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# Tafasitamab Plus Lenalidomide Versus Standard of Care Including 3 Rituximab-Based Treatments or Lenalidomide Monotherapy in Patients With Non–Transplant-Eligible Relapsed or Refractory Diffuse Large B-Cell Lymphoma: A Matching Adjusted Indirect Treatment Comparison


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## Introduction

- **In the primary analysis of the phase 2 study of tafasitamab plus lenalidomide (TAFA + LEN) in relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL), 60% (48/80; 95% confidence interval [CI], 48–71) of patients had an objective response (L-MIND, NCT02399085; data cutoff November 30, 2018)[1]**
- **An updated efficacy analysis (data cutoff, October 30, 2020) with ≥35 months of follow-up demonstrated median duration of response (DOR) of 43.9 months (95% CI, 26.1–not reached [NR]); median DOR was not reached in patients who achieved complete response (95% CI, 43.9–NR)[2]**
  - **Median overall survival (OS) was 33.5 months (95% CI, 18.3–NR; median follow-up 42.7 months), and median progression-free survival (PFS) was 11.6 months (95% CI, 6.3–45.7; median follow-up, 33.9 months)**
- TAFA + LEN has received accelerated US Food and Drug Administration approval for adult patients with R/R DLBCL not otherwise specified, including DLBCL arising from low-grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT)[3]
- TAFA + LEN is also authorized for use in the European Union (EU) for patients with R/R DLBCL who are ineligible for ASCT, and has received "orphan" designation in the EU[4,5]
- Since the L-MIND trial was a single-arm study and there are no head-to-head clinical studies directly comparing TAFA + LEN with other treatment regimens used in the second- or later-lines in patients with R/R DLBCL, indirect treatment comparison methodologies are required to evaluate the relative efficacy of TAFA + LEN compared with other available treatments

## Objective

- **The objective of this analysis was to perform matching adjusted indirect treatment comparisons (MAICs) to evaluate the comparative efficacy of TAFA + LEN versus 4 standard-of-care treatment regimens (bendamustine with rituximab [BR]; polatuzumab vedotin with BR [POLA + BR]; rituximab with prednisolone, etoposide, chlorambucil, lomustine [R-PECC]; and lenalidomide monotherapy [LEN-mono]) for the treatment of transplant-ineligible R/R DLBCL**

## Methods

*Study Selection*

- **A systematic literature review was conducted to identify suitable sources of comparator data in non–transplant-eligible R/R DLBCL**
- Populations were matched for all clinically validated effect modifiers and prognostic factors with available data in published studies, as per the National Institute for Health and Care Excellence (NICE) guidelines[6]
- **Retrospective studies and studies that recruited ASCT-eligible patients, large proportions of patients with non-DLBCL non-Hodgkin's lymphoma, patients with double- and triple-hit lymphoma, or large proportions of patients treated in the fourth-line or later setting were excluded**
- BR, POLA + BR and rituximab + chemotherapy are some of the most commonly used National Comprehensive Cancer Network– or European Society of Medical Oncology–recommended treatments for R/R DLBCL; comparisons reported here are a subset of a larger MAIC study whose results will be published elsewhere. Comparisons versus LEN-mono were performed to quantify the benefit of adding tafasitamab on top of LEN-mono

*MAIC Methodology*

- The MAIC analyses were conducted using methods described by Signorovitch et al. 2012[7] and following the NICE guidelines[6]
- **Patient-level data from L-MIND were assigned statistical weights that adjust for their over- or under-representation relative to baseline characteristics available in each comparative evidence source; in determining the covariates appropriate for patient matching, 3 scenarios were considered:**

**Scenario 1** — **All Available Baseline Characteristics**
Adjusting for all available baseline characteristics

**Scenario 2** — **All Available PFs and EMs**
Adjusting for all known and available prognostic factors (PFs) and effect modifiers (EMs) in DLBCL, as identified by clinical experts: general health, disease characteristics, prior therapies

**Scenario 3** — **Factors Prioritized by Clinical Experts**
Based on clinical expert opinion, population adjustment on the following factors should be prioritized:
- Age
- Eastern Cooperative Oncology Group performance status
- International Prognostic Index score
- Refractoriness of patients
- Number of prior treatment lines
- Prior stem cell transplantation
- Cell of origin of the disease

