

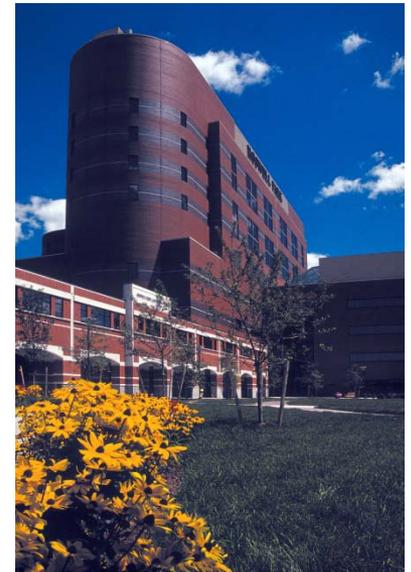
**Protocol I199911:
A PHASE I CLINICAL TRIAL OF mTOR INHIBITION WITH
SIROLIMUS FOR ENHANCING ALVAC(2)-NY-ESO-
1(M)/TRICOM VACCINE INDUCED ANTI-TUMOR IMMUNITY
IN OVARIAN, FALLOPIAN TUBE AND PRIMARY
PERITONEAL CANCER**

Kunle Odunsi, M.D., Ph.D. ^{1, 2}

Protul Shrikant, Ph.D. ²

**Departments of Gynecologic
Oncology ¹ and Immunology ²
Roswell Park Cancer Institute
Buffalo, NY**

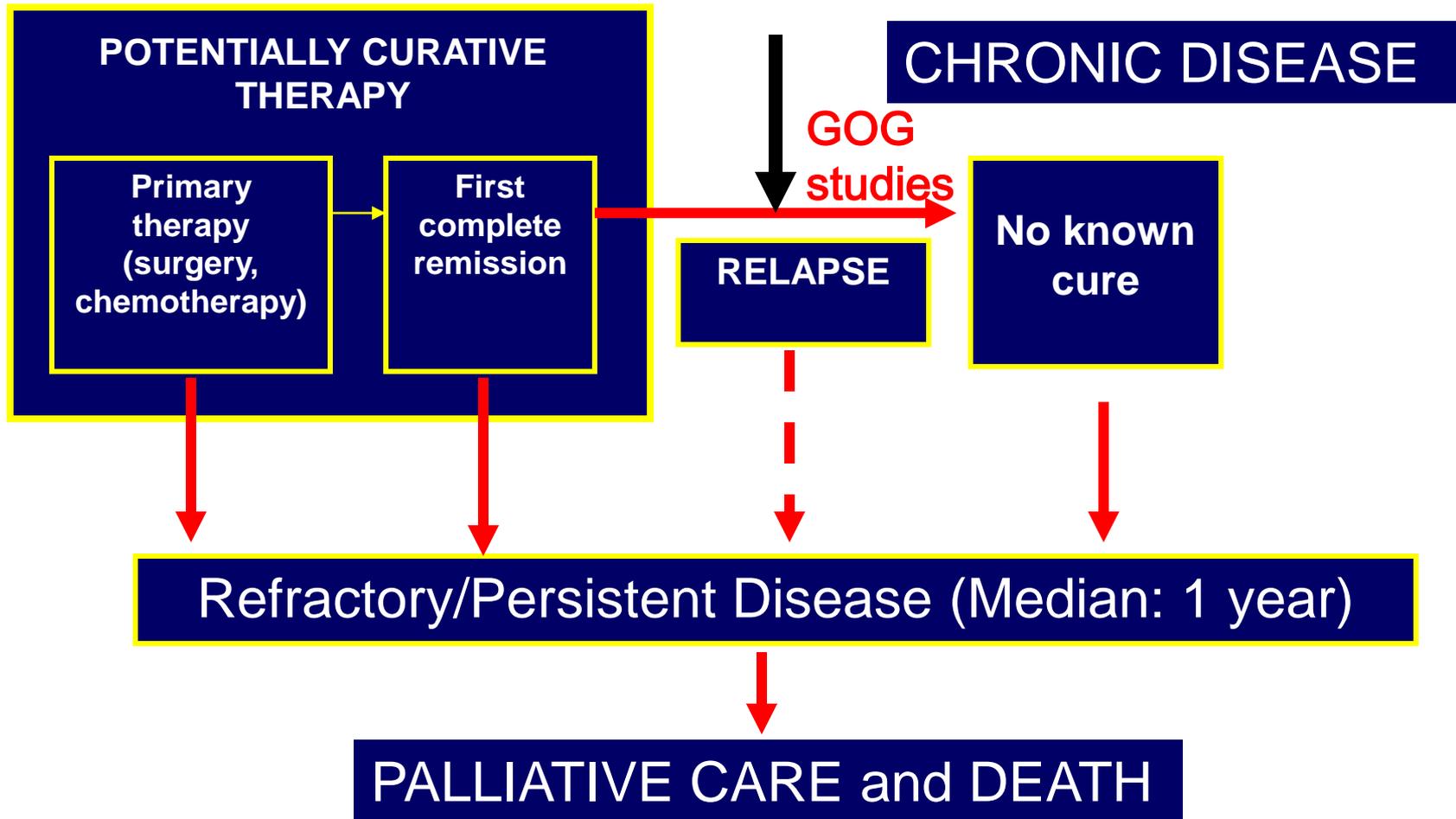
Funding: NIH 1RO1CA158318-01A1



GOALS

- Rationale for the study
- Preliminary studies in support of the clinical trial
- Study design:
 - Vaccine
 - Rapamycin dose
- Reviewers' concerns

Ovarian cancer: the need to minimize risk of relapse



The goal of our studies is to generate durable CD8+ T cell responses against epithelial ovarian cancer (EOC) for extending remission rates.

Characteristics of ovarian cancer patients in 1st or subsequent remission

- **70% of ovarian cancer patients who complete surgery and chemotherapy are declared to be in “complete remission”.**
- **Second look: 55% of patients in “complete remission” will have disease at the time of re-exploration.**
- **Even among those with a negative result, the risk of recurrence exceeds 50%.**
- **More than 80% of ovarian cancer patients in “complete remission” will relapse following 1st line therapy; and more than 90% in “complete remission” will relapse following 2nd or additional lines of therapy.**
- **Consolidation strategies to date in GOG studies: unsuccessful to date – unmet medical need.**
- **We propose that the generation of anti-tumor memory cells in this population may prolong PFS and lead to clinical benefit.**

Limitations of cancer vaccine strategies in ovarian cancer

- Immune recognition of ovarian cancer: targets include NY-ESO-1.
 - **Unique properties of NY-ESO-1**
- Low frequencies of high avidity, tumor-antigen specific effector CD8+ T cells.
- Lack of tumor-antigen specific memory CD8+ T cells.
 - rapamycin mediated inhibition of mammalian target of rapamycin (mTOR) switches effector CD8+ T cells to memory.

