# Matching-adjusted indirect comparison (MAIC) of nivolumab + relatlimab (NIVO+RELA) vs. *BRAF/MEK* inhibitors for first-line treatment of *BRAF*-mutant advanced melanoma

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## Introduction

- Melanoma is one of the deadliest cancers in the United States, accounting for approximately 75% of skin cancer deaths despite only representing 4% of skin cancer cases.[1] In 2023, approximately 97,610 people will be diagnosed and 7,990 people are expected to die from melanoma[2]
- For patients with advanced melanoma with *BRAF* mutation, a common mutation reported in 41%-55% of metastatic melanomas[3], three targeted therapies that are *BRAF/MEK* inhibitor combinations have been approved by the FDA: dabrafenib + trametinib (DAB + TRAM), encorafenib + binimetinib (ENCO + BINI), and vemurafenib + cobimetinib (VEM + COBI)[4-6]
- Nivolumab (NIVO) is an anti-programmed cell death protein 1 (PD-1) antibody that relieves T-cell dysfunction and restores cytotoxic function,[7] and has been a standard of care in the treatment of unresectable or metastatic melanoma. Relatlimab (RELA) is a human lymphocyte-activation gene 3 (LAG-3) blocking antibody that restores the effector function of dysfunctional T-cells[8]
- RELATIVITY-047 (NCT03470922) investigated NIVO + RELA as a fixed-dose combination therapy vs. NIVO alone in patients with unresectable or metastatic melanoma.[8] NIVO + RELA was approved by the FDA in 2022 for this indication regardless of *BRAF* status[9]
- Matching-adjusted indirect comparisons (MAICs) demonstrated durable overall survival (OS) and progression-free survival (PFS) benefits for patients with *BRAF*-mutant advanced melanoma treated with NIVO + ipilimumab (NIVO + IPI) compared with *BRAF/MEK* inhibitors, with greatest benefits after 12 months[10]
  - The DREAMseq trial[11], a phase III trial in which patients with treatment-naïve *BRAF*-mutant metastatic melanoma received NIVO + IPI or DAB + TRAM at enrollment and the alternate therapy at disease progression, confirmed that combination therapy with NIVO + IPI followed by *BRAF/MEK* inhibitors (if necessary) should be the preferred treatment sequence
- The emergence of novel treatments for *BRAF*-mutant advanced melanoma motivates the need to assess the comparative clinical efficacy of approved options
- In the absence of head-to-head randomized trials, MAICs were used in this study to compare the efficacy of NIVO + RELA vs. *BRAF/MEK* inhibitors for first-line treatment of *BRAF*-mutant advanced melanoma

## Objectives

- The present study evaluated the efficacy of NIVO + RELA vs. *BRAF/MEK* inhibitors for first-line treatment of *BRAF*-mutant advanced melanoma using MAICs

## Methods

### Data sources

- Individual patient-level data (IPD) from the phase II/III RELATIVITY-047 trial were leveraged for the *BRAF*-mutant subset of patients who received NIVO + RELA (n=136; median OS follow-up: 30.1 months; median PFS follow-up: 44.9 months)
- Summary aggregate data and digitized versions of the Kaplan-Meier curves for comparators were extracted from publications:
  - Data for DAB + TRAM were extracted from the pooled COMBI-d/v trial publication (all outcomes: Robert et al. 2019; median follow-up: 22 months)[12]
  - Data for ENCO + BINI were extracted from the COLUMBUS trial publications:
    - OS: Dummer et al. 2022; median follow-up: 70.4 months[13]
    - PFS: Dummer et al. 2018; median follow-up: : 16.7 months[14]
    - Overall response rate (ORR): Ascierto et al. 2020; median follow-up: 48.8 months[15]
  - Data for VEM + COBI were extracted from the coBRIM trial publication (all outcomes: Ascierto et al. 2021; median follow-up: 21.2 months)[16]

