ASH Highlights and Commentary: Multiple Myeloma

Abstract 821

Clinical Outcomes of Relapsed/Refractory Multiple Myeloma Patients Following Treatment With Bispecific Antibodies (BiAbs)

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Background: Bispecific antibodies (BiAbs) are a novel off-the-shelf class of drugs currently being investigated in clinical trials for patients with relapsed/refractory multiple myeloma (RRMM) with promising efficacy in heavily pretreated patients. BiAbs simultaneously bind two antigens, thereby engaging CD3+ T cells with myeloma cells expressing specific antigens such as BCMA, GPRC5D, FcRH5 or CD38. However, the outcome of myeloma patients after relapse on BiAbs is unknown and effective approaches for salvage therapy are needed.

Methods: Demographics, disease characteristics and post-clinical trial outcomes were collected retrospectively on RRMM patients who relapsed after BiAb therapy at the Tisch Cancer Institute (The Mount Sinai Hospital, New York). We identified a total of 116 patients who were enrolled on trials with BiAbs targeting either BCMA or GPRC5D. Of these, 69 patients were no longer enrolled on the trials due to disease progression (including 5 patients who died on the trial). Clinical data was collected up until July of 2021. This retrospective study was approved by the institutional review board (IRB) and follows the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice (IRB: GCO#: 11-1433). Survival and response duration were calculated by Kaplan-Meier estimation.

Results: The 64 RRMM patients had a median age of 58.5 years (range: 46-82) at time of disease progression following BiAbs therapy, and 48% were male. Median time from diagnosis to initiation of BiAbs therapy was 5 years (range: 1.6-16.3) and patients had a median follow-up of 24.9 months from time of relapse from BiAb therapy. Fifty patients (78%) had high-risk cytogenetics, including gain1q21, del17p, t(4;14), t(14;16) and t(14;20). Most patients were highly pretreated with a median of 7 prior lines (range: 3-17) and 54 patients (84%) had received an autologous stem cell transplant (ASCT) prior to receiving BiAbs. Three patients were treated with chimeric antigen receptor (CAR) T cell therapy prior to BiAb and 5 patients were exposed to a BCMA antibody-drug conjugate prior to the BiAb. Furthermore, 89% of patients were triple-class refractory while 44% were penta-refractory.

Following treatment with a BiAb, 2 patients were lost to follow up, 1 patient decided to be monitored off treatment and 61 patients received a median of 2 lines of therapy (range: 1-8). Most common therapies included a second BiAb (n=20; 33%), CAR T cells (n=15; 26%) or intensive chemotherapy (n=36; 59%) such as melphalan, carmustine or VDPACE with stem cell rescue (n=13) or DCEP (n=23). Best response to initial treatment following the BiAb varied widely and included 12 complete responses, 5 very good partial responses, 17 partial responses, 2 minimal responses, 10 stable disease and 13 progressed disease for an overall response rate (ORR) of 58%. Encouraging responses

were seen in 10 patients who directly transitioned from one BiAb to another and 8 patients who directly transitioned to CAR T cell therapy. The progression-free survival of those 18 patients who directly transitioned to a T cell directed therapy was 28.9 months (95% CI: 21.6-NE) and their median overall survival was not reached. Furthermore, the overall survival for the whole cohort of patients was 17.6 months (95% CI: 12.0-NE).

Conclusion: Our data suggests that heavily pretreated, predominantly triple-class refractory, patients relapsing after BiAbs may still have good outcomes when sequentially treating with other immunological/T cell-directed therapeutics such as BiAbs and CAR T cells. Studying the appropriate sequence of these treatments is of paramount importance as BiAbs are expected to become part of the standard of care for RRMM patients.

The Advanced Practitioner Perspective: Kathryn T. Maples, PharmD, BCOP

Bispecific antibodies (BiAbs) are a novel, off-the-shelf class of drugs being investigated for the treatment of relapsed and refractory multiple myeloma (MM). Bispecific antibodies simultaneously bind to both the CD3 antigen on T cells as well as with a second antigen on myeloma cells, such as BCMA, GPRC5D, or FcRH5 (Mohan et al., 2021). While there is not yet an FDA-approved BiAb for the treatment of myeloma, early results from several clinical trials have shown promising efficacy and a tolerable safety profile with this drug class in heavily pretreated patients.