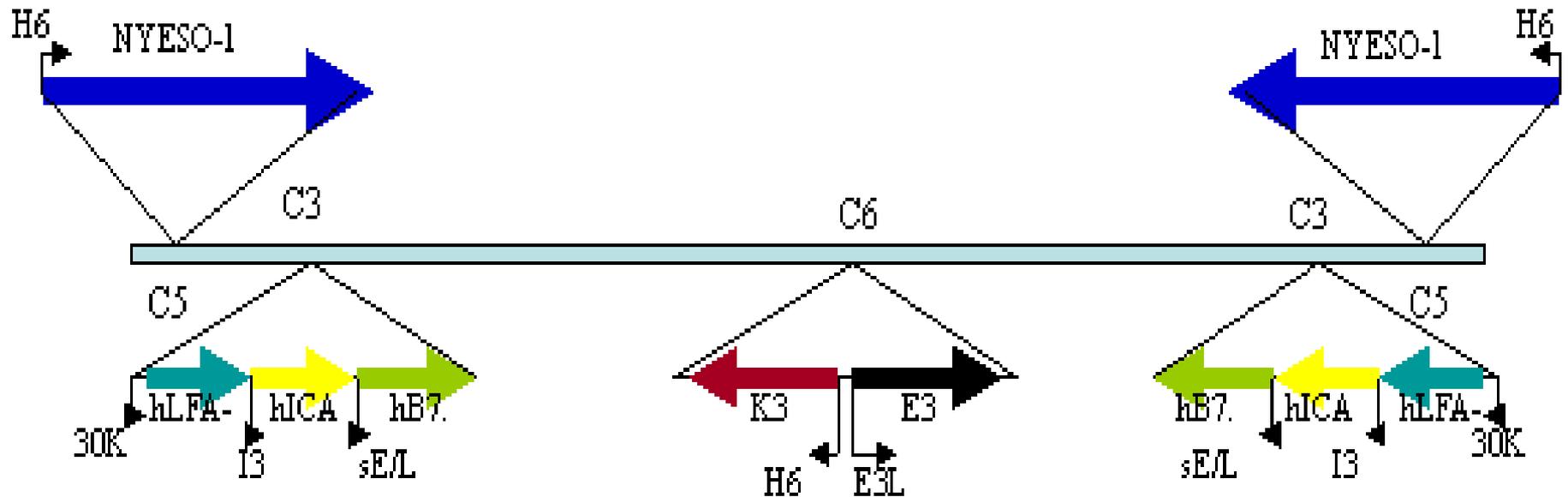
These results provide impetus to exploit the use of rapamycin to “re-program” vaccine induced T cells for **enhanced persistence, antigen recall and durable tumor immunity** in EOC patients, in order to prolong remission rates.

**Preliminary Clinical Studies:
Recombinant canarypox-NY-ESO-
1/TRICOM induce high avidity NY-
ESO-1 specific immune responses
fails to induce memory T cell
responses in ovarian cancer patients
(RPCI Protocol I125207)**

(n = 12 patients)

ALVAC(2)-NY-ESO-1(M)/TRICOM

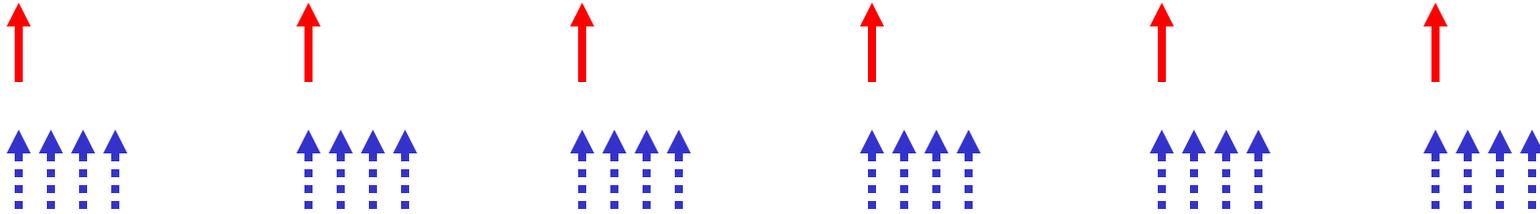
ALVAC(2)-NYESO-1-TRICOM (vCP2292)



- The expression of each of the structural genes is driven by a Vaccinia virus promoter.
- Amino acid at position 165 of NY-ESO-1 changed from cysteine to valine.

Vaccine Schedule: I125207

Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
---------	---------	---------	---------	---------	---------