### Statistical methods

- Separate MAICs were conducted to compare efficacy outcomes between NIVO + RELA vs. DAB + TRAM, NIVO + RELA vs. ENCO + BINI, and NIVO + RELA vs. VEM + COBI
  - Outcomes of interest were OS, investigator-assessed PFS (PFS per INV), investigator-assessed ORR (ORR per INV), any grade 3/4/5 adverse events (AEs), and any AEs leading to discontinuation
- IPD for NIVO + RELA from the *BRAF*-mutant subset of RELATIVITY-047 were weighted for each comparison separately to adjust for baseline characteristics which may impact treatment outcomes
- Baseline characteristics that were matched on for each comparison are listed in **Table 1**
  - These were determined based on data availability and clinical input and were determined to be clinically relevant for disease prognosis
- Effective sample sizes (ESS) after matching were calculated for the NIVO + RELA arm for each comparison
- Weighted Cox proportional hazard models and, due to violation of the proportional hazards assumption based on the scaled Schoenfeld residuals, interval weighted Cox models with a boundary point at 12 months, were used to compare PFS per INV and OS between treatments. Hazard ratios (HRs) along with their 95% confidence intervals (CIs) were reported
- Odds ratios (ORs) were used to compare ORR between treatments, and the corresponding 95% CI and p-value were calculated using Wald tests
- Risk differences (RDs) were used to summarize AE rates between treatments

**Table 1. Matched baseline characteristics for each comparison**

| Matched characteristics | NIVO + RELA vs. DAB + TRAM | NIVO + RELA vs. ENCO + BINI | NIVO + RELA vs. VEM + COBI |
|---|---|---|---|
| Age (% above comparator's median) | X | X | X |
| Sex (male, female) | X | X | X |
| ECOG performance status | X | X | X |
| LDH level | X | X | X |
| Metastasis stage | X | X | X |
| Number of disease sites | X | | |
| Prior immunotherapy | X | X | |
| History of brain metastases | | | X |

**Abbreviation:** ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase.

## Results

### Baseline characteristics (Table 2)

- After matching, all baseline characteristics were balanced, as assessed via Wald tests, between the two populations in each comparison
  - Exception: geographic region and race (which were only available in the VEM + COBI comparison); however, over 92% of patients in each trial were White
- The ESS for NIVO + RELA was 100 for comparison vs. DAB + TRAM, 77 vs. ENCO + BINI, and 111 vs. VEM + COBI

### Outcome comparisons

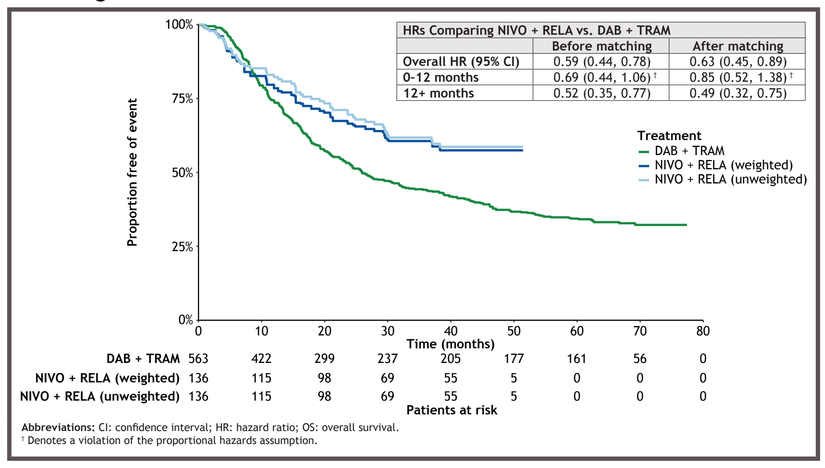
- After matching:
  - NIVO + RELA was associated with greater OS benefit after 12 months from treatment initiation in all comparisons (**Figures 1a, 2a, and 3a**)
  - There were no differences in PFS per INV from 12 months onward between NIVO + RELA and DAB + TRAM, ENCO + BINI had improved PFS per INV within the 0–12 month period but there were no differences from 12 months onward, and NIVO + RELA had improved PFS per INV than VEM + COBI from 12 months onward (**Figures 1b, 2b, and 3b**)
  - All comparators were associated with higher ORR per INV than NIVO + RELA (**Table 3**)
  - NIVO + RELA had lower rates of any grade 3/4/5 AEs and higher rates of AEs leading to discontinuation in all comparisons (**Table 4**)

