# Understanding the effect of NKTR-255 on circulating lymphocyte levels post-radiotherapy

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## Introduction

The ability of radiation therapy to damage the DNA inside a cancer cell, thus initiating its death, has led it to become one of the keystone options for treating an individual's cancer. However, the radiation applied not only kills the malignant cells, but also destroys the patient's lymphocytes, leading to a state of immunosuppression. The absence of lymphocytes, which normally function to generate a response against infections, makes the patient increasingly susceptible to attacks from viruses and bacteria and results in worse prognoses. A particular alternative that has emerged to address this concern is NKTR-255, a polymer-conjugated recombinant human IL-15 that is currently being administered as part of a single-arm phase II trial (RESCUE trial) to determine its efficacy while monitoring for toxicity. IL-15 has been specifically targeted since it acts by augmenting the activation and proliferation of NK and CD8+ T cells, but it does not drastically change the levels of regulatory T cells, which can actually aid tumor cells by suppressing the immune response. Studies in mice have shown that this drug does result in 2-fold and 2.5-fold increases in NK and CD8+ T cells respectively, while not influencing the regulatory T cell levels. The purpose of this experiment is to determine whether the effect that NKTR-255 has on mice can be safely replicated in non-small cell lung cancer (NSCLC) patients that have undergone radiotherapy. We predict that patients that receive NKTR-255 will achieve an absolute lymphocyte count (ALC) > 1 by 8 weeks post-radiotherapy, having much higher lymphocyte levels and quicker recovery rates than patients that do not receive NKTR-255.

## Hypothesis

NSCLC patients that receive NKTR-255 after radiotherapy will reach an ALC > 1 by 60 days post-radiation, exhibiting higher circulating lymphocyte levels and quicker lymphocyte recovery rates than those patients that are not given NKTR-255 following treatment.

## Methods

This investigation is part of the RESCUE trial, a single-arm phase II trial testing standard of care treatment for cancer together with NKTR-255. One of the goals of this experiment is to determine if this drug is safe and efficacious to reconstitute lymphocyte counts post-radiotherapy.

## Methods Continued…

The study continues as long as 1/5 or 2/10 patients show recovery (ALC>1) at 60 days post-radiation, being designated as futile otherwise. The control individuals retrospectively analyzed as part of this experiment were all NSCLC patients who received standard 30 fractions of radiation therapy with concurrent chemotherapy, alone or with durvalumab (PACIFIC group), between 2016 and 2023. The trial group are patients that underwent the treatment regimen described above, but also elected to receive NKTR-255. Demographic and complete blood count data, particularly the absolute lymphocyte count (ALC), was extracted from the charts of individuals belonging to the two groups described above in order to determine what factors account for lymphocyte values before, during and after radiotherapy. SPSS version 24 was utilized to run RM ANOVA and t-tests to determine the statistical significance of the data.

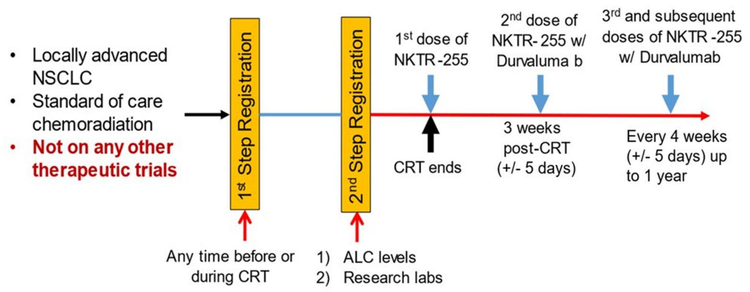



Figure 1: Study design of the RESCUE trial portraying the criteria for enrolment and the protocol followed. Eligible patients who enrolled underwent chemoradiation and subsequently received NKTR-255 doses 1-, 3- and 7-weeks post-treatment, with further doses being administered every 4 weeks. Durvalumab was administered together with NKTR-255 from the 2nd dose onwards.

## Results

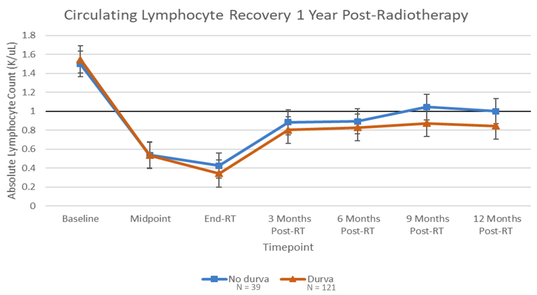



Figure 1: Line graph comparing the absolute lymphocyte count (ALC) at varying timepoints for control patients (no NKTR-255) that did (N=39) or did not (N=125) receive durva after radiation. Overall, control patients did not have lymphocyte recovery (ALC>1) in the first year after radiation. The "no durva" group recovered momentarily at 9 months, but by 12 months their mean ALC was once again below 1. RM ANOVA and t-test analysis showed no significant difference between treatments at all timepoints.