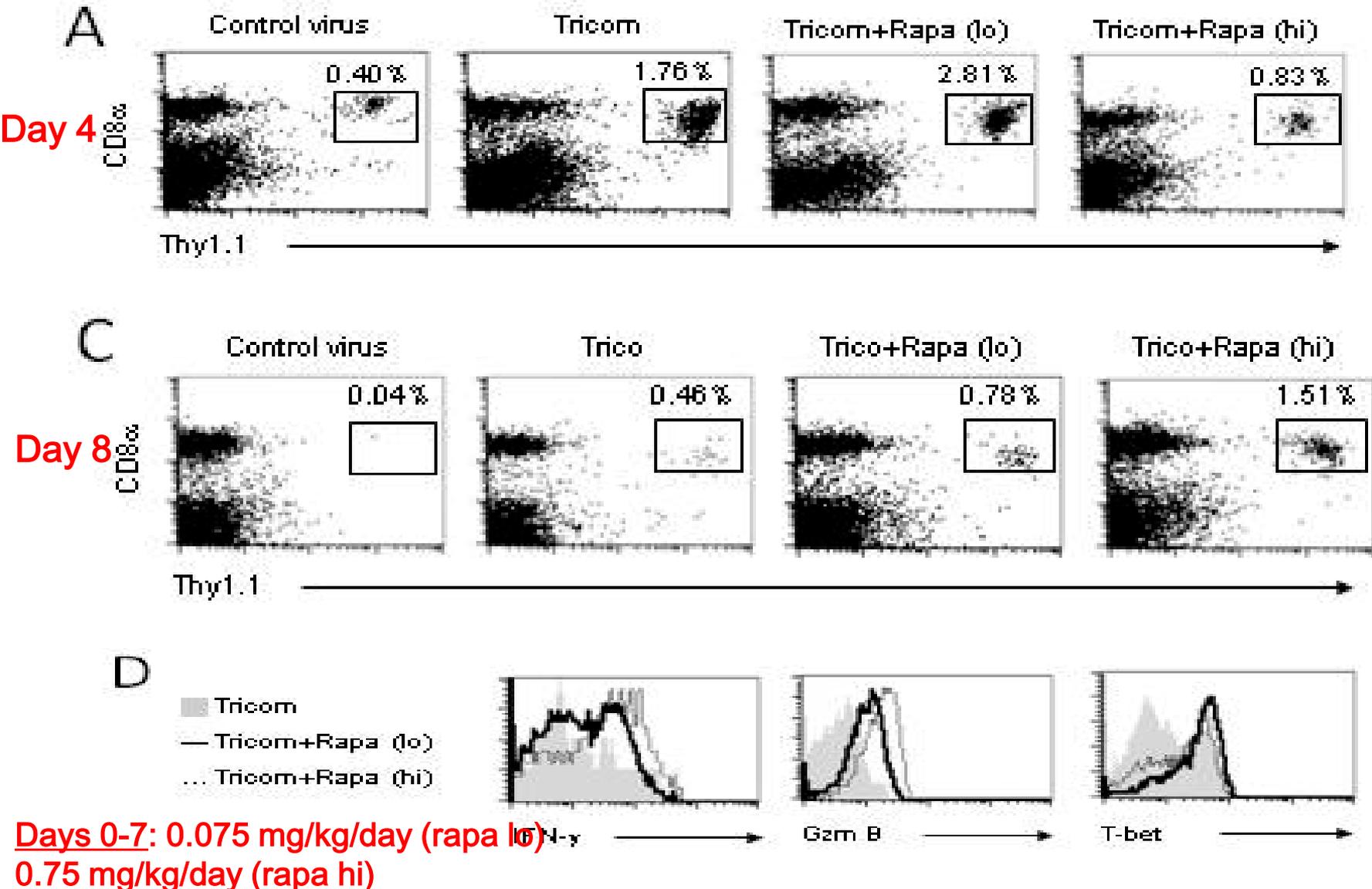
Legend:

