First-in-Human Study of Utomilumab, a 4-1BB/CD137 Agonist, in Combination with Rituximab in Patients with Follicular and Other CD20+ Non-Hodgkin Lymphomas

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Translational Relevance

Prior studies have shown that 4-1BB/CD137 agonistic antibodies can deliver costimulatory signals, enhancing antibody-dependent cellular cytotoxicity and potentially eliciting T-cell mediated antitumor immune responses. To evaluate new treatment strategies for relapsed/refractory disease after rituximab therapy, patients with follicular lymphoma (FL) and other CD20^+ relapsed/refractory non-Hodgkin lymphomas (NHLs) were treated with the anti-4-1BB/CD137 antibody utomilumab and rituximab. Utomilumab has previously demonstrated a well-tolerated safety profile and antitumor activity as monotherapy or in combination with the anti-programmed death 1 (PD-1) antibody pembrolizumab in patients with advanced solid tumors. In this phase I study, combined treatment with utomilumab plus rituximab showed a favorable safety profile and clinical activity in patients with relapsed/refractory FL and other CD20^+ NHLs.

Abstract

Purpose: In this phase I study (NCT01307267) we evaluated safety, pharmacokinetics, clinical activity, and pharmacodynamics of treatment with utomilumab plus rituximab in patients with relapsed/refractory follicular (FL) and other CD20^+ non-Hodgkin lymphomas (NHLs).

Experimental Design: Primary objectives were to assess treatment safety and tolerability for estimating the maximum tolerated dose (MTD), using a modified time-to-event continual reassessment method, and selecting the recommended phase II dose (RP2D).
**Results:** Sixty-seven patients received utomilumab (0.03-10.0 mg/kg every 4 weeks [Q4W]) and rituximab (375 mg/m² weekly) in the dose escalation groups or utomilumab (1.2 mg/kg Q4W) plus rituximab in the dose expansion cohort. No patient experienced DLT. The MTD for utomilumab in combination with rituximab was not reached and estimated to be ≥10 mg/kg Q4W. The majority of the utomilumab treatment-related adverse events (AEs) were grade 1-2; the most common AE was fatigue (16.4%). The pharmacokinetics of utomilumab in combination with rituximab was linear in the 0.03-10 mg/kg dose range. A low incidence (1.5%) of treatment-induced anti-drug antibodies against utomilumab was observed. The objective response rate was 21.2% (95% CI 12.1, 33.0%) in all patients with NHL, including 4 complete and 10 partial responses. Analysis of paired biopsies from a relapsed/refractory FL patient with complete response showed increased T-cell infiltration and cytotoxic activity in tumors. Biomarker correlations with outcomes suggested that clinical benefit may be contingent on patient immune function.

**Conclusions:** Utomilumab in combination with rituximab demonstrated clinical activity and a favorable safety profile in patients with CD20⁺ NHLs.
Introduction

Treatment with anti-CD20 antibodies, such as rituximab, induces responses in most patients with CD20+ non-Hodgkin lymphoma (NHL) and results in a significant reduction in the risk of death (1). The antitumor activity of rituximab is believed to be mediated in part by antibody-dependent cellular cytotoxicity (ADCC) (1). However, a substantial proportion of patients develop resistance to treatment, underscoring the need for more effective strategies (1-3). A variety of immunotherapeutic approaches including 4-1BB/CD137, programmed death 1 (PD-1), and PD-ligand 1 (PD-L1) targeted antibodies, as well as bispecific antibodies and chimeric antigen receptor (CAR) T cells are currently under investigation in patients with NHL and other hematological malignancies (4-14).

The anti-epidermal growth factor receptor (EGFR) antibody cetuximab has been reported to enable cross-presentation of tumor antigens by dendritic cells and enhance EGFR-targeted cytotoxic T lymphocyte (CTL) responses in patients with head and neck squamous cell carcinoma (HNSCC) (15). Treatment of HNSCC patients with a combination of cetuximab and the 4-1BB/CD137 agonist antibody urelumab was associated with elevated levels of activated natural killer (NK) cells, myeloid cells, and T cells in circulation (16). These data support the hypothesis that 4-1BB/CD137 agonist antibodies can increase innate and adaptive immune responses arising after treatment with ADCC-competent antibodies.

Utomilumab (PF-05082566) is a fully-human IgG2 agonist mAb that selectively binds human 4-1BB/CD137, resulting in NF-kB activation and downstream cytokine production in cell lines and primary lymphocytes (17). Utomilumab can induce human
leukocyte proliferation and has demonstrated significant antitumor activity as a single agent in human peripheral blood lymphocyte (PBL) severe combined immunodeficiency (SCID) xenograft tumor models (17).

Utomilumab was well tolerated and active both as a single agent and in combination with the anti-PD-1 antibody pembrolizumab, in patients with advanced solid tumors (18, 19). Durable responses (duration >6 months) have been observed following single-agent or combination treatment in patients with Merkel cell carcinoma, non-small-cell and small-cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, and thyroid cancer (18, 19). Treatment with utomilumab was associated with a favorable safety profile, with no dose-limiting toxicities (DLTs) and no treatment-related deaths at the doses evaluated. Treatment-emergent adverse events (AEs) were mostly mild or moderate in severity (18, 19).

