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New Drug Development and Clinical Pharmacology

A Phase I, First-in-Human Study of GSK2849330, an Anti-HER3 Monoclonal Antibody, in HER3-Expressing Solid Tumors

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. HER3 • Neuregulin-1 • GSK2849330 • *NRG1* fusion • Pharmacokinetics • Biomarkers

Abstract

Background. GSK2849330, an anti-HER3 monoclonal antibody that blocks HER3/Neuregulin 1 (NRG1) signaling in cancer cells, is engineered for enhanced antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. This phase I, first-in-human, open-label study assessed the safety, pharmacokinetics (PK), pharmacodynamics, and preliminary activity of GSK2849330 in patients with HER3-expressing advanced solid tumors.

Patients and Methods. Patients with various tumor types were prospectively selected for HER3 expression by immunohistochemistry; a subset was also screened for NRG1 mRNA expression. In the dose-escalation phase, patients received GSK2849330 1.4–30 mg/kg every 2 weeks, or 3 mg/kg or 30 mg/kg weekly, intravenously (IV). In the dose-expansion phase, patients received 30 mg/kg GSK2849330 IV weekly.

Results. Twenty-nine patients with HER3-expressing cancers, of whom two expressed NRG1, received GSK2849330 (dose escalation: $n = 18$, dose expansion: $n = 11$). GSK2849330 was well tolerated. No dose-limiting toxicities were observed. The highest dose, of 30 mg/kg weekly, expected to provide full target engagement, was selected for dose expansion. Treatment-emergent adverse events (AEs) were mostly grade 1 or 2. The most common AEs were diarrhea (66%), fatigue (62%), and decreased appetite (31%). Dose-proportional plasma exposures were achieved, with evidence of HER3 inhibition in paired tissue biopsies. Of 29 patients, only 1 confirmed partial response, lasting 19 months, was noted in a patient with *CD74-NRG1*-rearranged non-small cell lung cancer (NSCLC).

Conclusion. GSK2849330 demonstrated a favorable safety profile, dose-proportional PK, and evidence of target engagement, but limited antitumor activity in HER3-expressing cancers. The exceptional response seen in a patient with *CD74-NRG1*-rearranged NSCLC suggests further exploration in *NRG1*-fusion–positive cancers. ***The Oncologist*** 2021;26:e1844–e1853

Implications for Practice: This first-in-human study confirms that GSK2849330 is well tolerated. Importantly, across a variety of HER3-expressing advanced tumors, prospective selection by HER3/NRG1 expression alone was insufficient to identify patients who could benefit from treatment with this antibody-dependent cell-mediated cytotoxicity– and complement-dependent cytotoxicity–enhanced anti-HER3 antibody. The only confirmed durable response achieved was in a patient with *CD74-NRG1*-rearranged lung cancer. This highlights the potential utility of screening for *NRG1* fusions prospectively across tumor types to enrich potential responders to anti-HER3 agents in ongoing trials.

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Introduction

HER3 (*ERBB3*) is a member of the human epidermal growth factor receptor (HER or ERBB) family of receptor tyrosine kinases (RTKs). Although HER3 lacks intrinsic kinase activity, binding of HER3 ligands, such as heregulin (NRG1), and heterodimerization with other RTKs, including epidermal growth factor receptor HER2/ERBB2 or HER4 proteins [1–3], triggers activation of several signaling networks crucial for a variety of cellular processes, such as proliferation, differentiation, and survival [4, 5].

HER3 and/or its ligand, NRG1, are overexpressed to varying degrees in several cancers, including head and neck squamous-cell carcinomas (HNSCC), non-small cell lung cancer (NSCLC), gastric cancer, and other solid tumors [6–9]. HER3 protein expression has been associated with poor survival in various tumor types including breast, melanoma, and ovarian tumors [10–14], and therefore, HER3 has been postulated as a potential therapeutic target [9, 15]. Furthermore, elevated expression of NRG1 has been shown to induce HER3 activation and promotion of tumor growth in head and neck and ovarian cancer cells [16, 17]. Similarly, *NRG1* gene fusions can result in increased HER3 activity, activating downstream signaling and driving tumor growth and survival [18, 19].

GSK2849330 is a novel humanized IgG1/IgG3 monoclonal antibody (mAb) that binds with high affinity and specificity to the extracellular domain III of HER3 and prevents NRG1 ligand binding to HER3, thereby inhibiting receptor dimerization and downstream signaling. GSK2849330 is distinct from other HER3-directed mAbs in development because it is also glycoengineered for enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) via high-affinity binding to human FcγRIIIA and further modified to enhance complement-dependent cytotoxicity (CDC) via high-affinity binding to human complement protein C1q, thereby maximizing potential mechanisms of antitumor activity. In HER3 expressing cancer cell lines, GSK2849330 demonstrated increased ADCC and CDC activity relative to the parental antibody; the ADCC and CDC activity also correlated with the level of HER3 expression on the cell surface [20]. Based on these findings, we carried out the first-in-human trial of GSK2849330 in patients with HER3-positive advanced solid tumor malignancies.

Materials and Methods

Study Design

This was a phase I, first-in-human, open-label, dose-escalation study of the anti-HER3 mAb, GSK2849330, in patients with advanced solid tumors expressing HER3 (NCT01966445). The dose-escalation phase included patients with various tumor histologies. In the dose-expansion phase, patients with one of four histologies (melanoma, gastric/gastroesophageal cancer, HNSCC, and NSCLC) were enrolled.

This study was conducted at eight centers in the U.S., Australia, and The Netherlands. The first patient was enrolled on November 26, 2013, and the last patient completed the last visit on September 18, 2017. The study protocol, amendments, and informed consent were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board (detailed in supplemental online Table 1). All participants provided informed consent before taking part in the study.