- The effective sample size (ESS) was derived in each of the scenarios and represents the number of independent non-weighted individuals who would be required to provide an estimate with the same precision as the weighted sample estimate; **an ESS requirement of at least 16 was applied in these analyses, representing at least 20% of the original treated population in L-MIND**
- Multiple models based on the scenarios for covariate selection were investigated and a base-case model was selected based on model convergence and ESS (≥16)
- The relative efficacy estimates for OS and PFS were quantified as a hazard ratio (HR) with 95% CI
  - HRs were obtained using a Cox regression analysis fitted on the L-MIND data and the reconstructed individual-patient data (RIPD) of the comparator study used in the matching; RIPD were generated from digitized coordinates using the Guyot algorithm[8]
  - The assumption of proportionality of hazards was assessed with visual and analytic tests. When a deviation from the proportional hazard assumption was identified, time-dependent HRs were calculated
- For binary outcomes (objective response rate [ORR], complete response rate [CRR]), logistic regression analyses were applied on the L-MIND data and the RIPD of the comparator study used in the matching to derive an adjusted odds ratio (OR) and 95% CI
- When multiple comparative analyses for the same comparator were possible, pooled estimates of relative efficacy were determined through a direct meta-analysis of the estimates (HRs or ORs) generated by the MAICs performed vs individual studies.

## Results

- Six treatment arms from 5 studies with similar inclusion and exclusion criteria, designs, and outcomes definitions compared with L-MIND were included in the comparisons (**Table 1, Figure 1**)

**Table 1. Characteristics and Endpoints for L-MIND and Comparator Studies**

| Characteristic | TAFA + LEN (L-MIND) Salles et al. 2020[1] | POLA + BR vs BR (GO29365)[9] Sehn et al. 2020[9] | Sehn et al. 2018[10], 2019[11] | BR (Ohmachi et al. 2013[12]) | BR (Vacirca et al. 2014[13]) | R-PECC (Lugtenburg et al. 2019[14]) | LEN-monotherapy (DLC-001) (Czuczman et al. 2017[15]) |
|---|---|---|---|---|---|---|---|
| **Study design** | Multicenter, open-label, single-arm, phase 2 | Multicenter, open-label, phase 2 | | Multicenter, open-label, single-arm, phase 2 | Multicenter, open-label, single-arm, phase 2 | Multicenter, open-label, single-arm, phase 2 | Multicenter, open-label, randomized, 2-stage, phase 2/3[§] |
| **Number of patients** | 80 | 80 (40 POLA + BR arm, 40 BR arm) | | 59 | 59 | 62 | 102 (51 LEN arm) |
| **Reported median follow-up** | 13.2 months | 30 months | | 4.7 months | Not reported | 59 months | NA |
| **Key inclusion criteria** | • ≥18 years<br>• R/R to 1–3 tx (incl ≥1 anti–CD20)<br>• SCT ineligible | • ≥18 years<br>• R/R to ≥1 tx<br>• SCT ineligible<br>• ECOG PS 0–2<br>• Grade ≤1 PN | | • 20–75 years<br>• R/R to 1–3 tx<br>• SCT ineligible<br>• ECOG PS 0–1<br>• CD20+ tumor cells<br>• Lesions >1.5 cm<br>• Life expectancy ≥3 months | • R/R to ≥1 tx<br>• SCT ineligible<br>• ECOG PS 0–2<br>• At least 1 tumor of >1.5 cm<br>• Life expectancy ≥3 months | • >17 years<br>• Biopsy-proven CD20+ DLBCL or FL grade 3b<br>• Ineligible or R/R after ASCT<br>• WHO performance status 0–2 | • ≥18 years<br>• R/R to ≥1 tx<br>• SCT ineligible<br>• ECOG PS 0–2<br>• Measurable disease (≥2 cm diameter)<br>• Life expectancy ≥3 months |
| **Treatment arms** | **≤12 × 28-day cycles**[†]<br>TAFA 12 mg/kg on days 1, 8, 15, 22/cycle for cycles 1–3 (with 1 additional loading dose on day 4 of cycle 1); days 1 and 15/cycle for cycles 4–12<br>+<br>LEN 25 mg QD on days 1–21 of each cycle | **≤6 × 21-day cycles**<br>POLA 1.8 mg/kg on day 2/cycle 1, day 1/cycle thereafter<br>+<br>BEN 90 mg/m² on days 2 and 3/cycle 1, days 1 and 2/cycle thereafter<br>+<br>RTX 375 mg/m² on day 1/cycle<br>OR<br>BEN + RTX alone (as described above) | | **≤8 × 21-day cycles**<br>BEN 120 mg/m² on days 2 and 3/cycle<br>+<br>RTX 375 mg/m² on day 1/cycle | **≤6 × 28-day cycles**<br>BEN 120 mg/m² on days 1and 2/cycle[‡]<br>+<br>RTX 375 mg/m² on day 1/cycle | **4 × 28 -day R-PECC cycles by followed by radio-immunotherapy**<br>RTX 375 mg/m² on day 1/cycle + lomustine 80 mg/m² on day 1/cycle + prednisolone 40 mg/m², etoposide 100 mg/m², chlorambucil 8 mg/m² QD on days 1–5/cycle | LEN (25 mg/day, 21 days of 28-day cycle) OR<br>IC (gemcitabine, RTX, etoposide, or oxaliplatin) |
| **Primary efficacy endpoints** | ORR | CRR | | ORR | ORR | FFS | ORR |
| **Outcome criteria used** | IWG 2007 | Modified Lugano response criteria | | IWG 2007 | IWG 2007 | IWG 2007 | IWRC 1999 |
| **Investigator or IRC review** | IRC | IRC | | IRC | N/S | IRC | IRC |