 **0.5ml ALVAC(2)-NY-ESO-1(M)TRICOM Vaccine SC once monthly ($\geq 1 \times 10^7$ CCID₅₀/mL of the ALVAC virus)**

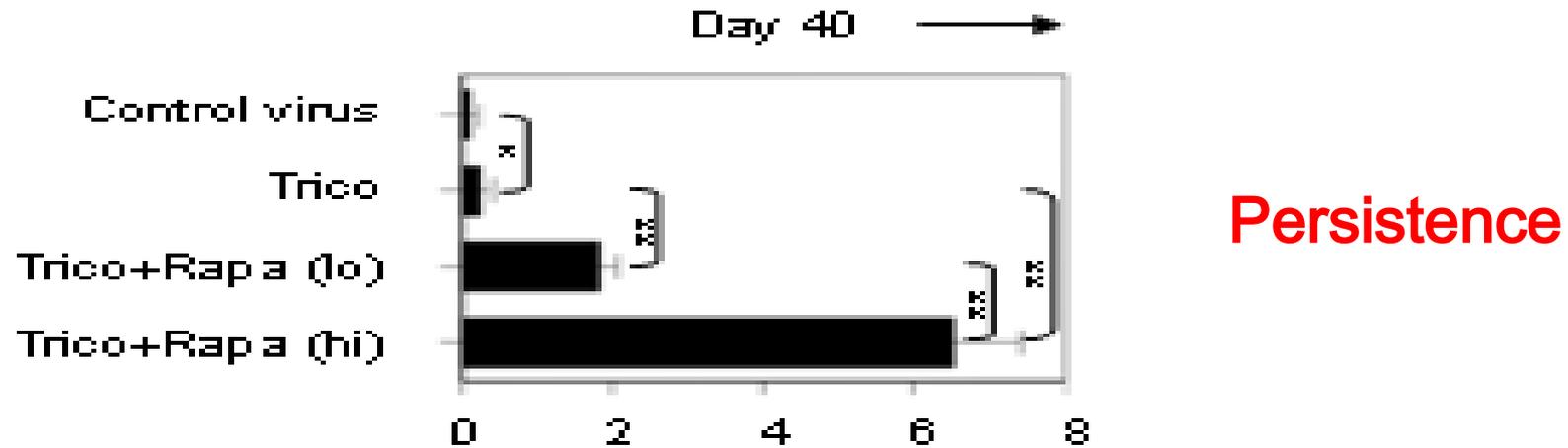
 **GM-CSF 100mcg/day Day 0-4 SC**

- (i) the use of viral vector-based vaccines to enhance presentation of the TA (NY-ESO-1).
- (ii) the use of T-cell co-stimulation to enhance T-cell responses (second signal), which could preferentially induce and expand high avidity CD8+ and CD4+ T cells
- (iii) the use of GM-CSF to enhance the efficacy of APCs.

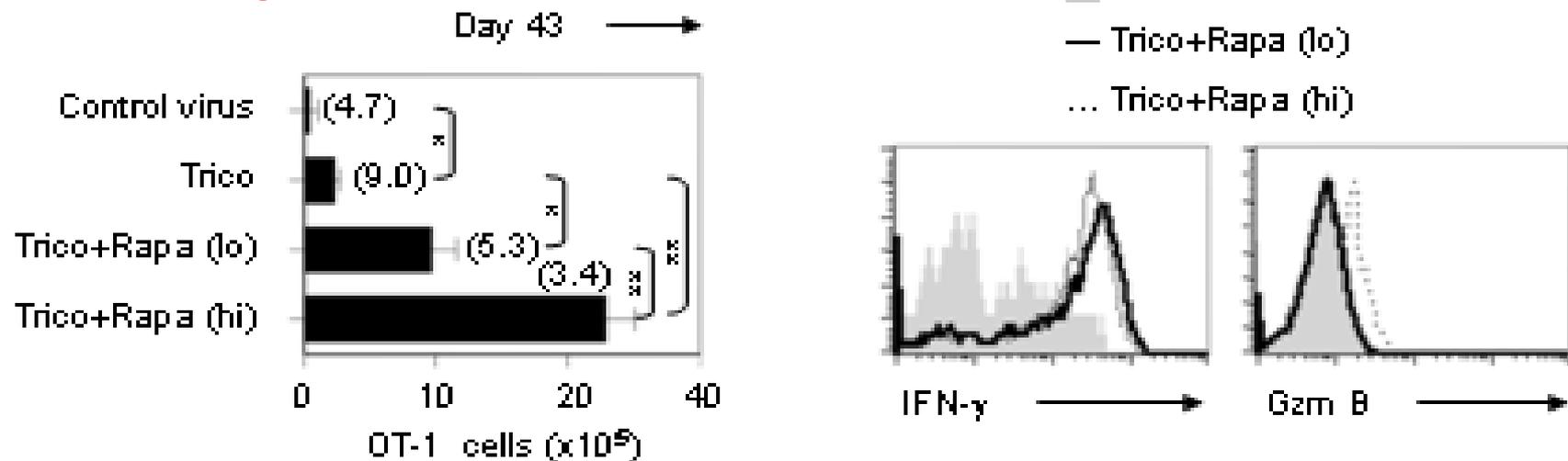
Regimen of rapamycin use regulates activation, proliferation, effector maturation and memory precursor phenotype in vaccine-induced OT-1 cells.