Patient Population

Eligible patients were aged ≥18 years, with Eastern Cooperative Oncology Group (ECOG) performance status score 0 or 1. Patients were required to have archival tumor specimens or fresh biopsy for screening assessment of tumor HER3 expression; heregulin (*NRG1*) mRNA expression was also determined during screening for patients with NSCLC and HNSCC in the dose-expansion phase. For dose escalation, eligible patients had HER3-positive (immunohistochemistry [IHC] 2+/3+ membrane staining) solid tumors by IHC, for which no standard therapeutic alternatives were available. For dose expansion, eligible patients were required to have measurable disease defined by RECIST version 1.1 and previously treated (more than four lines of systemic therapy), unresectable stage III/IV cancer of the following types: melanoma or gastric/gastroesophageal cancer with high HER3 protein expression (IHC 3+), or HNSCC or NSCLC expressing HER3 protein (IHC ≥1+) and high NRG1 mRNA expression (by reverse transcriptase polymerase chain reaction [RT-PCR]), to test the hypothesis that high HER3 and/or NRG1 expression may increase the likelihood of response to GSK2849330. See Supplemental online Materials and methods for full inclusion/exclusion criteria.

Interventions

GSK2849330 was administered by intravenous (IV) infusion over 1 hour. The starting dose in dose escalation was 1.4 mg/kg, administered once weekly in a single patient. Dose escalation progressed to 3, 10, and 30 mg/kg administered every 2 weeks, followed by 3 mg/kg and 30 mg/kg once-weekly cohorts, with a target of three patients enrolled per cohort.

The occurrence of any dose-limiting toxicities (DLTs) was evaluated using a Neuenschwander-Continual Reassessment Method (N-CRM) [21] to provide a model-based recommendation for dose-escalation decisions. Such dose-escalation decisions were based on review of safety data, available pharmacokinetics (PK) and pharmacodynamics (PD) data, and the N-CRM output.

Up to three additional patients who consented to provide pre- and on-treatment tumor biopsies could be enrolled into the PK/PD cohorts at any dose level previously determined to be tolerable.

Study Objectives

The primary study objective was to determine the safety and tolerability of GSK2849330. Secondary objectives were to characterize PK, evaluate preliminary evidence of target engagement and PD, immunogenicity, determine the recommended dose regimen(s) for further exploration, and evaluate preliminary clinical benefit of GSK2849330 in the dose-expansion phase.

Safety Assessments

Physical examination, vital signs, 12-lead electrocardiograms, echocardiography, and clinical laboratory tests, ECOG performance status, and monitoring for adverse events (AEs) and serious AEs (SAEs) were performed at prespecified timepoints. More details are provided in the supplemental online materials and methods.

PK and Immunogenicity Assessments

Blood samples were collected for measurement of GSK2849330 concentrations and antidrug antibodies as described in the supplemental online materials and methods.

Clinical Activity

Disease progression and tumor response were assessed every 8 weeks according to RECIST 1.1 [22].

PD Assessments

Pretreatment and on-treatment (day 15) biopsy tissues (tumor and normal skin) were analyzed for HER3 target engagement and immune markers using IHC. Whole blood was collected for peripheral immune cell profiling by flow cytometry. Core or punch biopsies were obtained in patients who consented to these procedures at screening and on day 15. HER3 immunoreactivity on the cell surface of invasive tumor cells was assessed for staining intensity (weak [1+], moderate [2+], or strong [3+]) and quantified using the H-score method. CD16a, CD68, and Granzyme B were also measured. More details of the IHC and flow cytometry assays are provided in the supplemental online materials and methods.

Statistical Analysis

Standard summary statistics were generated as appropriate for the data. An N-CRM model supported dose-escalation decisions; the minimum number of patients anticipated to complete dose escalation was 13 if no DLTs were observed. As per this approach, the recommended dose was the dose level with the highest probability of having a DLT rate in the acceptable toxicity range (16%–33%), provided no dose was skipped during dose escalation. Once the recommended dose(s) and schedule(s) were confirmed, 12–30 patients per group were planned to be enrolled in the dose-expansion phase.

The all-treated population comprised all patients who received one or more dose of GSK2849330; this population was used for safety assessment. The PK concentration population consisted of patients for whom one or more post-dose PK sample was obtained and analyzed. The PK parameter population consisted of all patients from the PK concentration population for whom valid PK parameters were derived. The PD population consisted of patients from the all-treated population for whom evaluable paired pre-treatment and on-treatment PD samples were obtained and analyzed.

Results

Patient Population

Patient demographics and baseline characteristics are shown in Table 1. Twenty-nine patients were enrolled and treated with GSK2849330 (supplemental online Fig. 1). In the dose-escalation phase, 18 patients in 6 cohorts received GSK2849330 (1.4 mg/kg, 3 mg/kg, and 30 mg/kg weekly, and 3 mg/kg, 10 mg/kg, and 30 mg/kg every 2 weeks). In the dose-expansion phase, 11 patients were enrolled and administered a dose of 30 mg/kg weekly.

All cancers were HER3-positive (IHC 2+ or 3+) by IHC, with the most common histologies being gastrointestinal (28%), colorectal (24%), and ovarian carcinomas (14%). Per study inclusion criteria, two patients with NSCLC in the dose-expansion cohort were also NRG1-positive by RT-PCR, but only one patient harbored a *CD74-NRG1* fusion (Table 1).

