SYNERGY: A Phase 1b/2 Study of Nenocorilant, a Selective Glucocorticoid Receptor Antagonist, Plus Nivolumab in Patients With Advanced Solid Malignancies

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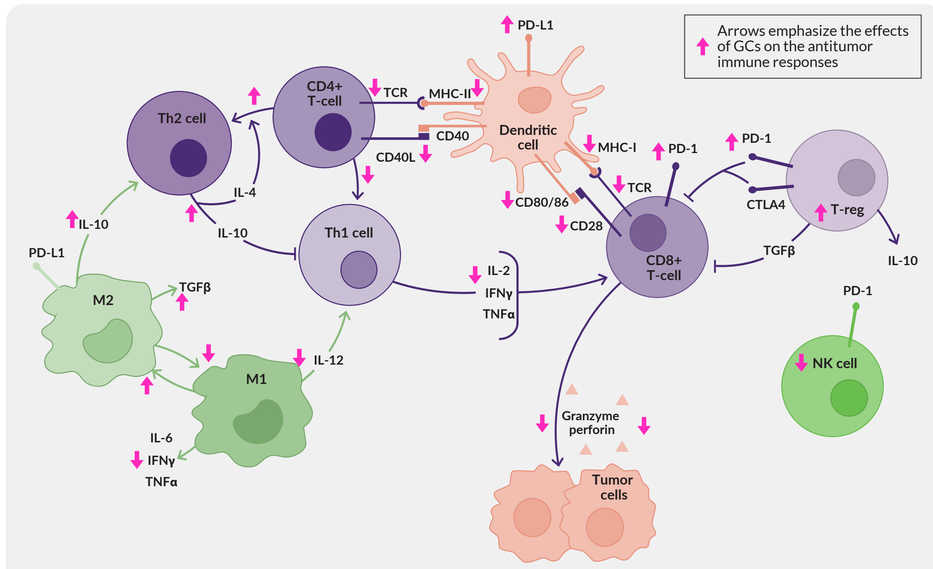
SUMMARY

- The glucocorticoid receptor (GR) is widely expressed on cancer cells and tumor-infiltrating immune cells. Activation of the GR suppresses the anticancer immune response, and use of glucocorticoids is associated with poor outcomes in patients treated with anti-programmed cell death protein 1 ligand 1 (PD[L]1) therapy
- Selective GR antagonists (SGRAs) inhibit the effects of glucocorticoids at the GR and enhance tumor growth inhibition when combined with anti-PD(L)1 therapy in syngeneic tumor models
- The SGRA relacorilant, in combination with nab-paclitaxel, significantly improved overall survival in adult patients with platinum-resistant ovarian cancer who have received 1–3 prior lines of therapy, at least one of which included bevacizumab, leading to its recent FDA approval in this population
- SYNERGY is evaluating whether the investigational SGRA nenocorilant may enhance or restore sensitivity to the anti-PD(L)1 agent nivolumab
  - Phase 1b aims to determine the optimal dose and schedule of nenocorilant + nivolumab
  - These data will be used to inform a phase 2 study to further evaluate the efficacy and safety of this combination in selected tumor types

BACKGROUND AND OBJECTIVE

- Anti-PD[L]1 antibodies target a key immune checkpoint that tumors use to evade immunosurveillance[1,2]
- However, many tumors are refractory to anti-PD(L)1 therapy or eventually develop secondary resistance[3]
- The GR, a ligand-activated transcription factor, is expressed by tumor cells and a wide range of tumor-infiltrating immune cells[4,5]
- Glucocorticoids—GR agonists—interfere with the anticancer immune response by decreasing antigen presentation, exhausting CD8+ T-cell effector function, and enhancing the suppressive phenotype of regulatory T-cells and myeloid-derived suppressor cells (**Figure 1**)[5-8]
- Dysregulated endogenous cortisol or use of exogenous glucocorticoids prior to or with anti-PD(L)1 therapy are associated with poor outcomes[9-11]

Figure 1. GR-mediated Effects in the Tumor Microenvironment



CD, cluster of differentiation; CTLA, cytotoxic T-lymphocyte–associated protein; GCs, glucocorticoids; IL, interleukin; INF, interferon; M, macrophage; MHC, major histocompatibility complex; NK, natural killer; PD, programmed cell death protein; PD-L, PD-ligand; TCR, T-cell receptor; TGF, transforming growth factor; Th, T-helper cell; TNF, tumor necrosis factor; T-reg, regulatory T-cell.