**Table 2. Patient baseline characteristics before and after matching for NIVO + RELA vs. comparators**

| | NIVO + RELA vs. DAB + TRAM | | | | NIVO + RELA vs. ENCO + BINI | | | | NIVO + RELA vs. VEM + COBI | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Before matching | | After matching | | Before matching | | After matching | | Before matching | | After matching | |
| Baseline characteristics | NIVO + RELA N=136 | DAB + TRAM N=563 | NIVO + RELA ESS=100 | DAB + TRAM N=563 | NIVO + RELA N=136 | ENCO + BINI N=192 | NIVO + RELA ESS=77 | ENCO + BINI N=192 | NIVO + RELA N=136 | VEM + COBI N=247 | NIVO + RELA ESS=111 | VEM + COBI N=247 |
| Age (above comparator median)[1] | 55 (40.4%) | 282 (50.0%) | 50.0% | 50.0% | 63 (46.3%) | 96 (50.0%) | 50.0% | 50.0% | 58 (42.6%) | 124 (50.0%) | 50.0% | 50.0% |
| Female | 66 (48.5%) | 244 (43.3%) | 43.3% | 43.3% | 66 (48.5%) | 77 (40.1%) | 40.1% | 40.1% | 66 (48.5%) | 101 (40.9%) | 40.9% | 40.9% |
| Male | 70 (51.5%) | 319 (56.7%) | 56.7% | 56.7% | 70 (51.5%) | 115 (59.9%) | 59.9% | 59.9% | 70 (51.5%) | 146 (59.1%) | 59.1% | 59.1% |
| ECOG 0 | 97 (71.3%) | 403 (71.6%) | 71.6% | 71.6% | 97 (71.3%) | 136 (70.8%) | 70.8% | 70.8% | 97 (71.3%) | 184 (74.5%) | 74.5% | 74.5% |
| ECOG 1[2] | 39 (28.7%) | 155 (27.5%) | 28.4% | 27.5% | 39 (28.7%) | 56 (29.2%) | 29.2% | 29.2% | 39 (28.7%) | 59 (23.9%) | 25.5% | 23.9% |
| ECOG missing | 0 (0.0%) | 5 (0.9%) | 0.0% | 0.9% | 0 (0.0%) | 0 (0.0%) | 0.0% | 0.0% | 0 (0.0%) | 4 (1.6%) | 0.0% | 1.6% |
| LDH > upper limit of normal | 47 (34.6%) | 194 (34.5%) | 34.5% | 34.5% | 47 (34.6%) | 55 (28.6%) | 28.6% | 28.6% | 47 (34.6%) | 112 (45.3%) | 45.3% | 45.3% |
| LDH ≤ upper limit of normal | 89 (65.4%) | 365 (64.8%) | 65.5% | 64.8% | 89 (65.4%) | 137 (71.4%) | 71.4% | 71.4% | 89 (65.4%) | 130 (52.7%) | 54.7% | 52.7% |
| Metastatic status M0 or M1a[3] | 43 (31.6%) | 94 (16.7%) | 16.7% | 16.7% | 43 (31.6%) | 35 (18.2%) | 18.2% | 18.2% | 43 (31.6%) | 61 (24.7%) | 24.7% | 24.7% |
| Metastatic status M1b | 33 (24.3%) | 105 (18.7%) | 18.7% | 18.7% | 33 (24.3%) | 34 (17.7%) | 17.7% | 17.7% | 33 (24.3%) | 40 (16.2%) | 16.2% | 16.2% |
| Metastatic status M1c or M1d | 60 (44.1%) | 363 (64.5%) | 64.7% | 64.5% | 60 (44.1%) | 123 (64.1%) | 64.1% | 64.1% | 60 (44.1%) | 146 (59.1%) | 59.1% | 59.1% |
| Number of disease sites ≥ 3 | 56 (41.2%) | 275 (48.8%) | 48.8% | 48.8% | – | – | – | – | – | – | – | – |
| Number of disease sites < 3 | 80 (58.8%) | 287 (51.0%) | 51.2% | 51.0% | – | – | – | – | – | – | – | – |
| Prior immunotherapy | 16 (11.8%) | 117 (20.8%) | 20.8% | 20.8% | 16 (11.8%) | 57 (29.7%) | 29.7% | 29.7% | – | – | – | – |
| History of brain metastases | – | – | – | – | – | – | – | – | 4 (2.9%) | 1 (0.4%) | 0.4% | 0.4% |
| No history of brain metastases | – | – | – | – | – | – | – | – | 132 (97.1%) | 246 (99.6%) | 99.6% | 99.6% |
| White race | – | – | – | – | – | – | – | – | 134 (98.5%) | 227 (91.9%) | 98.0% | 91.9% |
| Other race | – | – | – | – | – | – | – | – | 1 (0.7%) | 20 (8.1%) | 1.7% | 8.1% |
| North America | – | – | – | – | – | – | – | – | 19 (14.0%) | 25 (10.1%) | 12.8% | 10.1% |
| Europe | – | – | – | – | – | – | – | – | 67 (49.3%) | 182 (73.7%) | 49.3% | 73.7% |
| Other geographic location | – | – | – | – | – | – | – | – | 50 (36.8%) | 40 (16.2%) | 37.9% | 16.2% |