*Only data from phase 2 POLA + BR versus BR at March 15, 2019 cutoff was used in MAIC analysis and is reported in the table. †After 12 cycles, TAFA was administered as monotherapy until progressive disease. ‡First 2 patients received 90 mg/m²; prior to US Food and Drug Administration approval; subsequently, patients received 120 mg/m² on days 1and 2 of 21-day cycle. §Only stage 1 results were used for comparison versus L-MIND.

BEN, bendamustine; BR, bendamustine + rituximab; CI, confidence interval; CRR, complete response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; FFS, failure-free survival; FL, follicular lymphoma; IC, investigator's choice; IRC, independent review committee; IWG, International Working Group response criteria for malignant lymphoma; IWRC, International Workshop Response Criteria; LEN, lenalidomide; MAIC, matching indirect treatment comparisons; NA, not available; N/S, not specified; ORR, objective response rate; PFS, progression-free survival; PN, peripheral neuropathy; POLA, polatuzumab vedotin; QD, once daily; R-PECC, rituximab with prednisolone, etoposide, chlorambucil, lomustine; R/R, relapsed or refractory; RTX, rituximab; SCT, stem cell transplant; TAFA, tafasitamab; tx, treatment.

**Figure 1. Baseline Characteristics of the Unadjusted and Weighted L-MIND Populations Compared With (A) GO29365 Trial for POLA + BR, (B) GO29365 Trial for BR, (C) Vacirca et al. 2014 for BR, (D) Ohmachi et al. 2013 for BR, (E) HOVON Study for R-PECC, and (F) DLC-001 Trial for LEN-Mono***