In this phase I, dose-finding study, we assessed the safety, tolerability, pharmacokinetics (PK), preliminary clinical activity, and pharmacodynamics of treatment with utomilumab in combination with rituximab in patients with relapsed or refractory follicular lymphoma (FL) and other CD20⁺ NHLs. Potential associations between clinical outcomes and biomarkers were also evaluated in tumor and blood samples from treated patients.

**Methods**

**Study objectives**

This multi-center, open-label, multiple-dose, phase I study consisted of a dose-escalation and a dose-expansion component. The primary objectives were to evaluate
safety and tolerability of treatment with utomilumab in combination with rituximab, in order to estimate the maximum tolerated dose (MTD) and select the recommended phase II dose (RP2D) for patients with relapsed/refractory CD20⁺ NHL. Secondary objectives included overall safety, pharmacokinetics, immunogenicity (anti-drug antibodies [ADAs] and neutralizing antibodies [NAbs] against utomilumab), and anti-lymphoma activity. Assessments of peripheral blood T cells, circulating soluble 4-1BB/CD137 (s4-1BB/CD137) levels, and immune-related biomarkers in tumors were incorporated as exploratory objectives.

Patients

Patients ≥18 or ≥20 years of age (if required by local, regulatory authorities) were eligible if they had histologically confirmed, relapsed/refractory CD20⁺ NHL or small lymphocytic lymphoma (SLL)/chronic lymphocytic leukemia (CLL) with nodal disease and ≤10,000 lymphocytes/µL, with no available, effective therapy. Patients were enrolled into the expansion cohort if they had FL refractory to previous rituximab therapy or relapsed/refractory diffuse large B-cell lymphoma (DLBCL).

Patients were required to have measurable disease with at least 1 extranodal tumor mass >1 cm in the greatest transverse diameter (GTD) or malignant lymph nodes >1.5 cm in the GTD, and the product of the diameters >2.25 cm²; Eastern Cooperative Oncology Group (ECOG) performance status ≤1; absolute neutrophil count ≥1.0 x 10⁹/L; platelet count ≥75 x 10⁹/L; hemoglobin ≥8.0 g/dL; and adequate renal, hepatic, and cardiac functions.
Exclusion criteria included prior allogeneic hematopoietic stem cell transplant, any anti-cancer therapy or hematopoietic growth factors within 28 days or systemic corticosteroid therapy or radiation therapy within 14 days prior to the first dose of study treatment, prior treatment with a 4-1BB/CD137 agonist, an autoimmune disorder or an active, clinically significant infection, a severe allergic or anaphylactic reaction to antibodies or infused therapeutic proteins, and known utomilumab and/or rituximab anti-drug antibodies (ADAs). Furthermore, patients were not included if they had symptomatic brain metastases requiring steroid therapy. Patients were eligible if they had completed treatment for their brain metastases and recovered from the acute effects of radiation therapy or surgery, had discontinued corticosteroids for ≥4 weeks, and were neurologically stable.

The study was approved by the institutional review board or independent ethics committee of the participating institutions and followed the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All subjects provided written informed consent. The study was sponsored by Pfizer and registered at ClinicalTrials.gov (NCT01307267).

Treatment

Utomilumab was administered as a 1-hour intravenous infusion every 4 weeks (Q4W). In dose-escalation, patients were assigned to receive utomilumab at a starting dose of 0.03 mg/kg, with the dose being escalated/de-escalated in subsequent dose cohorts to: 0.06, 0.12, 0.18, 0.24, 0.30, 0.60, 1.2, 2.4, 5.0 and 10 mg/kg, using the modified time-to-event continual reassessment method (TITE-CRM) (21-23). Intra-
patient dose escalation was not allowed. In the expansion cohort, patients received utomilumab at 1.2 mg/kg. Patients were allowed to continue treatment with utomilumab for up to 2 years or until unacceptable toxicity, disease progression, or withdrawal of consent, whichever occurred first. Rituximab (375 mg/m²) was administered once weekly for 4 weeks per institutional standards, with the first and second doses given 8 days and 1 day prior to the initial utomilumab infusion, respectively. Rituximab dosing could be repeated according to the standard of care and at the investigator’s discretion once every 8 weeks, starting on or after Cycle 4 (day 0) and continuing up to Cycle 10 (day 0).

**Study assessments**

**Safety.** Safety evaluations included vital signs, physical examination, review of treatment-emergent AEs and serious AEs (SAEs), electrocardiograms (12 lead), and laboratory assessments. AEs were characterized by type, frequency, timing, seriousness, and relationship to study drug; and graded by National Cancer Institute Common Terminology Criteria for Adverse Events v.4.03.

DLTs were defined as grade 4 neutropenia, febrile neutropenia, neutropenic infection, grade ≥3 thrombocytopenia with associated bleeding, grade 4 thrombocytopenia, grade 4 anemia, grade ≥3 hemolysis, or grade ≥3 non-hematologic toxicities (with the exception of grade 3 non-hematologic AEs [eg, nausea, vomiting, and diarrhea] that responded to treatment with standard supportive therapy within 48 hours) if they were attributable to combination treatment with utomilumab and rituximab.
and not to disease progression, and occurred within the first 2 treatment cycles (up to 28 days following the second treatment dose).