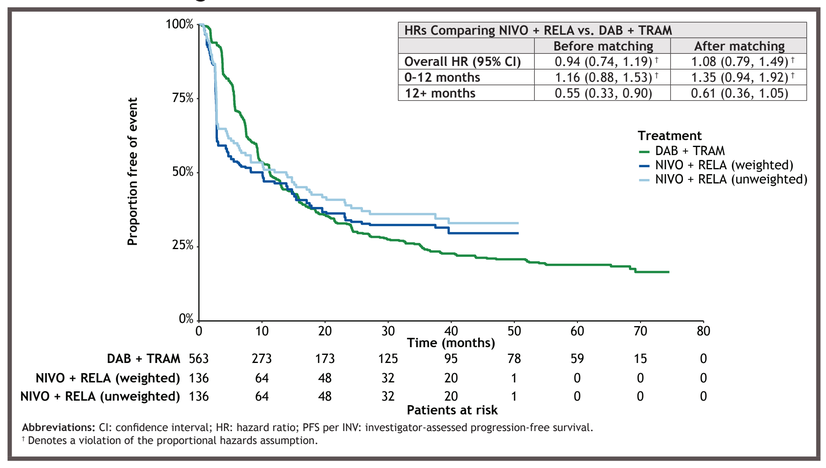
**Abbreviations:** ECOG: Eastern Cooperative Oncology Group; ESS: effective sample size; LDH: lactate dehydrogenase.
[†]The median age for combi-d/v, COLUMBUS, and coBRIM were 55, 57, and 56 years respectively.
[2]One patient in the VEM + COBI trial had ECOG of 2 after randomization but before the first dose was received and was grouped into the category of ECOG 1 for this analysis. All patients in the NIVO + RELA trial had ECOG of 0 or 1.
[3]3.2% of patients in the VEM + COBI arm of the coBRIM trial had stage IIIc melanoma and was grouped in the Metastatic status M0 or M1a category.

**Figure 1a. OS comparisons of NIVO + RELA vs. DAB + TRAM, before and after matching**



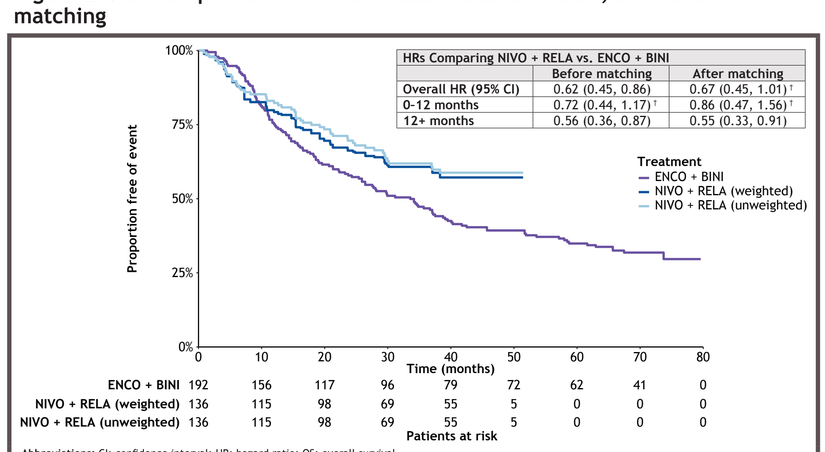

**Abbreviations:** CI: confidence interval; HR: hazard ratio; OS: overall survival.
[†] Denotes a violation of the proportional hazards assumption.