With the success of BiAbs in early trials, there is a need for data on the outcomes of MM patients after they progress on a BiAb. At the 2021 ASH annual meeting, Dr. Mouhieddine from Mount Sinai in New York presented on the Mount Sinai experience with 64 relapsed/refractory MM patients who had progressed on a BCMA or a GPRC5D BiAb. Notably, this was a heavily pretreated patient population, with the majority having high-risk cytogenetics and being triple-class refectory. It was also highlighted that eight patients had previous BCMA exposure (i.e., prior CAR T-cell therapy or BCMA antibody-drug conjugate), which adds to growing data on the sequencing of various BCMA-targeted agents. From the time of relapse, the median follow-up was 24.9 months, and the median overall survival for the entire cohort was 17.6 months. Dr. Mouhieddine also noted that some of these patients were on phase I studies and had not received the recommended phase II doses of the BiAb.

Implications for the Advanced Practitioner

The overall survival results from this study are an important factor for advanced practitio-ners to be aware of, as this demonstrates the improvement in the MM treatment landscape over the past few years. The MAMMOTH study from 2019 evaluated outcomes in 275 patients with MM refractory to CD38 monoclonal antibodies and reported a median overall survival of 8.6 months (95% confidence interval [CI] = 7.6–9.9) from the time of CD38 monoclonal antibody refractoriness (Gandhi et al., 2019). The overall survival in this study of close to 18 months from time of BiAb relapse, with 89% of patients being triple-class refractory, is a great improvement and exciting for our MM patients.

Another critical question for MM practitioners is how to best sequence novel agents. Eighteen patients in this study subsequently received another T-cell directed therapy, which was either a second BiAb or CAR T-cell therapy. For these 18 patients, the median progression-free survival was 28.9 months, and the overall survival had not yet been reached. While further research on the ideal sequencing is needed, this study showed good outcomes in patients sequentially treated with two different T-cell directed therapies.

A key takeaway for advanced practitioners is to use these data to inform their treatment recommendations and incorporate novel agents into the treatment paradigm. Since the BiAbs are currently only available as part of a clinical trial, it is important to note the eligibility criteria for these trials and how a patient's current treatment may or may not impact their eligibility.

Disclosure: Dr. Maples has served as a consultant for GlaxoSmithKline, Janssen, Karyopharm, and Sanofi.

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Abstract 895

Elranatamab (PF-06863135), a B-Cell Maturation Antigen (BCMA) Targeted CD3-Engaging Bispecific Molecule, for Patients With Relapsed or Refractory Multiple Myeloma: Results From MagnetisMM-1

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Introduction: MagnetisMM-1 (NCT03269136) is a Phase 1 study of elranatamab (PF-06863135), a humanized bispecific molecule that targets BCMA expressed on multiple myeloma (MM) and engages CD3 on T cells, for patients (pts) with relapsed or refractory MM (RRMM). We report results from the subcutaneous (SC) cohorts: dose escalation (Part 1), monotherapy with priming (Part 1.1), lenalidomide (LEN) combination (Part 1C), pomalidomide (POM) combination (Part 1D), and monotherapy expansion with priming (Part 2A).

Methods: In Part 1, pts received elranatamab at 80, 130, 215, 360, 600, and 1000μg/kg weekly guided by a modified toxicity probability interval method. For monotherapy at the recommended Phase 2 dose (RP2D; Parts 1.1 and 2A), a single priming dose (600μg/kg or equivalent fixed dose of 44mg) was followed one week later by the full dose (1000μg/kg or equivalent fixed dose of 76mg) weekly (Q1W) or every 2 weeks (Q2W) thereafter. For LEN or POM combination therapy, a single priming dose (32mg) was followed one week later by the full dose (44mg) Q1W thereafter in combination with either LEN (25mg) or POM (4mg) on Days 1 to 21 of a 28-day cycle. Dose-limiting toxicity (DLT) was monitored to the end of the first cycle. Treatment-emergent adverse events (TEAEs) were graded by Common Terminology Criteria for Adverse Events (v4.03), and cytokine release syndrome (CRS) by American Society for Transplantation and Cellular Therapy criteria. Pharmacokinetics, cytokine profiling, and T cell immunophenotyping were performed. Response was assessed by International Myeloma Working Group (IMWG) criteria. Minimal residual disease (MRD) was assessed by next generation sequencing at a sensitivity of 1×10^{-5}, in accordance with IMWG criteria.