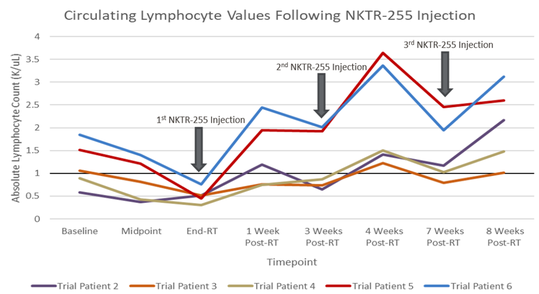
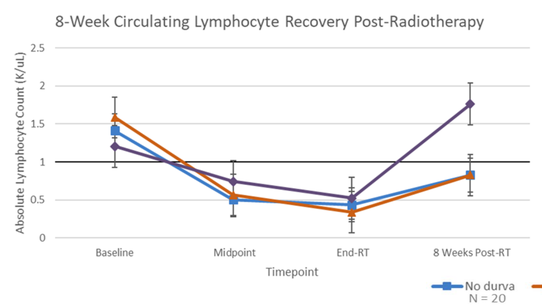
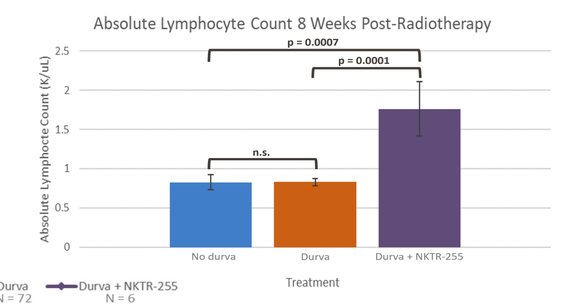



Figure 2: Line graph portraying the absolute lymphocyte count (ALC) for 5 different patients belonging to the trial group. Much quicker lymphocyte recovery (ALC>1) times can be observed, with 3 patients recovering by the 1st week and 2 patients doing so by the 4th week. The particular ALC trend in the graph also demonstrates how NKTR-255 injection initiates an upsurge in ALC which then decreases slightly prior to the next dose.




Figures 3-4: Graphs comparing circulating lymphocyte levels and recovery between control patients that do not receive durva (N=20), control patients that do receive durva (N=72), and trial patients that are given durva together with NKTR-255 (N=6). Both figures indicate that there is no difference between control groups in absolute lymphocyte count (ALC), with neither one achieving circulating lymphocyte recovery (ALC>1) by eight weeks after radiation. Meanwhile, patients that were injected NKTR-255 after radiotherapy actually did present lymphocyte recovery and had a greater ALC eights weeks post-radiation than both control groups. For both figures, AM ANOVA and t-test analysis confirmed a significant difference between trial and control groups at the eight-week mark, while control groups had no significant difference between them at any timepoint. Additionally, there is no significant difference in ALC between all groups until the injection of NKTR-255, which occurs at the end of radiation.

## Discussion

Overall, the data suggest that NKTR-255 does result in increased circulating lymphocyte levels and faster lymphocyte recovery rates post-radiation. Figure 1 shows that control patients, independently of whether they are given durvalumab or not, do not tend to recover to normal lymphocyte levels after radiation. The individuals that did not receive durva did show recovery after 9 months, but by 12 months the ALC was below 1 again. The results from figure 1 also indicate that there is no significant difference between patients that are provided durva and those that are not, suggesting that the improvements in lymphocyte recovery observed in this experiment are mainly due to NKTR-255 alone.

## Discussion Continued…

Meanwhile, figure 2 demonstrates that patients injected with NKTR-255 have much quicker recovery times, with 3 of them achieving an ALC>1 one week following radiation and the other 2 reaching the same mark by the 4th week. Additionally, an interesting ALC trend can be observed, rising 1 week after injection and then decreasing before the next dose. Figures 3 and 4 further support the implementation of NKTR-255 as they show that its injection, together with durva, leads to significantly greater circulating lymphocyte levels 8 weeks post-radiotherapy when compared to the patients that do not receive NKTR-255.

## Conclusion

- Radiation therapy has numerous negative consequences, one of the biggest challenges being radiation induced lymphopenia
- Several factors account for degree of recovery, the main one being baseline ALC
- Our data support the hypothesis that patients that receive NKTR-255 following radiation will have significantly greater post-treatment lymphocyte levels and quicker lymphocyte recovery rates
- Next steps…
  - Enroll more patients to the RESCUE study
  - Finish designing flow cytometry panels
  - Perform deep analysis on how NKTR-255 impacts immune repertoire and lymphocyte clonality

## Acknowledgements

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