Safety and Tolerability

The observed overall safety and tolerability profile of GSK2849330 was favorable and manageable. No DLTs were observed, no dose reductions were required, and a maximum tolerated dose (MTD) was not identified. As no DLTs or MTD was identified in the dose-escalation phase, the highest dose tested (30 mg/kg weekly) was chosen for the dose-expansion phase to ensure full target engagement and increase the likelihood of efficacy signals.

The median time on study treatment for all patients was 6.1 weeks (range, 2–82). Twenty-five (86%) patients completed the study; 3 (10%) discontinued treatment for reasons outlined in supplemental online Table 2.

All 29 patients experienced treatment-emergent AEs (TEAEs), which were mostly grade 1 or 2 (Table 2). The most frequently reported TEAEs were gastrointestinal events (including diarrhea, which was the most commonly reported AE overall), fatigue, decreased appetite, abdominal pain, and nausea (Table 2; supplemental online Table 3). There were no grade 4 events. Most patients (27/29, 93%; supplemental online Table 4) experienced a treatment-related adverse event (TRAE). Seven of 13 patients experienced grade 3 TRAEs. A total of eight TRAEs were reported in seven patients: diarrhea ($n = 3$), increased gamma-glutamyltransferase ($n = 2$), and abdominal pain, fatigue, and anemia ($n = 1$ each).

There were six SAEs during the study, each experienced by a single patient. Only one (grade 2 decreased ejection fraction) was considered by the investigator as possibly related to study treatment. This patient had an ejection fraction on day 30 that showed a 15% decrease from baseline; no overt cardiac symptoms were observed, and treatment was interrupted with unknown outcome as the patient progressed and was unable to attend the follow-up visit or undergo a follow-up echocardiogram. Five patients died, four from disease progression and one from *Escherichia coli* sepsis unrelated to study drug. With the exception of this *E. coli* fatality, no other patients experienced clinically meaningful changes in laboratory parameters.

Table 1. Summary of patient demographics and baseline characteristics (all-treated population)

Parameter	Total population ($n = 29$)
Sex, *n* (%)	
Female	13 (45)
Male	16 (55)
Age, median (range), yr	63 (31–86)
Race, *n* (%)	
Asian	1 (3)
White	28 (97)
ECOG performance status, *n* (%)	
0	14 (48)
1	15 (52)
Primary tumor type, *n* (%)	
Gastric/gastroesophageal junction adenocarcinoma	8 (28)
Colorectal carcinoma	7 (24)
Ovarian carcinoma	4 (14)
Melanoma	3 (10)
Non-small-cell lung cancer	3 (10)
Bladder carcinoma	1 (3)
Breast carcinoma	1 (3)
Head and neck squamous-cell carcinoma	1 (3)
Pancreatic carcinoma	1 (3)
HER3 status by IHC, *n* (%)	
Positive[a]	29 (100)
NRG1 status, *n* (%)	
Positive[b]	2 (7)
Not assessed	27 (93)
Number of lines of previous anticancer therapy, *n* (%)	
1	9 (31)
2	15 (52)
3	3 (10)
4	2 (7)

[a]IHC 2+ or 3+ (dose-escalation cohort); IHC3+ for gastric cancer and melanoma, and IHC ≥1+ for head and neck squamous-cell carcinoma and non-small-cell lung cancer (dose-expansion cohort).
[b]Assessed by reverse transcriptase polymerase chain reaction in only a subset of patients in dose expansion per study inclusion criteria. One patient harbored a *CD74-NRG1* fusion based on MSK-IMPACT assay performed at Memorial Sloan Kettering Cancer Center [24].
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; *NRG1*, neuregulin 1.

Among patients with AEs of special interest, 3 experienced infusion reactions and 10 experienced events potentially associated with allergic reactions (6 with dyspnea; 4 with rash). All were grade 1–2 and none resulted in discontinuation of study treatment. No antidrug antibodies were detected in any evaluable patients receiving drug. There was no obvious correlation observed between GSK2849330 dose and occurrence of AEs; however, a relationship cannot be definitively ruled out because patient numbers were low in some dose groups (supplemental online Table 4).

Pharmacokinetics

Mean plasma GSK2849330 concentrations following the first dose are shown in Figure 1. Plasma concentrations increased with increasing doses for both dose regimens and profiles were consistent with a typical IgG monoclonal antibody. PK parameters are summarized in supplemental online Table 5. Briefly, median T_{max} occurred around 2 hours after dosing across dose regimens except one patient in the 3 mg/kg weekly group whose T_{max} was at 6 hours; geometric mean C_{max} was 779 μg/mL (coefficient of variation 14.5 between patients) at the highest dose of 30 mg/kg weekly, with an $AUC_{0–168}$ of 54,388 h*μg/mL (where AUC is the area under the curve).

HER3 Inhibition in Skin Tissue

Downregulation of HER3 membrane expression measured by IHC in skin biopsies was used to evaluate target engagement by GSK2849330, based on preclinical data (supplemental online Fig. 2), ease of tissue access, and previously reported results using skin biopsies by the first-in-human study of lumretuzumab, an anti-HER3 mAb [23]. During the dose-escalation phase of the study, evaluable paired skin biopsies for 15 patients were analyzed for changes in HER3 expression at day 15 following first dose of GSK2849330 compared with pretreatment baseline levels. On average, 66% downregulation (range, −3.8 to 100%; $p < .001$ by Wilcoxon signed rank test) of HER3 membrane expression was observed, with a decrease in signal observed in 14/15 patients and > 90% inhibition observed in 6 of 15 patients (Fig. 2). There was no apparent association in the degree of inhibition with dose level, tumor type or clinical response.