Results: 58 pts received elranatamab SC as a single agent (n=50) or in combination with either LEN (n=4) or POM (n=4) as of 4-Feb-2021. Pts had a median (range) age of 64 (32-86) years, and 26% were Black/African American or Asian. Pts had a median of 6 prior regimens, 98% had triple-class relapsed/refractory disease, 45% had prior high-dose chemotherapy with stem cell transplantation, and 22% had prior BCMA-targeted therapy. The most common all causality TEAEs included CRS (n=48, 83%; none higher than G2), lymphopenia (n=37, 64%; 12% G3, 52% G4), neutropenia (n=37, 64%; 31% G3, 29% G4), anemia (n=32, 55%; 38% G3, 0% G4), injection site reaction (n=31, 53%; none higher than G2), and thrombocytopenia (n=30, 52%; 14% G3, 17% G4). At the RP2D of 1000μg/kg, median duration of CRS decreased by 50% from 4 days to 2 days with priming. Two of 58 pts had DLT including G4 thrombocytopenia (Part 1.1) and G4 neutropenia (POM). Exposure increased with dose, cytokine increases occurred with the first dose, and increased T-cell proliferation was observed in peripheral blood. Median duration of follow-up was 7.5, 2.3, and 1.9 months for the dose escalation, priming, and LEN/POM combination cohorts, respectively. For pts treated across the efficacious dose range (215-1000μg/kg) in Part 1, confirmed overall response rate (ORR) was 70% (14/20) with complete response (CR)/stringent CR (sCR) rate of 30% (6/20). For the 14 pts with confirmed responses, median duration of response

had not yet been reached; the probability (95% CI) of responders being event free at 6 months was 92.3% (56.7-98.9). Confirmed ORR at the RP2D was 83% (5/6). Responses in this RRMM population included sCR (n=5), CR (n=1), very good partial response (VGPR; n=7), and partial response (n=1). Median time to response was 22 days. Importantly, 100% (4/4) of evaluable pts with baseline dominant sequence and on-treatment sample at CR/sCR achieved MRD negativity at 1×10^{-5} by IMWG criteria, and 75% (3/4) of pts with prior BCMA-targeted therapy achieved response (1 sCR, 2 VGPR). Updated efficacy, safety, and MRD results will be presented for SC parts of the study.

Conclusions: Elranatamab as a single agent, administered either Q1W or Q2W, had a manageable safety profile for pts with RRMM. Across the efficacious dose range, elranatamab achieved confirmed ORR of 70% and CR/sCR rate of 30%, with confirmed ORR of 83% at the RP2D. Importantly, elranatamab induces deep and durable clinical responses in RRMM pts with and without prior BCMA-targeted therapy and 100% MRD negativity in MRD evaluable pts. These results, along with emerging combination data, support continued development of elranatamab as a single agent and in combination with standard therapies for MM.

The Advanced Practitioner Perspective: Kathryn T. Maples, PharmD, BCOP

BCMA is a receptor expressed ubiquitously on multiple myeloma (MM) cells, but it is rarely found on healthy naive and memory B cells. BCMA is also required for the survival of malignant plasma cells, which makes BCMA a favorable target for immune-based therapy because it is highly selective to MM and critical to MM cell survival (Lee et al., 2016). Elranatamab is an off-the-shelf, humanized bispecific antibody (BiAb) paired on an IgG2a backbone by hinge-mutation technology that simultaneously engages CD3 on T cells and BCMA on MM cells (Lesokhin et al., 2020). This agent has been granted Fast Track designation by the FDA. The MagnestisMM-1 trial was a phase I study investigating elranatamab for the treatment of relapsed or refractory MM. At the 2021 ASH meeting, Dr. Sebag presented the results from the subcutaneous cohorts of the study, which included the monotherapy dose escalation and dose expansion cohorts as well as the combination cohorts with lenalidomide and pomalidomide. Unique to this study is that prior BCMA exposure was allowed and 22% of patients had prior BCMA-targeted therapy.