Increased mTOR inhibition enhances vaccine-induced persistence of CD8+ T cells and antigen-recall response.

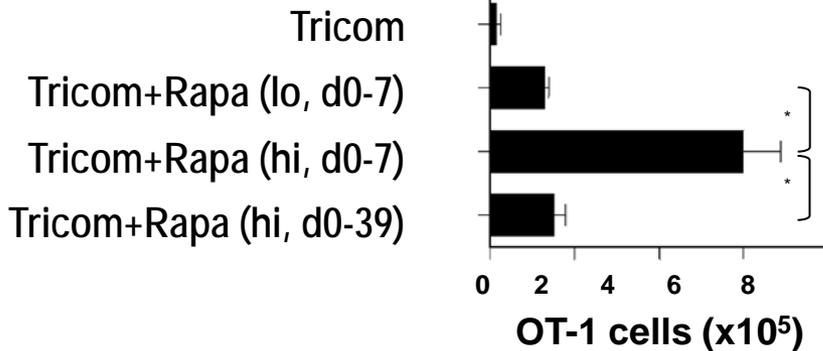


Antigen recall

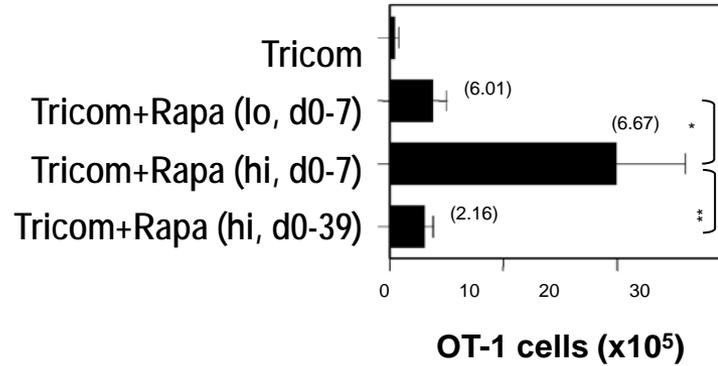


Rapamycin mediated CD8+ T cell memory and tumor efficacy is dose and duration dependent