**PK and ADA analyses.** Blood samples were collected for the evaluation of PK parameters at multiple, protocol-defined time points and analysed using a validated enzyme-linked immunosorbent assay (18). Standard plasma PK parameters for utomilumab were estimated using non-compartmental analysis. Blood samples for the determination of ADAs against utomilumab were collected at protocol-specified time points and analyzed using a validated, electrochemiluminescent bridging assay (18). ADA-positive samples were further evaluated for the presence of NAbs using a cell-based assay (18).

**Response assessments.** Tumor responses were assessed by computed tomography or magnetic resonance imaging scans of chest, abdomen, and pelvis, approximately every 8 weeks until Cycle 10, and subsequently every 16 weeks until disease progression, end of treatment, or study withdrawal (if not done in the previous 6 weeks). Responses were determined using the Cheson 2007 criteria for NHL (20).

**Pharmacodynamics.** Peripheral blood samples were collected for flow cytometry as previously described (18) with the addition of a draw prior to administration of the first rituximab dose (on day -7 relative to the first utomilumab dose). Absolute numbers and relative proportions of T, B, and NK cells were assessed using an antibody panel containing: CD3, CD9, CD16, and CD56. T-cell phenotypes were determined using antibody panels containing: CD3, CD4, CD8, CD45RO, CCR7, CD137, Ki67, CD28, PD-1, and CD57. NK phenotypes were assessed using antibody panels containing:
CD3, CD16, CD56, CD69, CD25, VCAM/CD106, Ki67, and CD137. Antibodies were obtained from BD Biosciences (San Jose, CA), BioLegend (San Diego, CA), and ThermoFisher (San Diego, CA). Lymphocyte subpopulations were assessed using a FACScanto II flow cytometer (BD Biosciences). Serum samples were analyzed for soluble 4-1BB/CD137 (s4-1BB/CD137) using a Luminex-xMAP LEGENDplex™ custom assay (BioLegend Inc.), previously validated in the presence of utomilumab, as described (18).

**Biomarker association analyses.** Flow marker data were compared in patients experiencing clinical benefit, defined as complete or partial response and/or progression-free survival (PFS) >6 months, versus patients with PFS ≤6 months. The comparison between responders and non-responders was assessed using a Wilcoxon rank-sum test. *P* values were not corrected for multiple comparisons. The receiver operating characteristics (ROC) curve was plotted using sensitivity versus specificity when sliding the cut-off on the marker value. The 95% confidence interval (CI) was estimated using bootstrapping methods. All analyses were performed in R software 3.3.3.

Tumor and lymph node biopsies were collected for biomarker assessments when clinically feasible. Immunohistochemistry was performed on formalin-fixed paraffin-embedded sections (Mosaic Laboratories, Lake Forest, CA) using antibodies specific for PD-L1 (E1L3N, Cell Signaling, Danvers, MA), CD8 (C8/144B, Dako, Carpinteria, CA), FoxP3 (236A/E7, Abcam, Danvers, MA), pSTAT3 (D3A7, Cell Signaling), CD3 (Leica, Buffalo Grove, IL), granzyme B (GrB-7, Dako, Carpinteria, CA), and perforin (5B10, 11
Leica). Assay results were evaluated by image analysis using whole-slide scans (Aperio ImageScope, Leica) except for granzyme B and perforin, which were assessed on manually selected 20x fields.

Peripheral blood samples for RNA-Seq analysis were collected on day 1, Cycle 1 (prior to the first utomilumab dose) in RNA PAXgene tubes (PreAnalytiX, QIAGEN/BD, Franklin Lakes, NJ) and maintained at -80°C until processing. RNA-Seq was performed using TruSeq Stranded mRNA kits on a HiSeq 2500 platform (Illumina, San Diego, CA). RNA-Seq reads were processed by alignment to hg19 UCSC transcriptome using STAR aligner (v2.4) and gene expression was quantified using RSEM (v1.2.14) (24, 25). RNA deconvolution was implemented using the nu-support vector regression (nuSVR) method in Matlab, as described (26). Cox proportional-hazards regression model was used to assess the dependence of PFS on gene expression. Genes with low expression levels or low variance across samples were filtered out, leaving 6,272 genes. Specifically, a low-variance filter was applied using varFilter in the nsFilter R package. In addition, genes with <3 samples with non-zero expression were excluded. Regression was performed for each gene post-filtering, according to its median expression level (coded into a binary variable) stratified by dose levels. Multivariate analysis was also carried out adjusting for age, sex, race, stage, and whether patients had progressed on prior rituximab-containing therapy. Gene set enrichment analysis (GSEA) was run pre-ranked by hazard ratio (HR) from the Cox regressions, using classic statistics with 1,000 permutations (27). Gene sets evaluated were from the LM22 signatures and the hallmark gene set collection in the Molecular Signatures Database (MSigDB) (excluding size <10) (26, 28).
**Statistical analyses**

The primary study endpoint was DLT in the first 2 cycles of treatment with utomilumab in combination with rituximab. The MTD was estimated as the highest dose level associated with a ≤25% estimated DLT rate per the modified TITE-CRM (21-23). The TITE-CRM design was implemented in this study as described with cyclical adaptive weight function (22). A dose-escalation steering committee was established to facilitate the trial conduct process (23). As previously described (18), a sample size of 45 patients (with early stopping rules) was estimated to provide an accurate estimate of the MTD and to detect unexpected toxicities occurring at a 5% rate with a probability of 0.90 and at a 10% rate with a probability of 0.99. The objective response was summarized with objective response rates (ORR) and exact 2-sided 95% CI calculated using the Clopper-Pearson method. Time-to-event endpoints (duration of response [DOR], PFS) were analyzed using the Kaplan–Meier (KM) method. Point estimates of KM rates and median times were presented with 95% CIs. The CIs for the KM rates were calculated using log-log transformation with back transformation to a CI on the untransformed scale. The CIs for the median were calculated according to the Brookmeyer and Crowley method.