Efficacy

Of the 29 enrolled patients with HER3-expressing cancers treated at various doses, 1 (3%) patient had a partial response, 7 (24%) had stable disease, 1 had noncomplete response/nonprogressive disease, 16 (55%) had progressive disease, and 4 (14%) were not evaluable per RECIST 1.1 criteria (Fig. 3; supplemental online Table 6). The single responder was an 86-year-old man with NSCLC, harboring a *CD74-NRG1* fusion (Fig. 3; supplemental online Table 6). This patient was treated with GSK2849330 at the recommended phase II dose of 30 mg/kg weekly followed by an optional change to every 2 weeks after 24 weeks of treatment. This confirmed partial response lasted for 1 year and 7 months. Details of this case report have been published previously [24].

The seven patients with stable disease had various HER3-expressing cancers, received a range of GSK2849330 doses, and were on treatment for an average of 11.8 weeks (range, 9.1–24.1 weeks; Fig. 3). Of these seven patients, three were on treatment for >22 weeks (gastric tumor: 24.1 weeks, pancreatic tumor: 23.3 weeks, ovarian tumor: 22.4 weeks). Given the small numbers of patients, no discernible relationship could be determined between the response, dose, and tumor type. Furthermore, we did

Table 2. Treatment-emergent grade 1–3 adverse events reported in ≥15% of patients (all-treated population)

Preferred term, *n* (%)	Grade 1	Grade 2	Grade 3	Total ($n = 29$)
Patients with any event				29 (100)
Diarrhea	16 (55)	0	3 (10)	19 (66)
Fatigue	5 (17)	12 (41)	1 (3)	18 (62)
Decreased appetite	3 (10)	6 (21)	0	9 (31)
Abdominal pain	2 (7)	3 (10)	2 (7)	7 (24)
Nausea	4 (14)	2 (7)	1 (3)	7 (24)
Dyspnea	4 (14)	2 (7)	0	6 (21)
Headache	5 (17)	1 (3)	0	6 (21)
Vomiting	6 (21)	0	0	6 (21)
Back pain	1 (3)	4 (14)	0	5 (17)
GGT increased	0	1 (3)	4 (14)	5 (17)
Myalgia	3 (10)	2 (7)	0	5 (17)

Adverse events were Medical Dictionary for Regulatory Activities–coded preferred terms and graded according to Common Terminology Criteria for Adverse Events, Version 4.0. There were no grade 4 events and one grade 5 event (*Escherichia coli* sepsis resulting in death; not considered drug-related) reported.
Abbreviation: GGT, gamma-glutamyl transferase.

not observe any correlation between response and level of HER3 expression, assessed by HER3 IHC H-score at baseline (supplemental online Fig. 3).

Tumor Microenvironment Effects

To explore potential treatment-related changes in the tumor microenvironment, IHC data for tumor-associated immune cells and markers of activation (CD16, CD68, granzyme B) were available for paired tumor biopsies corresponding to eight patients in the study. Consistent with the drug's efficacy, of the eight paired samples, the majority did not show any evidence of increased immune cell infiltration or activation at day 15 following the first dose of GSK2849330 relative to predose samples. However, in the patient with *NRG1*-fusion–positive NSCLC who achieved durable PR, there was a significant increase in $CD16^+$ natural killer cell and $CD68^+$ macrophage tumor infiltration, as well as granzyme B–positive immune cell tumor infiltrates (Fig. 4).

Furthermore, immunophenotyping by flow cytometry analysis did not reveal any notable significant or sustained changes to peripheral immune cell populations in pre-treatment and on-treatment samples collected at various timepoints (supplemental online Table 7).

Discussion

Herein we report the results of the first-in-human study of GSK2849330, an ADCC- and CDC-enhanced anti-HER3 mAb in patients with advanced solid tumor malignancies that were prospectively selected for HER3 or HER3 and NRG1 positivity. The rationale for this study design was based on maximizing clinical efficacy with multiple modes of action tested in HER3 positive preclinical models (signaling blockade, ADCC, and CDC, see summary of preclinical results in supplemental online data and supplemental online Fig. 2).

Overall, GSK2849330 was associated with a favorable safety and tolerability profile. No MTD was determined and no DLTs were observed. There was no apparent relationship between GSK2849330 dose (or PK exposure) and observed AEs, recognizing that therapeutic mAbs pose challenges in discerning dose–toxicity relationships in first-in-human trials owing to their unique pharmacological properties. These include target selectivity with limited off-target activity, longer half-lives, and rare/delayed toxicities, which preclude determination of DLTs and MTD [25, 26].

The highest dose tested (30 mg/kg once-weekly, with the option to switch to every-other-week dosing after 24 weeks of treatment) was carried forward into the dose-expansion phase. The most common AE, diarrhea, is consistent with the AE profile reported for other HER2/HER3 agents [27, 28]. HER3 is expressed in normal epithelial tissues including the intestinal tract [29], and loose stools were observed in preclinical toxicology studies (unpublished data), suggesting an on-target effect.