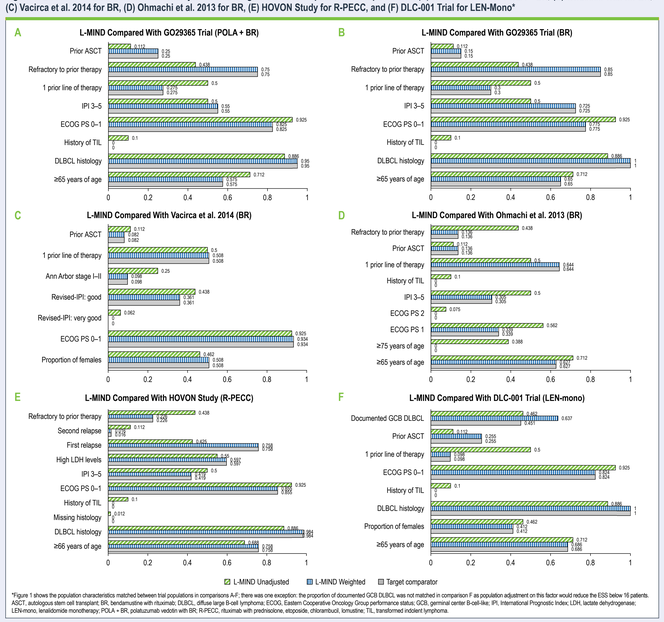



*Figure 1 shows the population characteristics matched between trial populations in comparisons A-F; there was one exception: the proportion of documented GCB DLBCL was not matched in comparison F as population adjustment on this factor would reduce the ESS below 16 patients. ASCT, autologous stem cell transplant; BR, bendamustine with rituximab; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell-like; IPI, International Prognostic Index; LDH, lactate dehydrogenase; LEN-mono, lenalidomide monotherapy; POLA + BR, polatuzumab vedotin with BR; R-PECC, rituximab with prednisolone, etoposide, chlorambucil, lomustine; TIL, transformed indolent lymphoma.

- **TAFA + LEN demonstrated a significant advantage in OS over BR (*P* = 0.014), POLA + BR after 4 months of follow-up (*P* = 0.026), R-PECC (*P* = 0.02), and LEN-mono (*P* = 0.005), with HRs (95% CI) ranging from 0.39 (0.18–0.82) to 0.51 (0.29–0.90) (Table 2)**
- **Significant advantages in PFS were observed compared with BR (*P* < 0.001) and LEN-mono (*P* = 0.04), and a numerical advantage over POLA + BR (*P* = 0.065) after 4 months (Table 2)**
  - PFS comparison was unavailable for R-PECC since it was not investigated in the HOVON study
- **Significant advantages were also observed with TAFA + LEN compared with BR and LEN-mono in CRR, and numerical advantages in CRR over R-PECC and in ORR over BR, R-PECC and LEN-mono (Table 2)**
  - **Significantly longer DOR was observed with TAFA + LEN compared with POLA + BR (HR [95% CI]: 0.34 [0.12–0.98]; *P* = 0.045) and BR (pooled HR [95% CI]: 0.35 [0.25–0.50]; *P* < 0.001);** DOR was not available for LEN-mono and R-PECC comparator studies
- Kaplan-Meier curves for OS and PFS before and after the MAIC adjustment for TAFA + LEN (and available in the comparator studies) are shown in **Figures 2–5**

**Table 2. Summary of Comparative Efficacy Results Between TAFA + LEN and Standard-of-Care Regimens (Population-Adjusted Comparisons)**

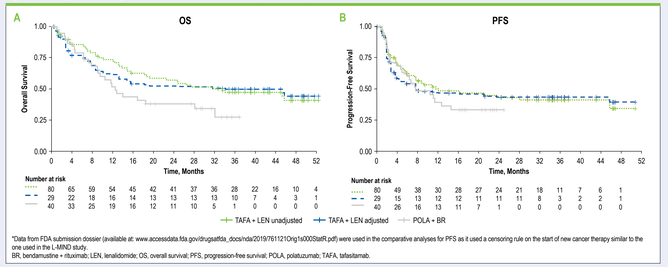
| Efficacy Outcome | TAFA + LEN Treatment Comparison (95% CI) [*P* value] POLA + BR* | BR† | R-PECC | LEN-monotherapy |
|---|---|---|---|---|
| OS | HR: 1.82 (0.58–5.65) [0.302] before 4 months<br>**HR: 0.41 (0.19–0.90) [0.026] after 4 months** | **HR: 0.39 (0.18–0.82) [0.014]** | **HR: 0.51 (0.29–0.90) [0.020]** | **HR: 0.41 (0.22–0.76) [0.005]** |
| PFS | HR: 1.42 (0.65–3.09) [0.376] before 4 months<br>HR: 0.39 (0.14–1.06) [0.065] after 4 months | **HR: 0.39 (0.29–0.53) [<0.001]** | Not investigated in the HOVON R-PECC study | **HR: 0.55 (0.31–0.97) [0.04]** |
| CRR | OR: 0.74 (0.27–2.07) [0.571] | **OR: 2.43 (1.33–4.41) [0.004]** | OR: 1.89 (0.71–5.04) [0.204] | **OR: 4.70 (1.35–16.35) [0.015]** |
| ORR | OR: 0.68 (0.25–1.86) [0.450] | OR: 1.59 (0.94–2.69) [0.086] | OR: 1.13 (0.44–2.90) [0.793] | OR: 2.15 (0.80–5.72) [0.127] |