**Results**

**Patients and treatment**
In this study, a total of 67 patients were treated with rituximab and utomilumab at the dose levels of 0.03 \( (n = 3) \), 0.06 \( (n = 3) \), 0.12 \( (n = 4) \), 0.18 \( (n = 3) \), 0.24 \( (n = 3) \), 0.30 \( (n = 3) \), 0.60 \( (n = 4) \), 1.2 \( (n = 32) \), 2.4 \( (n = 3) \), 5.0 \( (n = 5) \), and 10.0 \( (n = 4) \) mg/kg Q4W. The 1.2 mg/kg Q4W group included patients treated at this dose level in dose escalation and patients with rituximab-refractory FL enrolled in the dose expansion cohort. Rituximab-refractory disease was defined as no response to a rituximab-containing regimen or disease progression within 6 months following the last dose of rituximab. One patient was enrolled but discontinued, after a repeat biopsy showed no lymphoma recurrence.

Thirty-eight (56.7%) patients were men and 29 (43.3%) were women, with a mean age of 62.3 (range 38–84) years. Thirty-one (46.3%) patients were ≥65 years of age. Primary cancer diagnoses are listed in Table 1; the majority of patients (70.1%) had FL. More than half of the patients had stage IV at diagnosis (58.2%), Eastern Cooperative Oncology Group (ECOG) performance status 0 (65.7%), and had received ≥3 prior systemic anticancer therapies (55.2%).

**Safety**

None of the patients experienced a DLT event at the utomilumab doses evaluated (0.03–10 mg/kg). The MTD for utomilumab in combination with rituximab was not reached and estimated to be ≥10 mg/kg per the modified TITE-CRM design.

Among all patients, 64 (95.5%) patients had at least one treatment-emergent all-causality AE and 35 (52.2%) patients experienced utomilumab treatment-related AEs of any grade. The majority of the treatment-related AEs were grade 1-2 and the most
common treatment-related AE was fatigue (16.4%) (Table 2). One patient each (1.5%) developed treatment-related grade 3 neutropenia and grade 3 diarrhea (both in the 1.2 mg/kg dose group). Most of the laboratory abnormalities were grade 1-2. A grade 3 increase in alanine aminotransferase \( (n = 1, 1.5\% ; 2.4 \text{ mg/kg group}) \) was the only grade 3-4 liver function test abnormality reported (Supplementary Table S1).

No patient experienced a treatment-related death. Fifty-two (77.6%) patients discontinued treatment with utomilumab, due to disease progression \( (n = 38, 56.7\% ) \), global deterioration of health status \( (n = 4, 6.0\% ) \), AE \( (n = 3, 4.5\% ) \), unwillingness to continue on the study \( (n = 3, 4.5\% ) \), or other reason \( (n = 4, 6.0\% ) \). No patient had a dose reduction for utomilumab; 5 (7.5%) patients had 1 or 2 dose reductions for rituximab. The median duration of treatment was 5.0 (range, 1–27) cycles for utomilumab across all dose levels and 4.0 (range 1-6) cycles for rituximab.

Pharmacokinetics and immunogenicity

Utomilumab exposure (area under the serum concentration-time curve [AUC] and maximum observed serum concentration \([C_{\text{max}}]\)) increased in a dose-dependent manner across all the doses evaluated (Supplementary Table S2). Three (4.5%) of 66 patients had positive ADAs against utomilumab at baseline, likely due to pre-existing host antibodies that were cross-reactive with utomilumab. One (1.5%) patient developed treatment-induced ADAs and exhibited positive NAbs against utomilumab. None of the patients had treatment-boosted ADAs.

Clinical activity
Best overall response (BOR) of CR or PR was observed in patients with FL (4 CRs and 7 PRs) and MCL, DLBCL or NLPHL (1 PR each). All CRs and most PRs occurred at dose levels of utomilumab ≤ 1.2 mg/kg (Figure 1). The ORR across all dose levels of utomilumab evaluated in the study was 21.2% (95% CI 12.1, 33.0%) (n = 66) (Table 3). Among patients with rituximab-refractory FL, 4 patients achieved a CR and 5 patients had a PR, as BOR (Figure 1). The median time to response was 2.1 (range, 1.9, 7.4) months, median DOR was 20.3 (95% CI 2.6, not estimable [N. E.]) months, and median PFS for all treated patients with NHL (n = 66) was 4.6 (95% CI 3.9, 7.5) months. Overall, 28 (42.4%) patients achieved stable disease as BOR and 21 (31.8%) had progressive disease. Three (4.5%) patients were not evaluable for BOR owing to the lack of post-baseline disease assessments, due to death. One patient with granuloma (and no active disease at baseline) was excluded from efficacy evaluations.