**Figure 1b. PFS per INV comparisons of NIVO + RELA vs. DAB + TRAM, before and after matching**



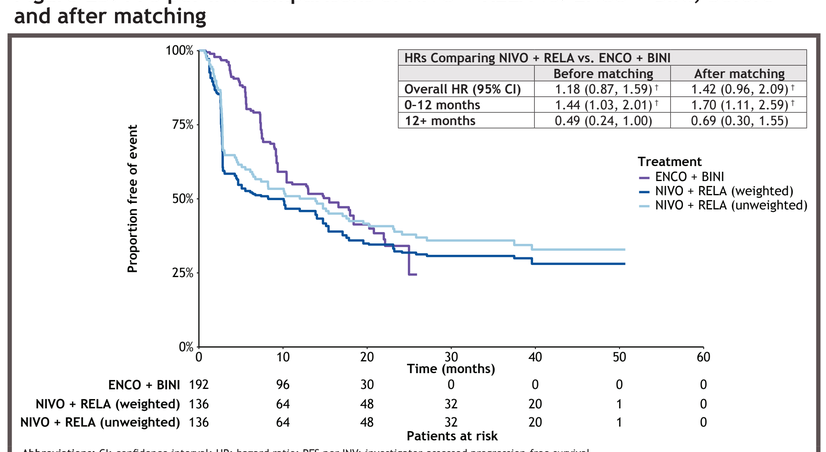

**Abbreviations:** CI: confidence interval; HR: hazard ratio; PFS per INV: investigator-assessed progression-free survival.
[†] Denotes a violation of the proportional hazards assumption.

**Figure 2a. OS comparisons of NIVO + RELA vs. ENCO + BINI, before and after matching**



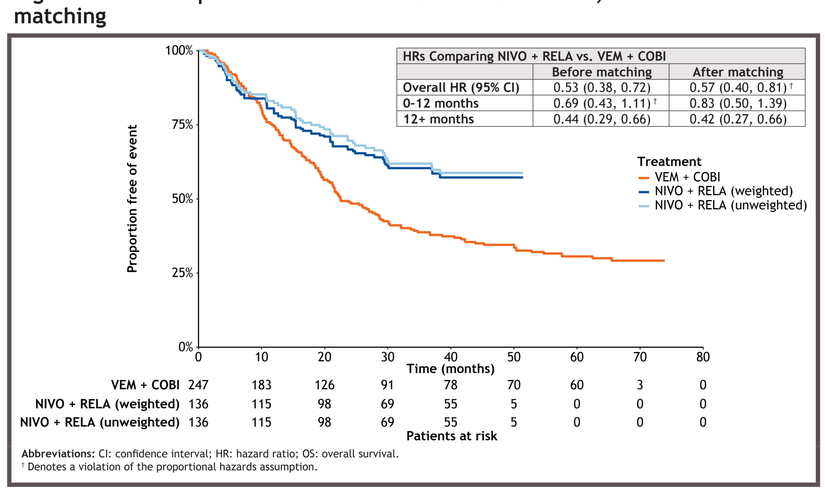

**Abbreviations:** CI: confidence interval; HR: hazard ratio; OS: overall survival.
[†] Denotes a violation of the proportional hazards assumption.