To understand whether the clinical hypothesis was appropriately tested, it is important to consider whether adequate target engagement was achieved by GSK2849330. For all dose levels studied, maximum and trough plasma concentrations (C_{max} ~30–779 μg/mL, C_{trough} ~5–69 μg/mL) ranged from ~450 to ~70,000 times greater than the half-maximal inhibitory concentration for blockade of HER3 signaling in vitro (0.011 μg/mL [76 pM], supplemental online Fig. 2D, E). For the 30 mg/kg IV weekly dose regimen selected for expansion, the C_{trough} was 188 μg/mL (Fig. 1) after the first dose, indicating target coverage >9-fold above concentrations associated with antitumor activity in mouse xenograft models (C_{trough} ~20 μg/mL). Unfortunately, there were limited evaluable data from paired tumor biopsies in this study, and no conclusions could be drawn regarding target engagement in tumor tissue. However, HER3 membrane expression by IHC was available for paired skin biopsies, which served as surrogate tissue to assess target engagement. Greater than 65% average reduction of HER3 membrane expression was noted, regardless of dose tested, suggesting significant target engagement at all dose levels studied. These results were consistent

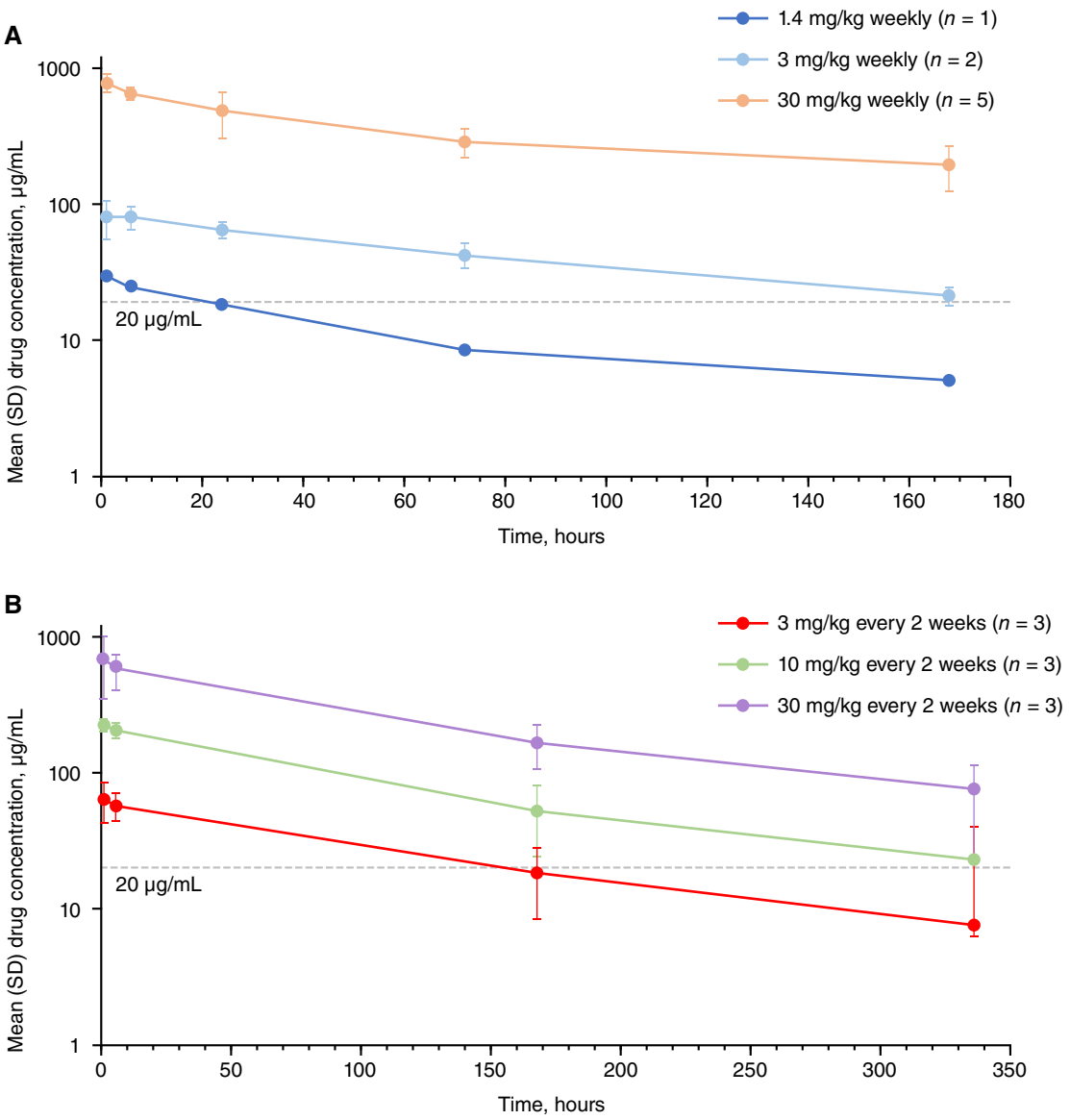

Figure 1. Pharmacokinetic profiles following the first dose of GSK2849330. Plasma concentration-time graphs for **(A)** weekly dosing regimen over days 1–8 following the first dose, and **(B)** every 2-week dosing regimen over days 1–15 following the first dose are shown. Preclinical mouse xenograft efficacy studies showed that antitumor efficacy may be achieved with systemic plasma trough concentrations ≥20 µg/mL (dashed line).

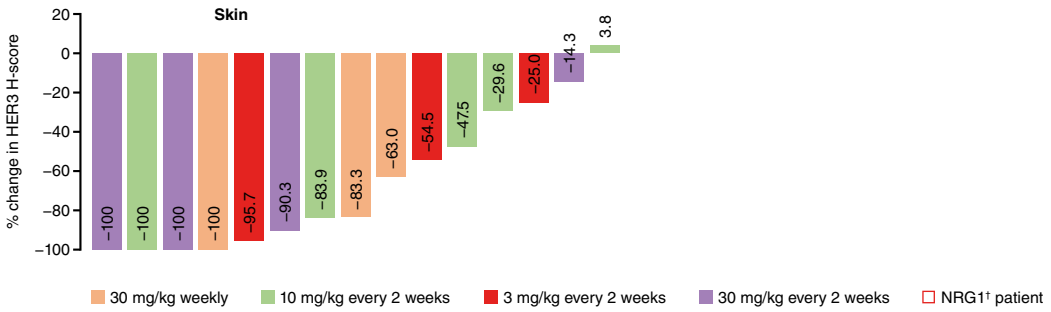

Figure 2. Pharmacodynamic effects of GSK2849330 in skin biopsies by immunohistochemistry. Figure shows percentage change in HER3 expression levels in paired skin biopsies at day 15 following first dose of treatment relative to baseline in the dose-escalation phase of the study ($n = 15$). Skin biopsies were not taken for the patient with *NRG1*-fusion–positive non-small cell lung cancer who achieved durable partial response. Each bar represents one patient.