**Pharmacodynamics**

Increases in circulating s4-1BB/CD137 were observed in individual patients following combination treatment, at utomilumab doses between 0.18 and 10 mg/kg (Supplementary Fig. S1A). Levels of s4-1BB/CD137 typically peaked at 50-100 hours after utomilumab dosing, returning to baseline in some but not all cases. An expansion in circulating CD8+ T cells was observed in some patients following combination treatment (utomilumab 0.06 to 10 mg/kg; Supplementary Fig. S1B). No relationship was noted between CD8+ T-cell expansion and treatment dose or tumor response.

The reported connection between intratumoral CTLs and outcome following rituximab treatment suggested that the combination of utomilumab and rituximab could
be associated with increased CTL activity in the tumor (29, 30). This possibility could be assessed using pre- and on-treatment, paired tumor biopsies from a patient (1.2 mg/kgatumilumab plus rituximab group), who achieved a CR after 12 treatment cycles.

Immunohistochemistry analysis showed increased CD8⁺ T-cell infiltration, reduced PD-L1 expression, and destruction of follicular architecture (Fig. 2A). Expression of 4-1BB/CD137 appeared to be high on PD-1⁺ cells at baseline but was reduced following combination treatment. The staining pattern of cytotoxic proteins granzyme B and perforin in the baseline specimen was consistent with primary localization in cytoplasmic granules (Fig. 2B), whereas it indicated redistribution to the plasma membrane in the paired on-treatment specimen. The changes in staining pattern are consistent with the hypothesis that the objective benefit observed in this patient may have been mediated by increased, antitumor CTL activity.

**Association of biomarkers with clinical outcome**

Associations between outcome and biomarkers in baseline tumor biopsies were investigated by immunohistochemistry analysis of PD-L1, CD8, FoxP3, pSTAT3, granzyme B, and perforin (Fig. 2C). A significant association between clinical benefit and biomarker (p <0.05) was only observed for elevated FoxP3, although similar trends were observed for the other biomarkers as well.

Prior analyses of circulating lymphocytes in patients with FL treated with single-agent rituximab suggested a positive correlation between systemic T-cell levels and response to therapy (31). In this study, a significant, positive association was observed between clinical benefit (defined as CR/PR and/or PFS >6 months) and circulating CD8⁺
central memory T cells at baseline (Wilcoxon rank-sum test \( p = 0.002 \) [Cycle 1, day 1]) (Fig. 3A). ROC analysis with a 95% CI identified a CD8\(^+\) central memory T cell cut-off that generated 68% specificity and 76% sensitivity (dashed lines in Fig. 3B). The area under the ROC curve was 0.80 (CI 0.66–0.94).

The association between circulating lymphocytes and clinical benefit was further examined using RNA-Seq analysis of peripheral blood samples collected immediately prior to utomilumab dosing (after 2 rituximab treatments administered over the previous 8 days). Deconvolution analysis demonstrated significant correlations between gene signatures for lymphocytes and T cells and the corresponding subpopulations detected by flow cytometry (Supplementary Fig. S2). GSEA analysis identified gene sets characteristic of CD4\(^+\) and CD8\(^+\) T-cell subsets that were associated with better PFS; in contrast, gene sets characteristic of monocytes, neutrophils, and some B cell populations were associated with poorer PFS (Figure 3C). Broader GSEA analysis identified additional pathways characteristic of inflammation that were associated with poorer PFS (Supplementary Fig. S3).

Discussion

This is a first-in-human study evaluating the 4-1BB/CD137 agonist mAb utomilumab in combination with rituximab for the treatment of patients with relapsed/refractory FL and other CD20\(^+\) NHLs. The safety of the combination in this patient population was favorable and consistent with previous studies of utomilumab in patients with solid tumors (18, 19), including a study of utomilumab in combination with the PD-1 inhibitor pembrolizumab, in which there were no DLTs or treatment-related
grade 5 AEs (19). As the highest dose of utomilumab evaluated in this study was 10 mg/kg, with no DLTs observed across the dose levels evaluated, the MTD for utomilumab in combination with rituximab was estimated to be at least 10 mg/kg Q4W in patients with NHL.

The PK of utomilumab was linear in the 0.03 to 10 mg/kg dose range when administered in combination with rituximab, which is similar to that previously observed with single-agent treatment (18). The 1.2 mg/kg Q4W dose level was selected for the expansion cohort based on prior findings that adequate exposure was achieved at utomilumab dose levels ≥0.24 mg/kg Q4W and target modulation was detected in the 0.24 to 1.2 mg/kg Q4W dose range (18).

Administration of utomilumab plus rituximab was associated with a very low incidence (1.5%) of treatment-induced ADAs against utomilumab, different from previous studies with single-agent utomilumab or combined treatment with pembrolizumab in patients with solid malignancies, in which 42-65% of patients developed ADAs against utomilumab (18, 19). In addition, only 1 patient (1.5%) had treatment-induced utomilumab NAbs. Both these patients did not receive rituximab past Cycle 1 and had grade 1-2 IRRs to rituximab. They received utomilumab through Cycle 8 and 24, respectively. B-cell depletion induced by rituximab in these patients may have been responsible for the lower ADAs observed, compared with patients treated with utomilumab in other clinical studies, as rituximab-containing regimens have been reported to reduce ADA responses to other therapeutic proteins (1, 18, 19, 32).