Implications for the Advanced Practitioner
Similar to other BiAbs, cytokine release syndrome (CRS) is the most common nonhematologic toxicity observed with elranatamab and an important side effect for advance practitioners to discuss with patients. In the MagnestisMM-1 study, 83% of patients experienced CRS; however, none were higher than grade 2, which is important to highlight to patients. Additionally, at the recommended phase II dose of 1,000 µg/kg, the median duration of CRS decreased by 50% from 4 days to 2 days when priming doses were utilized. This will be a key point for advanced practitioners, as these therapies may possibly transition from inpatient to outpatient administration in the future.

In the ongoing MagnestisMM-3 study, which is an open-label, multicenter, phase II study, the dose of elranatamab is a fixed dose of 76 mg administered as a subcutaneous injection weekly after a priming dose of 44 mg (ClinicalTrials.gov, 2021). There are a variety of step-up dose administration strategies that are being explored with this agent, so it will be important for advanced practitioners to be aware of which strategy will be used as this agent continues to be developed.

Similar to the teclistamab study, other key side effects with elranatamab include lymphopenia and neutropenia. Infection risk for these patients is something that advanced practitioners always want to think about and monitor for closely. For patients who are experiencing profound neutropenia, granulocyte colony-stimulating factor prophylaxis or monthly intravenous immunoglobulin infusion can be considered. Elranatamab continues to be investigated in various combinations as well as monotherapy in patients with different prior therapies. Future results from the MagnetisMM studies will help demonstrate how to best sequence and utilize this novel drug.

Disclosure: Dr. Maples has served as a con-

sultant for GlaxoSmithKline, Janssen, Karyo-pharm, and Sanofi.

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Abstract 896

Updated Results from MajesTEC-1: Phase 1/2 Study of Teclistamab, a B-Cell Maturation Antigen x CD3 Bispecific Antibody, in Relapsed/Refractory Multiple Myeloma

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Introduction: Teclistamab (JNJ-64007957) is a T-cell redirecting, bispecific IgG4 antibody that targets both B-cell maturation antigen (BCMA) and CD3 receptors to induce T-cell mediated cytotoxicity of BCMA-expressing myeloma cells. Teclistamab is under investigation in MajesTEC-1, an ongoing phase 1/2 study in patients (pts) with heavily pretreated relapsed/refractory multiple myeloma (RRMM). Results from the phase 1 study (parts 1 and 2; NCT03145181) indicated that teclistamab is well tolerated at the recommended phase 2 dose (RP2D) and has encouraging efficacy, with an overall response rate (ORR) of 65% and very good partial response or better (≥VGPR) rate of 58% in 40 pts after a median of 6.1 mo of follow-up. Here we report for the first time initial data from the phase 2 portion of MajesTEC-1 (part 3; NCT04557098) and updated results for phase 1 pts treated at the RP2D.

Methods: Pts (aged ≥18 years) were diagnosed with MM per International Myeloma Working Group (IMWG) criteria, had measurable disease and were exposed to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody. In phase 1, pts were relapsed, refractory or intolerant to established therapies. In phase 2, pts received ≥3 prior lines of therapy. The primary objectives in phase 1 were to identify the RP2D and to characterize safety and tolerability of teclistamab at the RP2D. The primary objective in phase 2 is to evaluate the efficacy of teclistamab at the RP2D (primary endpoint: ORR). Pts treated at the RP2D received a weekly dose of subcutaneous teclistamab 1500 µg/kg following step-up doses of 60 and 300 µg/kg. Responses reported here were investigator-assessed per IMWG criteria. Adverse events (AEs) are graded according to CTCAE v4.03. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to ASTCT criteria.

Results: As of June 14, 2021, 159 pts (median age 64.0 y [range 33-84]; 15% ≥75 y; 59% male) were treated at the RP2D (phase 1: 40 pts; phase 2: 119 pts). Pts received a median of 5 prior lines of therapy (range: 2-15); 100% were triple-class exposed, 69% were penta-drug exposed, 77% were triple-class refractory, and 29% were penta-drug refractory.