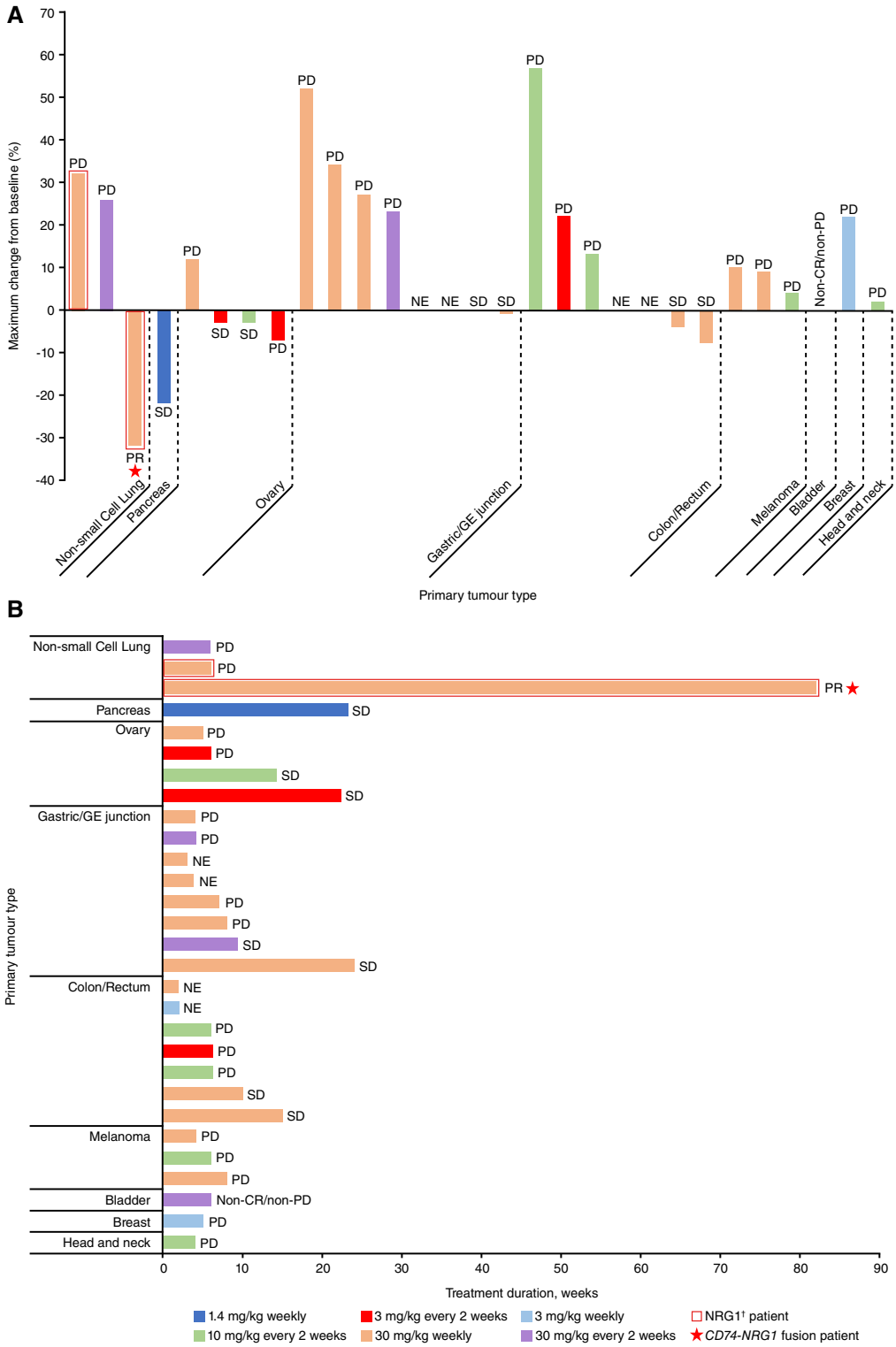

Figure 3. Overall antitumor activity of GSK2849330 based on objective response (per RECIST version 1.1) and duration of treatment. **(A):** Waterfall plot showing maximum percentage change from baseline in the sum of the longest diameters of target lesions. **(B):** Swimmer plot showing the length of treatment duration of patients grouped by tumor type across all doses of GSK2849330. The best confirmed responses (per RECIST) are annotated for each patient in these plots. The red outlined bars indicate *NRG1*-positive patients ($n = 2$) who were assessed by reverse transcriptase polymerase chain reaction and enrolled per study inclusion criteria. †, *NRG1*-fusion-positive patient.

Abbreviations: CR, complete response; GE, gastroesophageal; *NRG1*, neuregulin 1; PD, progressive disease; PR, partial response; SD, stable disease.