*In the analyses of OS and PFS, the proportional hazards assumption appeared not to hold as the TAFA + LEN and POLA + BR curves were observed to cross around 4 months, thus time-varying HRs using a splitting time point at 4 months were investigated. The overall HR (95% CI) [*P* value] for OS and PFS when comparing the entire duration of the study were 0.68 (0.35–1.34) [0.268] and 0.88 (0.45–1.73) [0.719], respectively. †Pooled estimates from 3 studies (GO29365 Trial, Vacirca 2014, Ohmachi 2013) are shown for PFS, CRR, and RR; estimate from 1 study (GO29365 Trial) is shown for OS as data were not available from other studies.

**Bold blue text** signifies statistically significant estimates and Non-bold blue text signifies numerically higher estimates for TAFA + LEN versus SoC regimens; Gray text signifies numerically higher estimates for SoC regimens versus TAFA + LEN (or analyses not performed).

BR, bendamustine + rituximab; CI, confidence interval; CRR, complete response rate; HR, hazard ratio; LEN, lenalidomide; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POLA, polatuzumab; R-PECC, rituximab with prednisolone, etoposide, chlorambucil, lomustine; SoC, standard-of-care; TAFA, tafasitamab

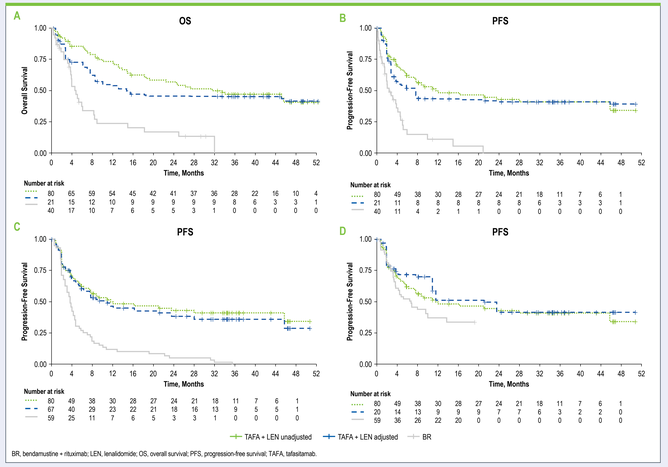
**Figure 2 . Unadjusted and Adjusted Kaplan-Meier Estimates of (A) OS and (B) PFS* for TAFA + LEN Versus POLA + BR**




*Data from FDA submission dossier (available at: www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761121Orig1s000StatR.pdf) were used in the comparative analyses for PFS as it used a censoring rule on the start of new cancer therapy similar to the one used in the L-MIND study.

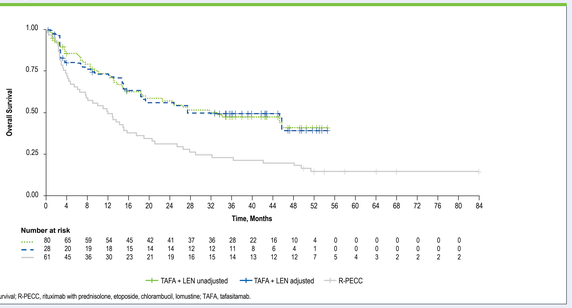
BR, bendamustine + rituximab; LEN, lenalidomide; OS, overall survival; PFS, progression-free survival; POLA, polatuzumab; TAFA, tafasitamab.