Combination treatment was associated with preliminary evidence of clinical activity in patients with CD20+ NHL, including relapsed/refractory FL following prior
therapy with rituximab-containing regimens. In 6 of the 9 responders with rituximab-refractory FL, response to utomilumab in combination with rituximab exceeded the 6-month period used to define rituximab-refractory status following prior rituximab-containing therapy (33). Safety, PK, pharmacodynamic, and clinical activity results from the expansion cohort provided multiple lines of evidence that utomilumab at 1.2 mg/kg Q4W in combination with rituximab was clinically active and well tolerated. Therefore, this dose was chosen as the RP2D for utomilumab in patients with CD20+ NHL.

The first dose of utomilumab was administered after the second of 4 weekly doses of rituximab based on the hypothesis that 4-1BB/CD137 agonism would be most effective after a period of time, to allow for innate and adaptive immune activation by rituximab. Pharmacodynamic changes consistent with 4-1BB/CD137 agonism were observed, including increases in s4-1BB/CD137 levels and expansion of CD8+ T cells in the circulation as seen in prior studies (17,18). Analysis of paired biopsies from a patient with relapsed/refractory FL, who achieved a CR following combination treatment, showed increased T-cell infiltration and cytotoxic activity in tumors, consistent with findings in murine tumor models following agonistic engagement of 4-1BB/CD137 (34). Since only one combination schedule was evaluated, the relative contributions of rituximab and utomilumab to these effects cannot be distinguished in this study.

Analyses of both tumor and blood biomarkers suggested that T-cell immunity is a component of response to the combination but may be limited by factors in the local tumor microenvironment or in the systemic circulation (35). Tumor biopsies from the study patients could generally be assigned to 2 categories: immunologically “hot”, which contained elevated proportions of CD8+ and PD-L1+ cells, and immunologically “cold,”
which did not (36). Objective responses were observed primarily in patients whose tumors had the “hot” phenotype, although this phenotype was also observed in patients with progressive disease. Patients with “cold” tumors generally showed progressive disease. These results are consistent with previous studies of patients treated with rituximab monotherapy or rituximab plus IFN-α2a, in which an association between favorable outcome and tumor-infiltrating T cells was noted (31). In this study, clinical benefit could be observed in some patients even in the presence of immunosuppressive biomarkers such as PD-L1 and FoxP3. It is possible that in these patients an active, antitumor immune response induced adaptive resistance, but the magnitude and/or location of the resistance mechanisms may have been inadequate to protect the tumor (36). Alternatively, as 4-1BB/CD137 can be induced on activated NK cells, utomilumab may have overcome this induced resistance through activation of NK cells, which could be less susceptible to down-modulatory mechanisms. In the patients with “hot” tumors that progress on therapy, the resistance mechanisms may be able to disable the active immune response; in these patients, the addition of antagonists to the PD-1/PD-L1 pathway may be needed for clinical benefit.

Associations between circulating CD8$^+$ T cells and clinical outcome were noted for single-agent utomilumab and a combination of utomilumab and pembrolizumab (18, 19) as well as with single-agent rituximab (31); it is therefore unsurprising that similar associations were observed with the combination of utomilumab and rituximab. The mechanistic basis for the inverse association between gene signatures of myeloid cell populations and inflammatory gene pathways requires further investigation. Elevated neutrophil-to-lymphocyte ratios have been associated with poor prognosis in multiple
cancer settings (37). It remains to be determined whether the observations reported in this study are reflective of systemic immune dysfunction that reduces the ability to maintain an effective antitumor immune response, or a generally poor prognosis for non-immune as well as immune-based therapy.

In other studies, single-agent activity has been observed with the phosphatidylinositol 3-kinase (PI3K) inhibitors idelalisib, copanlisib, and duvelisib, with ORRs of ~50% and PFS of ~1 year in relapsed/refractory FL (38-40). However, treatment was associated with significant toxicity, including hepatitis, gastrointestinal toxicity, risk of infections, and cytopenias. The ORR reported with the Bruton’s kinase inhibitor ibrutinib in a phase II trial was just 16.7% in patients with refractory FL (41). A similar ORR (20.9%) was observed with single-agent ibrutinib in the larger, single-arm, phase II DAWN study conducted in patients with relapsed/refractory FL who had received ≥2 prior lines of chemoimmunotherapy (42). Dose-finding, phase I studies evaluating a triple combination of the PI3K-δ inhibitor idelalisib with lenalidomide and rituximab in patients with relapsed/refractory FL or MCL were terminated due to the excessive toxicity observed (43). Other investigational combinations have been explored for the treatment of patients with relapsed/refractory FL. In a phase Ib study, administration of rituximab and the anti-CD47 antibody Hu5F9-G4 (which enhances antibody-dependent tumor cell phagocytosis by macrophages) was associated with an ORR of 71% (CR 43%) in a small number of patients with FL (44). Treatment with lenalidomide plus rituxumab in phase II-III trials demonstrated ORRs of ~76-77% in relapsed/refractory FL and significant improvement in PFS, while combination of
lenalidomide with obinutuzumab was associated with an ORR of ~63% in an early study (45-47).