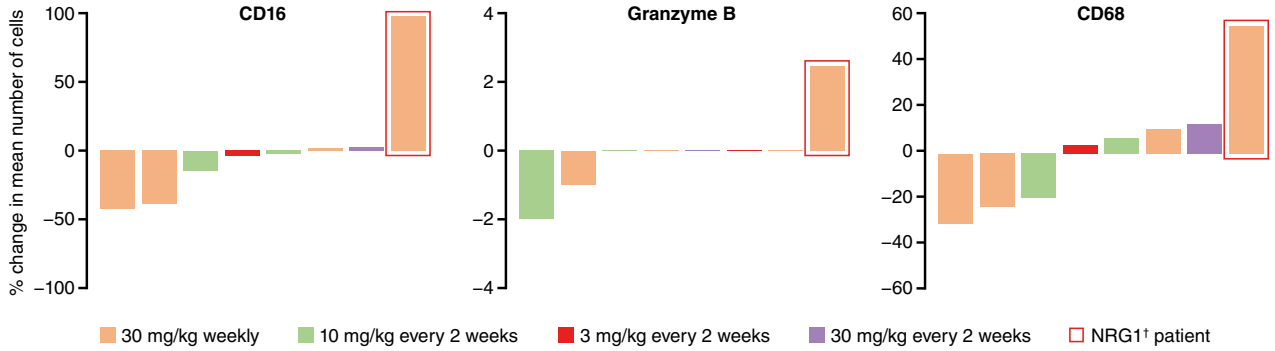

Figure 4. Tumor micoenvironment effects of GSK2849330 in tumor tissues by immunohistochemistry. Figure shows percentage change in CD16, CD68, and granzyme B in all evaluable paired tumor biopsies at day 15 following first dose of treatment relative to baseline ($n = 8$). Each bar represents one patient.
†, *NRG1*-fusion-positive patient.
Abbreviation: *NRG1*, neuregulin 1.

with the findings reported by the first-in-human study of lumretuzumab [23].

Furthermore, in a previously published immune–positron emission tomography (PET) imaging study [30], ^{89}Zr-labelled GSK2849330 was administered to patients with HER3-positive advanced solid tumors, wherein modeling suggested 90% target inhibition in tumor at a dose of ~18 mg/kg. Taken together, these findings suggest that the 30 mg/kg weekly dosing that was taken forward into dose expansion cohorts in the study achieved full target engagement in tumor tissue.

Patients with HER3-positive tumors were enrolled in this study with the intent of maximizing potential response to GSK2849330 as higher HER3 expression was related to higher ADCC and CDC activity of GSK2849330 in preclinical studies [20]. However, limited antitumor activity was observed in this study, consisting of one partial response and seven stable disease responses. There was no apparent relationship between tumor lesion changes and pretreatment HER3 expression (supplemental online Fig. 3). Furthermore, for most of the patients, no sustained or significant increases in relevant immune cell populations or effector function were observed in available tumor biopsy (Fig. 2) and peripheral flow cytometry data (supplemental online Table 7). Collectively, these data suggest that HER3 expression alone was insufficient to confer tumor sensitivity to GSK2849330 in most patients.

These results are consistent with studies of other anti-HER3 mAbs, which have been assessed in clinical trials across a range of tumor types and been found to be tolerable, but with limited monotherapy efficacy. They generally do not elicit dramatic objective responses but have been associated with stable disease or disease control, as demonstrated by seribantumab (MM-121) [31], patritumab (U3-1287) [32], lumretuzumab [23], KTN3379 [33], LJM716 [34, 35], and AV-203 [36], in patients with advanced solid tumors.

Notably, the only partial response in the present study was also in a patient with NSCLC of the invasive mucinous adenocarcinoma (IMA) subtype, harboring a *CD74-NRG1* fusion, with a prolonged response lasting 19 months (described in detail in [24]). Even though clinical responses to GSK2849330 were limited to this one patient, it is noteworthy that we have observed profound antitumor activity by way of durable tumor regressions and substantial PD effects in multiple patient-derived models, harboring other *NRG1* fusions and constitutive activation/dependence on the pathway [37, 38]. Furthermore, this patient expressed HER3 levels comparable to or even lower than nonresponders and was the only patient in which GSK2849330 elicited a robust immune response in paired tumor biopsy data, particularly increased CD16 tumor infiltrating cells, suggesting ADCC activity. Whether NRG1 fusions lead to HER3 receptor clustering and thereby invoke ADCC by GSK2849330 or trigger immunogenic cell death mediated by cytotoxicity of GSK2849330 in this context is unclear and could be explored in future investigations.

NRG1 fusions have been observed in 27%–31% of patients with IMA [24] and at a low frequency in multiple tumor types, especially lung and pancreatic cancers [24, 39–41]. These rearrangements drive pathway activation and dependence on HER3 signaling, thus conferring sensitivity to HER3 inhibition. This is supported by emerging data from trials with MCLA-128, an HER2/HER3 bispecific mAb, in which three patients with *NRG1*-fusion–positive cancers exhibited tumor shrinkage [42, 43]. Notably, NRG1 overexpression alone does not appear to confer sensitivity to anti-HER3 mAbs, such as the failure of MM-121/seribantumab to improve progression-free survival in a randomized phase II study in patients with heregulin-positive NSCLC [44]. This is consistent with the lack of response observed in the other NRG1-positive patient in our study, who did not carry the fusion and progressed rapidly. Collectively, these data suggest that the genetic alterations of *NRG1* fusions are a driver of disease and may be associated with greater likelihood to respond to anti-HER3 agents as monotherapy. This hypothesis is currently being tested in several basket trials (NCT04383210, NCT04100694, NCT02912949, NCT03805841) in *NRG1*-rearranged cancers.

