**Immunological mechanisms of the response to TG4010, a viral-based vaccine, in patients with advanced NSCLC**

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**BACKGROUND**

Lung cancer is the second most common cancer in both men and women, and is by far the deadliest. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases of lung cancer and despite recent progress in immunotherapy, its prognosis remains dismal.

TG4010 is a non-replicative viral vector (MVA) encoding both human mucin 1 (Muc1), and IL-2. Encouraging results have been reported in clinical trials carried out in NSCLC, advanced BC and RCC [1]. The TIME trial (NCT01383148), a placebo controlled, double blind, randomized phase 2b study assessing the efficacy of TG4010 in combination with first-line chemotherapy in NSCLC, showed improved overall survival (HR 0.59 [0.39-0.93], p=0.0072, with doubling of OS from 19% to 40% at 24 months), higher response rate, and a longer duration of response, compared to standard CT [2].

TG4010 was shown to induce a strong specific CD4/CD8-mediated adaptive response [3].

**OBJECTIVES**

Our study aimed at establishing the link between TG4010-induced immune response, related features, and clinical outcome (mainly OS). These data will both support the results obtained for the combination with IL-2, and contribute to the rationale for combination with ICI, as currently assessed in a phase 2 trial evaluating TG4010 + nivolumab in the second line treatment of patients with non-squamous metastatic NSCLC.

**RESULTS**

TG4010 activity is driven by induction of a MUC1 specific T cell response, and broadening of response to other TAAs

Induction of specific CD8+ T cells upon treatment with TG4010 + CT

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Sequence (AA pos.)</th>
<th>Subgroup</th>
<th>Target</th>
<th>HLA</th>
<th>Epitope</th>
<th>Frequency</th>
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<tbody>
<tr>
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<td>MVA</td>
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**CONCLUSION**

Our results confirm that TG4010-induced specific T-cell response against Muc1 lead to improved survival in patients with advanced NSCLC. Additionally, for the first time, we have shown that vaccination with a viral vector can also induce epitope spreading to other TAAs. This enrichment of the diversity of the anti-tumor response has proven to be very important for clinical outcome, and possibly correlates with increased response rate to immune checkpoint blockade. Furthermore, TG4010 activity was confirmed in patients with unfavorable immune profile, in particular, patients with high Treg frequency, low NK mediated innate immunity (TrPAL, low IP10 and IL12p70) or with cytokine profiles associated with high inflammation (TNFα, IL-1β) and decreased adaptive response related cytokines (IFNy). Hence, TG4010 appears as a useful therapeutic option to maximize response rate and clinical benefit in a large set of patients. Its immunological properties might be highly synergistic with immunogenic therapies, and/or immune checkpoint inhibitors.

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