Initial results from a phase Ib study of the anti PD-1 antibody nivolumab showed a 40% ORR (10% CR rate) in hematologic malignancies and durable responses in a few patients with relapsed/refractory FL (48). Subsequent evaluations estimated a response rate of ~10% with anti-PD-1 monotherapy in relapsed/refractory FL (49). Preliminary activity was reported in a phase I/IIa combination study of nivolumab and ibrutinib in patients with relapsed FL (ORR, 33%) (50).

In conclusion, the favorable safety and tolerability profile of utomilumab in combination with rituximab and the preliminary evidence of clinical activity observed in patients with rituximab-refractory FL support further evaluation of this combination, especially in patients requiring treatment regimens with reduced toxicity. A subset of patients with elevated, tumor-associated CD8+ T cells that did not respond to the combination had elevated PD-L1 expression in the tumor. It is possible that in these patients PD-L1 is protecting the tumor from immune attack and that the addition of PD-1/PD-L1 inhibitors may restore the immune response and associated clinical benefit. As utomilumab was well tolerated in combination with a PD-1 inhibitor, this hypothesis is being tested in an ongoing study with a triplet combination of utomilumab, rituximab, and a PD-L1 inhibitor in patients with FL (NCT03636503).
Acknowledgments

The authors thank the patients and their families/caregivers, and the investigators, research nurses, study coordinators, and operations staff who contributed to this study; C. Deshpande for preparation of the biomarker data included in the association analyses; and E. Negre for data reconciliation and validation efforts. A. K. Gopal received philanthropic support from Frank and Betty Vandermeer and from Sonya and Tom Campion. This work is dedicated to the memory of Holbrook Kohrt, MD, PhD. Medical writing and editorial support was provided by S. Mariani, MD, PhD, of Engage Scientific Solutions and was funded by Pfizer.

Data Sharing Statement

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.
References


45. Leonard JP, Jung SH, Johnson J, Pitcher BN, Bartlett NL, Blum KA, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in


## Table 1. Patient demographics and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Utomilumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 67</td>
</tr>
<tr>
<td>Male : Female, n (%)</td>
<td>38 (56.7) : 29 (43.3)</td>
</tr>
<tr>
<td>Median age, yrs (range)</td>
<td>63 (38–84)</td>
</tr>
<tr>
<td>≥65 yrs, n (%)</td>
<td>31 (46.3)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>51 (76.1)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (3.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>6 (9.0)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (11.9)</td>
</tr>
<tr>
<td>Primary cancer, n (%)</td>
<td></td>
</tr>
<tr>
<td>FL</td>
<td>47 (70.1)</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>7 (10.4)</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>6 (9.0)</td>
</tr>
<tr>
<td>Small lymphocytic lymphoma/CLL</td>
<td>3 (4.5)</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>2 (3.0)</td>
</tr>
<tr>
<td>Nodular lymphocyte-predominant Hodgkin lymphoma</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Stage at diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>3 (4.5)</td>
</tr>
<tr>
<td>IB</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>IIA</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td>IIIA</td>
<td>14 (20.9)</td>
</tr>
<tr>
<td>IIIB</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td>IVA</td>
<td>29 (43.3)</td>
</tr>
<tr>
<td>IVB</td>
<td>10 (14.9)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>44 (65.7)</td>
</tr>
<tr>
<td>Prior anticancer radiation therapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Yes</td>
<td>14 (20.9)</td>
</tr>
<tr>
<td>No</td>
<td>53 (79.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior systemic anticancer treatment, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>67 (100)</td>
</tr>
<tr>
<td>1</td>
<td>13 (19.4)</td>
</tr>
<tr>
<td>2</td>
<td>17 (25.4)</td>
</tr>
<tr>
<td>3</td>
<td>8 (11.9)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>29 (43.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response to prior rituximab therapy, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory</td>
<td>43 (64.2)</td>
</tr>
<tr>
<td>Relapsed</td>
<td>6 (9.0)</td>
</tr>
<tr>
<td>Other/not reported</td>
<td>18 (26.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subsequent anticancer therapy, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>24 (35.8)</td>
</tr>
<tr>
<td>No</td>
<td>2 (3.0)</td>
</tr>
<tr>
<td>Not reported</td>
<td>41 (61.2)</td>
</tr>
</tbody>
</table>

*aOne patient was enrolled but discontinued, after a repeat biopsy showed no lymphoma recurrence. CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status Score; FL, follicular lymphoma.
Table 2. Utomilumab treatment-related adverse events reported in >2 patients (all cycles)

<table>
<thead>
<tr>
<th>AE (^a), (N = 67)</th>
<th>All Grades</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>35 (52.2)</td>
<td>25 (37.3)</td>
<td>8 (11.9)</td>
<td>2 (3.0)(^b)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (16.4)</td>
<td>8 (11.9)</td>
<td>3 (4.5)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (6.0)</td>
<td>4 (6.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (4.5)</td>
<td>2 (3.0)</td>
<td>0</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

\(^a\)No utomilumab treatment-related grade 4-5 AEs were reported. \(^b\)One (1.5%) patient developed grade 3 neutropenia. AE, adverse event.
Table 3. Best overall response in patients with CD20\(^+\) NHL