Memory



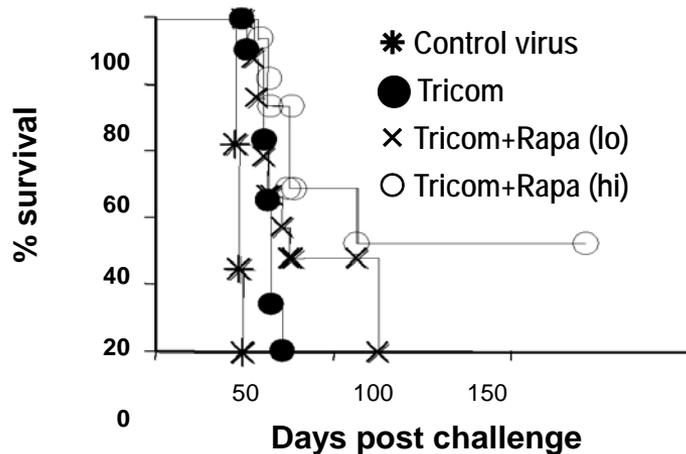
Persistence



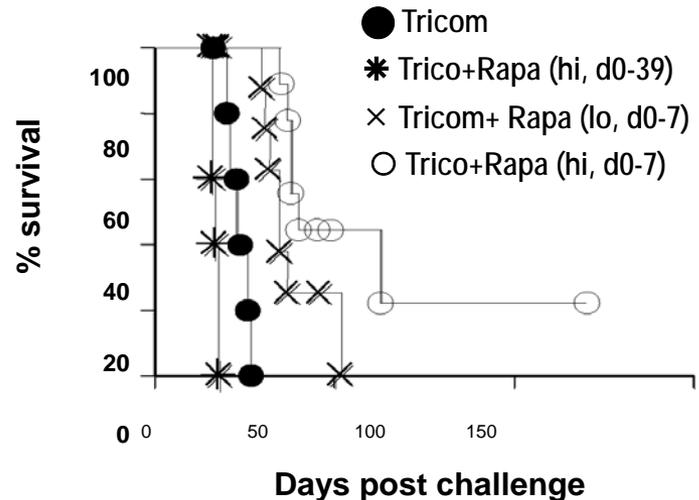
Ag recall

Tumor efficacy

Survival 1



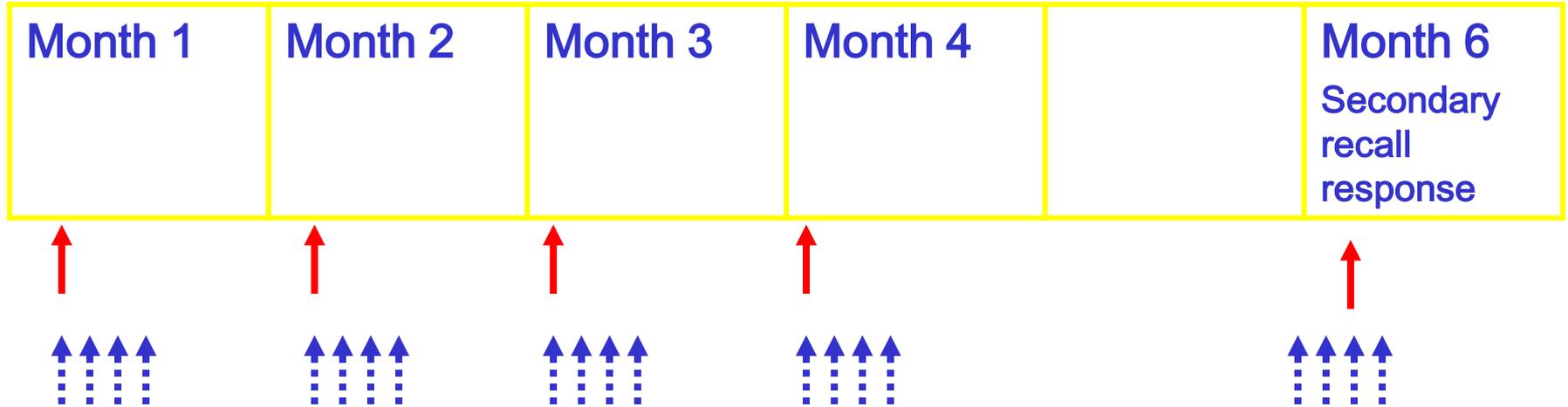
Survival 2



CLINICAL TRIAL OBJECTIVES

- **Primary:** To determine the safety of rCNP-NY-ESO-1/TRICOM vaccine with sirolimus at varying dose and schedule in ovarian cancer patients.
- **Secondary:**
 1. **To determine the regimen (dose and duration) of rapamycin that produces memory CD8+ T cell responses in ovarian cancer patients.**
 - Peripheral blood NY-ESO-1 specific CD8+ and CD4+ T-cells.
 - Peripheral blood NY-ESO-1 specific antibodies.
 2. **To determine the impact of rapamycin treatment regime on rCNP-NY-ESO-1/TRICOM induced CD4+ T cell response for CD8+ T cell memory generation.**
 - Frequency of CD4+CD25+FOXP3+ regulatory T-cells.
 3. **Exploratory: Time to disease progression.**

Study Design: I199911



Eligible patients: NY-ESO-1 expressing tumors, completed standard therapy for primary or recurrent disease; or with asymptomatic residual disease

Sirolimus orally at varying dose levels and schedules in 5 cohorts as follows:

Cohort 1a, 2 mg Day 1 – Day 14

Cohort 1b, 2 mg Day 15 - Day 28

Cohort 1c, 2 mg Day 1 - Day 28

Cohort 2a, 4 mg Day 1 – Day 14

Cohort 2b, 4 mg Day 15 – Day 28.