As of the clinical cutoff, no new safety signals were identified in phase 2. The most common non-hematologic AEs in all 159 pts treated at the RP2D were CRS (67%; grade 1/2: 99%; 1 pt had a transient grade 3 event; median time to onset 2 days [range 1-6]; median duration 2 days [range 1-9]), injection site erythema (23%; all grade 1/2), and fatigue (22%; grade 3/4: 2%). The most common hemato-

logic AEs were neutropenia (53%; grade 3/4: 45%), anemia (41%; grade 3/4: 27%), and thrombocytopenia (33%; grade 3/4: 18%). Four pts (2.5%) developed ICANS (all grade 1/2; all resolved). Pharmacokinetic and pharmacodynamic data from phase 2 support earlier phase 1 findings. Teclistamab exposure at the RP2D was sustained across the dosing interval and exceeded target exposure levels. Pharmacodynamic data for phase 1/2 pts treated at the RP2D showed induction of proinflammatory cytokines and T-cell activation, consistent with teclistamab's mechanism of action.

At clinical cutoff for this abstract, efficacy data for the phase 2 study are immature. At a median follow-up of 8.2 mo (range 1.2-15.2), response rates in the 40 phase 1 pts treated at RP2D were consistent with previously presented data (ORR: 65% [95% CI 48-79]; ≥VGPR rate: 60% [95% CI 43-75]; complete response or better rate: 40% [95% CI 25-57]). Responses deepened over time, and with longer follow-up of responders compared with previously presented data (median follow-up of 9.5 mo vs 7.1 mo) remained durable (Figure). No additional responders had disease progression, and 85% (22/26) of responders are continuing on treatment, including 1 pt with 15.2 mo of follow-up. Median duration of response (DOR) has not been reached; the 6-month DOR rate is 90% [95% CI 63-97]. The efficacy data will be updated at the time of congress to include a minimum follow-up of ~6 mo for 150 pts treated at the RP2D (prior to March 19, 2021).

Conclusions: Evaluation of teclistamab at the RP2D in 159 pts provides robust data to support safety; inclusion of phase 2 pts at the time of presentation will provide more robust efficacy data. Data from MajesTEC-1 continue to show that teclistamab monotherapy induces deep and durable responses in heavily pretreated pts with RRMM with a manageable safety profile.

Figure. Duration of Response

RP2D (n=26)[a]
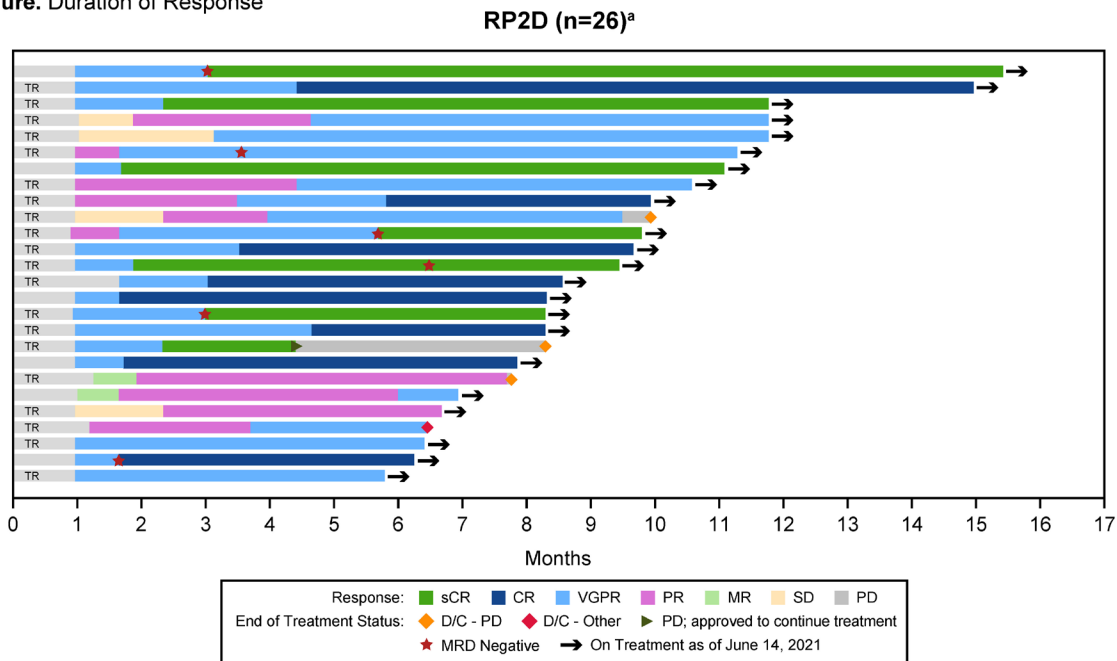
[a]Weekly SC dose of 1500 μg/kg with step-up doses of 60 and 300 μg/kg; phase 1 cohorts
CR, complete response; D/C, discontinued; MR, minimal response; MRD, minimal residual disease; PD, progressive disease; PR, partial response; RP2D, recommended phase 2 dose; SC, subcutaneous; sCR, stringent complete response; SD, stable disease; TR, triple-class refractory; VGPR, very good partial response