**Figure 2b. PFS per INV comparisons of NIVO + RELA vs. ENCO + BINI, before and after matching**



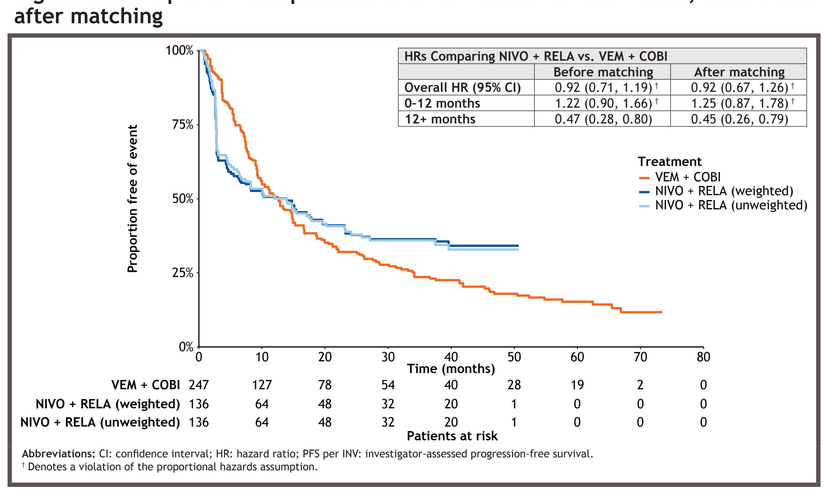

**Abbreviations:** CI: confidence interval; HR: hazard ratio; PFS per INV: investigator-assessed progression-free survival.
[†] Denotes a violation of the proportional hazards assumption.

**Figure 3a. OS comparisons of NIVO + RELA vs. VEM + COBI, before and after matching**




**Abbreviations:** CI: confidence interval; HR: hazard ratio; OS: overall survival.
[†] Denotes a violation of the proportional hazards assumption.

**Figure 3b. PFS per INV comparisons of NIVO + RELA vs. VEM + COBI, before and after matching**




**Abbreviations:** CI: confidence interval; HR: hazard ratio; PFS per INV: investigator-assessed progression-free survival.
[†] Denotes a violation of the proportional hazards assumption.

**Table 3. ORR per INV comparisons of NIVO + RELA vs. comparators, before and after matching**

| | NIVO + RELA vs. DAB + TRAM OR (95% CI) | | NIVO + RELA vs. ENCO + BINI OR (95% CI) | | NIVO + RELA vs. VEM + COBI OR (95% CI) | |
|---|---|---|---|---|---|---|
| | Before matching | After matching | Before matching | After matching | Before matching | After matching |
| Odds ratio | 0.43 (0.33, 0.57) | 0.38 (0.28, 0.52) | 0.30 (0.21, 0.42) | 0.26 (0.17, 0.39) | 0.40 (0.29, 0.55) | 0.38 (0.27, 0.53) |

**Abbreviations:** CI: confidence interval; OR: odds ratio; ORR per INV: investigator-assessed overall response rate.

**Table 4. AE RD (%) of NIVO + RELA vs. comparators, before and after matching**

| | NIVO + RELA vs. DAB + TRAM RD (95% CI) | | NIVO + RELA vs. ENCO + BINI RD (95% CI) | | NIVO + RELA vs. VEM + COBI RD (95% CI) | |
|---|---|---|---|---|---|---|
| | Before matching | After matching | Before matching | After matching | Before matching | After matching |
| Any grade 3/4/5 AEs | -22.4 (-31.5, -13.4) | -20.3 (-30.8, -9.7) | -31.5 (-41.9, -21.0) | -30.1 (-43.0, -17.1) | -39.0 (-48.7, -29.3) | -37.6 (-48.1, -27.0) |
| AEs leading to discontinuation | 11.7 (3.4, 20.0) | 9.7 (0.6, 18.9) | 19.0 (10.2, 27.8) | 16.4 (5.8, 27.1) | 2.4 (-7.0, 11.8) | 2.2 (-7.8, 12.2) |

**Abbreviations:** AE: adverse event; CI: confidence interval; RD: risk difference.

## Limitations

- Only available baseline factors that were consistently reported across trials for a given comparator were included among the matching covariates in the MAICs
- As with any comparison of non-randomized treatment groups, these comparisons are subject to potential bias due to unobserved or unmeasurable confounding factors
- Different subsequent treatments may have been available for each of the comparators after progression since trials were conducted in different timepoints, which may have had some impact on OS that cannot be adjusted via MAIC
- The results of the study may not be generalizable beyond the study sample

## Conclusions

- These MAICs suggest long-term (after 12 months) OS advantage of NIVO + RELA over DAB + TRAM, ENCO + BINI, and VEM + COBI, but lower ORRs for NIVO + RELA for first-line treatment of *BRAF*-mutant advanced melanoma. In addition, these comparisons demonstrated longer-term PFS (after 12 months) for NIVO + RELA over DAB + TRAM and VEM + COBI

## Disclosures

Conflicts of interest: FE, JP, BR, AM, DP, and AS are employees of Bristol Myers Squibb. DRS, MM, JZ, and VG-H are employees of Analysis Group, Inc., which received funding from Bristol Myers Squibb.

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