<table>
<thead>
<tr>
<th>Response Type</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>4</td>
<td>6.1</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>10</td>
<td>15.2</td>
</tr>
<tr>
<td>Stable disease</td>
<td>28</td>
<td>42.4</td>
</tr>
<tr>
<td>Objective progression</td>
<td>21</td>
<td>31.8</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3</td>
<td>4.5</td>
</tr>
<tr>
<td>Objective response rate (CR + PR)</td>
<td>14</td>
<td>21.2</td>
</tr>
<tr>
<td>(95% exact CI)</td>
<td></td>
<td>(12.1, 33.0)</td>
</tr>
</tbody>
</table>

\(^a\)One patient with granuloma was excluded from efficacy evaluations. CI, confidence interval; NHL, non-Hodgkin lymphoma.
Figure legends

Figure 1. (A) Waterfall plot of best percentage change from baseline in target lesions for patients with CD20+ NHL. One patient with granuloma was excluded from the analysis. Utomilumab was administered at the doses indicated in combination with rituximab (375 mg/m²). (B) Duration of treatment in responders with CD20+ NHL. Triangles indicate first CR, squares first PR, and circles progressive disease. White bars indicate patients with CR who completed the planned 8-month treatment. CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; PR, partial response; R, rituximab-refractory; SD, stable disease.

Figure 2. Associations between clinical outcome and tumor biomarkers. (A, B) On-treatment changes in lymphoid architecture and content versus baseline tumor biopsies, assessed by immunohistochemistry in a patient with complete response (utomilumab 1.2 mg/kg plus rituximab). (A) CD8, PD-L1, and 4-1BB/PD-1; and (B) CD3, CD16, granzyme B, and perforin expression. 20x objective, 200x overall magnification. (C) Expression of PD-L1, CD8, and other markers of immune activation in baseline tumors from patients with objective response and/or durable stable disease versus patients with objective progression. PD-L1, programmed death-ligand 1.

Figure 3. Correlation of clinical outcome with circulating immune cell subsets at Cycle 1, day 1 in patients with follicular lymphoma. (A) Absolute numbers (per µl) of CD8+ T central memory cells (CD3+CD8+CD45RO+CCR7+) in patients before receiving the first dose of utomilumab. Clinical benefit is defined as CR, PR, or PFS >6 month. Wilcoxon rank-sum test, \( p = 0.002 \). (B) ROC curve analysis. The gray zone identifies 95% Confidential.
confidence interval. Dashed lines indicate a cut-off with 68% specificity and 76% sensitivity. (C) Association with survival of immune cell subsets from expression signatures. NES were derived from GSEA with genes pre-ranked by hazard ratio from multivariate Cox proportional-hazards model stratified by dose levels and adjusting for age, sex, race, stage and whether patients had progressed on prior-rituximab-containing therapy. Gene sets assessed are from the LM22 signatures. Significant cell populations are highlighted in orange (FDR-adjusted q value <0.05). CR, complete response; FDR, false discovery rate; GSEA, gene set enrichment analysis; NES, normalized enrichment score; NK, natural killer; PFS, progression-free survival; PR, partial response; ROC, receiver operating characteristics.
Fig. 1A

![Graph showing best change from baseline for different treatment groups.](image-url)
**Fig. 2A**

<table>
<thead>
<tr>
<th>CD8</th>
<th>PD-L1</th>
<th>4-1BB/PD-1</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Baseline CD8" /></td>
<td><img src="image2" alt="Baseline PD-L1" /></td>
<td><img src="image3" alt="Baseline 4-1BB/PD-1" /></td>
</tr>
<tr>
<td><img src="image4" alt="On-treatment CD8" /></td>
<td><img src="image5" alt="On-treatment PD-L1" /></td>
<td><img src="image6" alt="On-treatment 4-1BB/PD-1" /></td>
</tr>
</tbody>
</table>

- **Baseline**
  - Increased infiltration by CD8+ cells on-treatment
  - Loss of follicular morphology

- **On-treatment**
  - Reduced PD-L1 expression between follicles after start of therapy
  - 4-1BB^PD-1^ cells around follicle at baseline
  - Infiltrating lymphocytes may shift to 4-1BB^PD-1^
Fig. 2B

- CD3
- CD16
- granzyme B/perforin
- hematoxylin

Baseline

On-treatment

Loss of follicular morphology
Redistribution of cytotoxic proteins
Fig. 2C

- PD-L1 H-Score (p = 0.17)
  - No
  - Yes

- CD8 % POS ALL (p = 0.154)
  - No
  - Yes

- FOXP3 % POS ALL (p = 0.027)
  - No
  - Yes

- PSTAT3 % POS ALL (p = 0.47)
  - No
  - Yes

- % GRB/PERF+ IM (p = 0.667)
  - No
  - Yes
Fig. 3 A, B

A

C1D1

CD8 T Central Memory Cell

No  Yes

Response

B

PFS6_CRPR

No  Yes

Sensitivity

0.0 0.2 0.4 0.6 0.8 1.0

Specificity

1.0 0.6 0.2
Clinical Cancer Research

First-in-Human Study of Utomilumab, a 4-1BB/CD137 Agonist, in Combination with Rituximab in Patients with Follicular and Other CD20⁺ Non-Hodgkin Lymphomas


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