The Advanced Practitioner Perspective: Kathryn T. Maples, PharmD, BCOP

Antibody therapy has become a critical component in the treatment of multiple myeloma (MM). Bispecific antibodies (BiAbs) are the latest monoclonal antibody to enter the MM treatment landscape. First-generation BiAbs had short half-lives, so the administration required an extended, continuous intravenous infusion, which posed limitations and challenges in the outpatient setting. The newer BiAbs have longer half-lives and subcutaneous administration, which offers a more convenient and streamlined dosing strategy (Maples et al., 2021). Several BiAbs for MM are in phase I trials where the recommended phase II dosing is being determined. Teclistamab is an off-the-shelf BiAb that engages CD3 on T cells and BCMA on myeloma cells. The MajesTEC-1 trial is an ongoing phase I/II study investigating teclistamab for use in patients with RRMM. Previously, results from the phase I portion of the study had been reported (Krishnan et al., 2021). At the 2021 ASH meeting, Dr. Moreau presented on the results from the phase II study, as well as updated results from patients who were treated in phase I portion at the recommended phase II dose, which is 1,500 µg/kg subcutaenously once weekly (following two step-up doses that are given in the hospital for monitoring).

Implications for the Advanced Practitioner

The results from the MajesTEC-1 trial are important for advanced practitioners to be aware of because while this novel drug class offers promising efficacy results, BiAbs also have a unique safety profile. Symptom burden for MM patients can be a result of the disease itself (e.g., bone pain, renal dysfunction) or it can also be a result of the treatment (e.g., myelosuppression, peripheral neuropathy; Kiely et al., 2016). Therefore, it is critical for advanced practitioners to understand the unique burdens of treatment that BiAbs can cause, which most notably are CRS and neurotoxicity. The MajesTEC-1 trial reported 71% all-grade CRS events, which were all grade 1 or 2, except for 1 patient who experienced a grade 3 event. An important counseling point for patients is that the median time to onset of CRS was 2 days, the median duration was also 2 days, and over 90% of these events occurred during the step-up doses, which is why they need to be hospitalized for monitoring. Explaining the timing around this unique side effect to patients can help give them a better expectation before starting therapy.

Another key point for advanced practitioners to consider in clinical practice is the hematologic toxicities seen with BiAbs. In this MajesTEC-1 study, 45% of patients experienced grade 3 or 4 neutropenia. It is important to closely monitor patients for this side effect and consider initiating granulocyte colony-stimulating factor prophylaxis or monthly intravenous immunoglobulin infusions to reduce the risk for infection.

Overall, the results from this study highlighted that teclistamab can produce deep and durable responses for heavily pretreated MM patients, which is very exciting. Future results from the MajesTEC-3 study, which is investigating teclistamab in combination with some of the traditional MM drugs like daratumumab and pomalidomide, as well as final results from MajesTEC-1 will help provide a better understanding of sequencing these agents as well as the optimal timing of utilization of this novel drug class.

Disclosure: Dr. Maples has served as a consultant for GlaxoSmithKline, Janssen, Karyopharm, and Sanofi.

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