results of the phase III PACIFIC trial which compared post-cCRT durvalumab against a placebo, [1] which has shown improved overall (OS) and progression-free survival (PFS) in the context of a favorable safety profile, and the durvalumab-mediated benefit appears to endure among a series of updated analyses. [1]

Unfortunately, not all patients derive benefit from immune checkpoint inhibitors (ICI) like durvalumab, and some patients experience early treatment failure on durvalumab, characterized by primary drug resistance or toxicity requiring durvalumab termination. [2] Primary resistance to first-line ICI is reported to be in the range of 7-27%, [2] and among PACIFIC trial participants, 16.5% demonstrated primary resistance to durvalumab, with a further 2.3% discontinuing durvalumab prior to response assessment. [3]

With clinical characteristics associated with early treatment failure on immunotherapy not well explored, [2] and recognized differences between highly selected clinical trial and more heterogeneous real-world populations, this study investigated the phenomenon of early durvalumab failure and endeavoured to identify predictors associated a lack of clinical benefit of durvalumab.

Methods

The institutional Glans-Look Lung Cancer Research Database contains demographic, clinical, pathological, treatment and outcome data from patients diagnosed with NSCLC living in the Canadian province of Alberta. This data repository was used to identify all patients with unresectable Stage III non-small cell lung cancer, diagnosed between 2018 and 2020. Included in the study cohort were those unresectable Stage III patients who received consolidation durvalumab following ≥2 cycles of platinum-doublet chemotherapy and concurrent definitive radiotherapy, without evidence of progression and suitable for immunotherapy treatment.

Patients were grouped according to response to durvalumab:

'Early-failure' was defined as those with progressive disease as best treatment response, or those with non-evaluable disease due to durvalumab discontinuation prior to treatment response assessment.

'Responders' were defined as those achieving a best response of stable disease or higher.

Univariate and multivariate methods compared the Early-Failure and Responder groups and identified factors predictive of early durvalumab failure while controlling for confounders.

Results & Interpretation

94 patients were identified:

Demographic and Clinical Characteristics of Cohort

- **53%** Female
- **54%** PD-L1 Positive (TPS ≥ 50)
- **91%** Good ECOG (<2)
- **89%** History of Smoking
- **6%** Oncogenic driver mutation (83% EGFR-mutant; 17% ROS1-rearranged)
- **69%** Overweight/Obese BMI
- **48%** Immune-related adverse event (irAE) while on durvalumab
- **69%** Under 70 years at diagnosis
- **23%** Systemic Therapy Post-Durvalumab

Response to Durvalumab

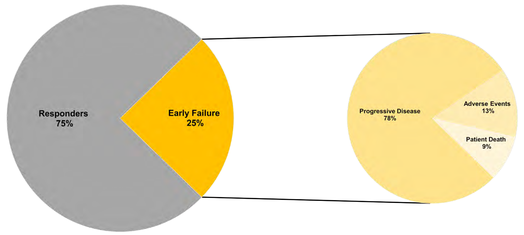


Figure 1: Responders and Reasons for Early Failure on Consolidation Durvalumab

The majority of the cohort were categorized as 'Responders' with a response (stable disease or better) to consolidative durvalumab.

Among patients with Early Failure on Durvalumab, progressive disease upon the first response assessment was the most common reason for durvalumab discontinuation.

Responders vs. Early Failure

Demographic and clinical characteristics were similar between Responders and Early Failure cohort, but differed with respect to:

- **Rates of irAE**:
  Responders vs. Early Failure: ***38% vs. 0%*** (p<0.001)
- **Rate of post-durvalumab systemic therapy**:
  Responders vs. Early Failure patients: ***14% vs. 52%*** p<0.001

These findings may reflect better treatment response and longer duration of therapy among Responders, and where the increased rate of early irAE among Responders has previously been shown to be associated with better outcome, [4] also observed in this cohort: (Figure 2)

Responders vs. Early Failure: ***Not reached vs. 13.1 months***

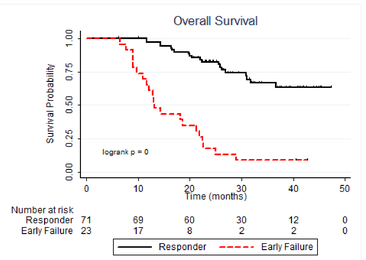


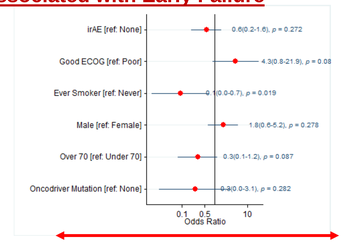
Figure 2: Median Overall Survival: Responders vs. Early Failure on Consolidation Durvalumab

Results & Interpretation

Factors Associated with Early Failure

In a multivariate model, only a history of smoking was associated with a decreased risk of early failure on consolidation durvalumab

HR: 0.1 [95% CI: 0 – 0.7] p=0.02



Decreased Risk of Early Failure *Increased Risk of Early Failure*

Figure 3: Factors Associated with Early Failure on Consolidation Durvalumab

Early Failure Management and Prognosis

Among patients experiencing Early Failure on durvalumab, additional systemic therapy failed to improve prognosis.

Overall Survival: Early Failure

Additional systemic therapy vs. None

18.1 vs. 11.6 months
log-rank p=0.61

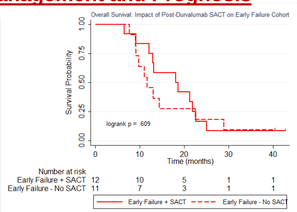


Figure 4: Impact of Additional Systemic Therapy for Early Failure on Consolidation Durvalumab

Conclusions

This study found 25% of patients in a real-world clinical setting failed to achieve clinical disease control on durvalumab, mostly by virtue of primary durvalumab resistance.

- Demographic and clinical features fail to distinguish those at risk of early failure on durvalumab.
- There may be other underlying and not routinely assessed features of the tumour microenvironment which could place patients at risk of early failure and poor outcome.
- Additional post-durvalumab systemic therapy appears to be limited in meaningfully impacting patient prognosis.

Further investigation to identify other factors associated with durvalumab response is crucial to understanding the mechanisms of primary resistance to ICI-therapy and provide options which optimise outcome for those who fail to respond effectively to this therapy.

References

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