Cohort 2c, 4mg Day 1-28: Eliminated

Cohort 3: “OBADS”

Safety concerns about Rapamycin (Section 4.3 of the clinical protocol; and section 8 of ICD)

- Undesirable side effects: hematologic and non-heme; including risk of immunosuppression.
- What safeguards are in place to minimize any immunosuppressive effects in the clinical trial population?
 - Patients in “remission”, minimal disease e.g. CA125 only

Dose of Rapamycin: I

- **Basis for choosing the doses proposed in the clinical trial:**
 - In low-to-moderate immunologic risk renal transplant patients, the adult maintenance dose of oral sirolimus is 2mg/day and 4-6mg/day in high immunologic risk.
 - Loading dose, prolonged daily administration for months or years.
- Sirolimus has been studied as an anti-cancer therapy in several types of cancer at doses of 0.5–10 mg orally daily.
- Literature Support.

Examples of Rapamycin Dose

- Reardon *et al* (*Clin Cancer Res.* 2006;12:860-8): Phase 1 Trial of Gefitinib Plus Sirolimus in Adults with Recurrent Malignant Glioma,
 - The MTD is 500 mg of gefitinib plus 5 mg of sirolimus for patients not on EIAEDs, and 1,000 mg of gefitinib plus 10 mg of sirolimus for those on EIAEDs.
- Phillips *et al* (*J Ophthalmic Inflamm Infect.* 2011;1:29-34): Oral low-dose sirolimus (1–4 mg daily) for severe, chronic uveitis. Blood levels were drawn serially, and sirolimus was titrated to 4–12 ng/mL.
- No increased incidence of immunosuppression.
- Everolimus is approved by the FDA at a dose of 10mg per day for use after progression of metastatic clear cell RCC.
- RCTs of sirolimus-based immunosuppressive regimens in solid organ transplantation have observed no increase in cumulative incidence of CMV disease in patients receiving sirolimus.
- No increased incidence of immunosuppression.
- The ability to mount effective anti-viral immune responses is preserved in transplant recipients receiving prolonged maintenance doses of sirolimus.

Safeguards

Given the concerns raised, we have modified the protocol:

- Exclusion of immuno-compromised patients (HIV, HbsAg, HCV, chronic corticosteroids use).
- Eliminate Cohort 2c (i.e. 4mg QD for 28 days X 4 months).
- Assessment of sirolimus levels: goal to keep levels no greater than 4–12 ng/mL.

(Note: For most indications, the target serum blood level of sirolimus is 10–20 µg/mL).

- measurement of CMV antigenemia
 - to readily identify patients with CMV antigenemia who may require anti-viral therapy and
 - to document the whether the proposed regimen compromises anti-viral immune responses as measured by CMV antigenemia.
- HbsAg, anti-
- “**Bystander effects**”: Monitoring for hematologic and non-hematologic toxicities.
- Lipid profile

Informed Consent Document and Others

- Revised to be clearer based on comments by reviewers 1 and 3.
 - Table of schedule of events
- Clarity on study oversight: Phase 1 committee; IRB.

Conclusions

- The experimental plan is designed to optimize the combinatorial use of
 - vaccination with viral vector expressing NY-ESO-1/TRICOM for generating high avidity tumor-specific CD8+ T cells with type 1 effector functions.
 - addition of rapamycin at varying doses (2mg Vs 4mg PO daily) and/or varying duration (2 Vs 4 weeks) after immunization of ovarian cancer patients.
- The observations and outcomes obtained are expected to determine the dose and schedule for optimizing the use of these combinatorial immunotherapy strategies against ovarian cancer in phase II trials