This study had limitations in fully evaluating the activity of GSK2849330. First, relatively few patients ($n = 9$) were enrolled in the dose-expansion cohort at the 30 mg/kg weekly IV dose, and a majority of them (6/9) were patients with aggressive gastric/gastroesophageal junction tumors. Therefore, the potential clinical benefit of this agent in other settings was not fully explored. However, the totality of evidence from other trials has suggested limited

antitumor activity of anti-HER3 mAbs as monotherapy in unselected populations studied to date, implying that patient-selection and/or combination strategies may be required for clinical benefit. Second, there was limited testing of alternative dosing regimens, such as every-other-week dosing, which may have offered greater convenience and flexibility while still achieving high target coverage; data generated in this study and from a prior immunoPET study [30] of GSK2849330 suggest that a dose of 30 mg/kg every 2 weeks is likely to provide adequate target coverage. However, there were no results available to inform dose selection for the expansion phase of the current trial because of contemporaneous conduct of the immunoPET study. Third, only two patients with *NRG1*-positive NSCLC were enrolled, of whom only one harbored an *NRG1* fusion and turned out to have a durable partial response, whereas the other patient whose cancer did not harbor an *NRG1* fusion progressed rapidly. Although this response has been intriguing, additional data would be required to fully characterize the activity of GSK2849330 in *NRG1*-fusion–positive tumors. Last, the limited response and lack of sufficient evaluable samples precluded the assessment of PD, HER3 pathway markers, immune effects on the tumor microenvironment, and other potential predictive biomarkers of response to GSK2849330 monotherapy or combination therapy.

Conclusion

GSK2849330 was well tolerated up to a dose of 30 mg/kg once weekly with evidence of adequate exposure and target engagement. Limited efficacy was observed as monotherapy in patients with HER3-positive solid tumors; however, a durable response noted in a patient with CD74-*NRG1*-fusion–positive NSCLC suggests screening of *NRG1* fusions as a patient selection strategy to enhance antitumor activity by GSK2849330. As these genomic alterations are reported at a low frequency across multiple tumor types, including NSCLC and pancreatic adenocarcinoma [24, 39–41], several basket trials investigating the clinical utility of anti-HER3 agents in *NRG1*-rearranged cancers are currently underway (NCT04383210, NCT04100694, NCT02912949, NCT03805841).

Acknowledgments

We thank our patients, their families, and the site staff for their participation and contributions to this study. We also acknowledge BioWa, Inc. (U.S. subsidiary of Kyowa Hakko Kirin Co., Ltd.) for their POTELLIGENT Technology and COMPLEGENT Technology in developing GSK2849330, an ADCC- and CDC-enhanced anti-ERBB3 mAb. Medical writing support was provided by Leigh O'Connor-Jones, Ph.D., of Fishawack Indicia Ltd., U.K., and was funded by GlaxoSmithKline.

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Disclosures

Michael Millward: AstraZenenca, Pfizer, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Takeda (C/A), AstraZeneca (Other), Bristol-Myers Squibb, Novartis, Roche, AstraZeneca, Takeda, GlaxoSmithKline, BeiGene, Eli Lilly & Co., Apollomics, PIN Pharma, Albion, AkesoBio, AbbVie, C-Stone Pharmaceuticals, Therapim, Five Prime Therapeutics, Dizal, Maxinovel, INXMED, Alpine Bioscience (RF); **Ignacio Garrido-Laguna:** Eisai, Array (C/A), Amgen, Bridgebio, Jacobio, Tolero, Trishula, Bayer, Seattle Genetics, Eli Lilly & Co., Incyte, GlaxoSmithKline, Pfizer, Redhill (RF—Institutional); **Jason D. Lickliter:** GlaxoSmithKline, Bristol Myers Squibb, Beigene, Incyte (RF); **Jan H. M. Schellens:** Modra Pharmaceuticals (E), Modra Pharmaceuticals (OI), Modra Pharmaceuticals (IP), other (patent holder oral; taxanes); **Martijn P. Lolkema:** Pfizer, Roche, Novartis, Bayer, Amgen, Johnson & Johnson, Merck, Sharpe & Dohme, Servier, Sanofi (C/A), Sanofi, Merck, Sharpe & Dohme, Johnson & Johnson, Astellas (RF); **Bruce Hug:** GlaxoSmithKline (E), GlaxoSmithKline (OI); **Bob Gagnon:** GlaxoSmithKline (E, OI); **Catherine Ellis:** GlaxoSmithKline (E, OI); **Gopi Ganji:** GlaxoSmithKline (E, OI); **Christopher Matheny:** GlaxoSmithKline (E, OI); **Alexander Drilon:** Ignyta/Genentech/Roche, Loxo/Bayer/Eli Lilly & Co., Takeda/Ariad/Millennium, TP Therapeutics, AstraZeneca, Pfizer, Blueprint Medicines, Helsinn, Beigene, BergenBio, Hengrui Therapeutics, Exelixis, Tyra Biosciences, Verastem, AbbVie, 14ner/Elevation Oncology, Remedica Ltd., ArcherDX, Monopteros, Novartis, EMD Serono, Melendi, Liberum, Repare (C/A), Pfizer, Exelixis, GlaxoSmithKline, Teva, Taiho, PharmaMar (RF—Institution), Wolters Kluwer (other—Royalties); Merck, Puma, Merus, Boehringer Ingelheim (other), Medscape, OncLive, PeerVoice, Physicians Education Resources, Targeted Oncology, Research to Practice, Axis, Peerview Institute, Paradigm Medical Communications, WebMD, MJH Life Sciences, Med Learning, Imedex, Answers in CME, Medscape, Clinical Care Options (H), Foundation Medicine (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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