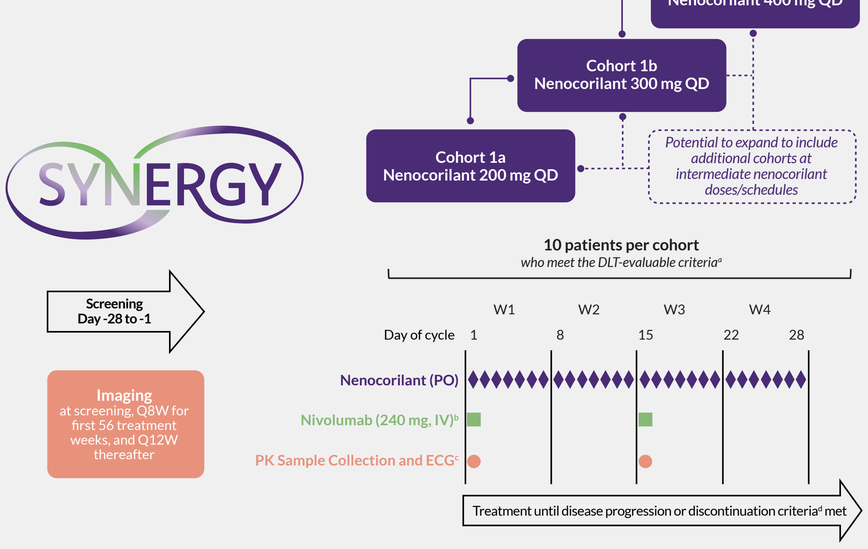
- SGRAs inhibit the antiapoptotic and immunosuppressive effects of glucocorticoids at the GR and have shown synergistic activity with cytotoxic chemotherapy[12,13]
  - In the phase 3 ROSELLA study, the SGRA relacorilant combined with nab-paclitaxel significantly improved progression-free survival (PFS) and overall survival in patients with platinum-resistant ovarian cancer who had received 1–3 prior lines of therapy, including bevacizumab, with a manageable safety profile; this regimen was recently FDA approved in this population[12-14]
- In nonclinical models, inhibition of GR signaling inhibited tumor growth via immune-mediated effects, including:
  - Increasing expression of major histocompatibility complex class-1 in tumor cells, leading to CD8+ T-cell infiltration[15]
  - Reducing checkpoint expression in T-cells and increasing CD8+ T-cell effector functions[16]
  - Reducing the immunosuppressive effects of regulatory T-cells and myeloid-derived suppressor cells[17,18]
- SGRAs also promote anticancer immune activity by:
  - Reversing glucocorticoid-induced immunosuppression in ex vivo human peripheral blood mononuclear cells
  - Enhancing the sensitivity of refractory syngeneic models to anti-PD(L)1 therapy
  - Increasing infiltration of effector T-cells
  - Reducing the infiltration of myeloid-derived suppressor cells[19,20]
- **Nenocorilant** is an investigational, orally administered, competitive, reversible SGRA with high selectivity for GR over other nuclear hormone receptors[21]

METHODS

Study Design

- SYNERGY (NCT07276373) is a phase 1b/2, open-label, multicenter, US-based study in patients with advanced solid malignancies; the dose-finding phase 1b is evaluating escalating doses of nenocorilant given with a fixed dose and schedule of nivolumab (**Figure 2**)

Figure 2. SYNERGY Study Schema (Dose-finding Phase 1b)



[a]Enrolled patients not meeting the DLT-evaluable criteria will be replaced.
[b]Patients may choose to switch to a nivolumab 480-mg IV Q4W dosing regimen after 3 months.
[c]PK sample collection will be conducted on C1D1 and C1D15, then C2+D1 thereafter. ECG testing will be conducted on C1D1, C1D15, C2D1, and EOT.
[d]Includes but not limited to unacceptable toxicity or AEs precluding further study treatment, patient refuses further treatment, or investigator decision.
AE, adverse event; C, cycle; D, day; DLT, dose-limiting toxicities; ECG, electrocardiogram; EOT, end of treatment; IV, intravenous; Q12W, every 12 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, daily; PK, pharmacokinetics; PO, oral; W, week.

Phase 1b Primary Endpoints

- Safety and tolerability, evaluated via dose-limiting toxicities (DLTs), adverse events (AEs), and dose modifications and treatment discontinuations due to AEs
- MTD and/or the optimal dose/schedule of nenocorilant when given in combination with nivolumab
- Safety endpoints will be summarized using descriptive statistics

Phase 1b Secondary Endpoints

- Objective response rate, duration of response, best overall response, duration of stable disease, and PFS by RECIST v1.1 and iRECIST, as assessed by the investigator
- Impact of nenocorilant on the QT interval
- Nenocorilant steady-state plasma pharmacokinetics parameters
- Time-to-event endpoints will be estimated using Kaplan-Meier methods, and exact 95% confidence intervals will be calculated using the Clopper-Pearson method

Phase 1b Eligibility Criteria

Table 1. Key Inclusion Criteria

Adults aged ≥18 years with solid malignancies who have received all available standard therapies for the specific tumor type or for which no standard therapy exists, unless the patient is intolerant of treatment
Life expectancy of ≥3 months
Evaluable disease based on RECIST v1.1
ECOG performance status of 0 or 1
Adequate organ function
Negative serum or urine pregnancy test where appropriate

ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 2. Key Exclusion Criteria

Past or current grade ≥3 immune-related AEs due to anti-PD(L)1 therapy or that resulted in anti-PD(L)1 therapy discontinuation
Medical history of adrenal insufficiency or an autoimmune or inflammatory disease requiring immunosuppressive therapy
Concurrent treatment with mifepristone or another GR modulator
Unable to swallow, retain, or absorb oral medication
Requires treatment with a prohibited medication, including but not limited to systemic corticosteroids and CYP3A inducers/inhibitors
Clinically significant uncontrolled condition(s) that may confound the results of the trial or interfere with safety or participation
Untreated/uncontrolled brain metastases
QTcF interval >450 msec, a family history of long QT syndrome or unexplained sudden death at young age

AEs, adverse events; CYP, cytochrome P450; GR, glucocorticoid receptor; PD(L)1, programmed cell death protein 1 ligand 1; QTcF, Fridericia-corrected QT interval.

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Presenter Disclosure

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