**Figure 3. Unadjusted and Adjusted Kaplan-Meier Estimates of (A) OS and (B) PFS for TAFA + LEN Versus BR in GO29365 Trial, (C) PFS for TAFA + LEN Versus BR in Vacirca et al. 2014, and (D) PFS for TAFA + LEN Versus BR in Ohmachi et al. 2013**



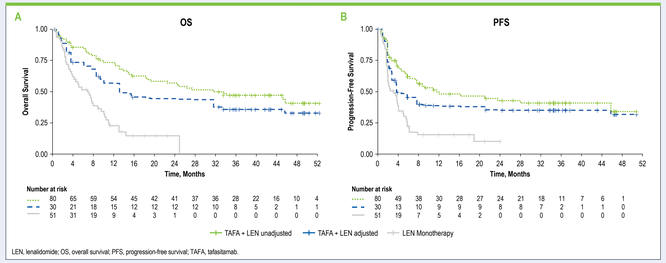

BR, bendamustine + rituximab; LEN, lenalidomide; OS, overall survival; PFS, progression-free survival; TAFA, tafasitamab.

**Figure 4. Unadjusted and Adjusted Kaplan-Meier Estimates of OS for TAFA + LEN Versus R-PECC**




LEN, lenalidomide; OS, overall survival; R-PECC, rituximab with prednisolone, etoposide, chlorambucil, lomustine; TAFA, tafasitamab.

**Figure 5. Unadjusted and Adjusted Kaplan-Meier Estimates of (A) OS and (B) PFS for TAFA + LEN Versus LEN Monotherapy (DLC-001 Study)**




LEN, lenalidomide; OS, overall survival; PFS, progression-free survival; TAFA, tafasitamab.

## Conclusions

- **Results from the MAIC analyses suggest that patients receiving TAFA + LEN for the treatment of R/R DLBCL are likely to experience improved clinical outcomes compared with common standard-of-care treatment alternatives such as BR, POLA + BR, and R-PECC, and help quantify the added benefit of TAFA in combination with LEN, when compared with LEN-mono (consistent with previous findings from the REMIND study[16])**
- **There are known methodological limitations of unanchored MAICs and population adjustment methods that should be considered when interpreting these results. These include differences in inclusion and exclusion criteria and outcomes measurement definitions across studies, limited data availability on patient baseline characteristics, small ESS, and unknown or unobserved confounding factors and treatment effect modifiers**
- **Nonetheless, having minimized whenever possible all known sources of bias, these results provide the most objective available framework to compare outcomes of the L-MIND study versus published prospective studies of selected comparators**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## Disclosures

**About Tafasitamab:** Tafasitamab is a humanized Fc-modified cytolytic CD19 targeting monoclonal antibody. In 2010, MorphoSys licensed exclusive worldwide rights to develop and commercialize tafasitamab from Xencor, Inc. Tafasitamab incorporates an XmAb® engineered Fc domain, which mediates B-cell lysis through apoptosis and immune effector mechanism including Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) and Antibody-Dependent Cellular Phagocytosis (ADCP). In January 2020, MorphoSys and Incyte entered into a collaboration and licensing agreement to further develop and commercialize tafasitamab globally. Following accelerated approval by the U.S. Food and Drug Administration in July 2020, tafasitamab is being co-commercialized by MorphoSys and Incyte in the United States. Incyte has exclusive commercialization rights outside the United States. XmAb® is a trademark of Xencor, Inc.

**Cordoba:** Speaker – *AbbVie, AstraZeneca, Celgene/BMS, Janssen, Kite Pharma, Roche, Takeda;* Advisory – *AbbVie, ADCT Therapeutics, AstraZeneca, Celgene/BMS, Incyte Corporation, Janssen, Kite Pharma, Kyowa Kirin, Roche, Takeda;* Travel and accommodation – *AbbVie, AstraZeneca, Celgene/BMS, Janssen, Kite Pharma, Kyowa Kirin, Roche, Takeda;* Research grant – *Pfizer.* **Prawitz:** Employee – *Evidera;* Stock ownership – *PPD, Inc.* **Westley, Sharma:** Employee – *Evidera.* **Kapetanakis:** Employee – *Evidera (commissioned by Incyte Corporation to conduct these analyses);* Stock ownership – *PPD, Inc.* **Sabatelli:** Employee and stock ownership – *Incyte Corporation*.

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