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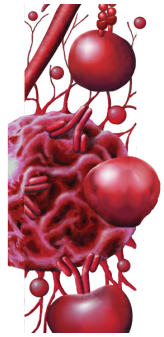
Plain Language Summary of Publication

Immunotherapy



Plain language summary of RACE study results: addition of eltrombopag to standard treatment of severe aplastic anemia

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Summary

What is this summary about?
Severe aplastic anemia (SAA) and very severe aplastic anemia (vSAA) are blood diseases of the **bone marrow**. If a suitable donor for bone marrow transplant as initial treatment is unavailable, standard **immunosuppression** is used. Standard immunosuppression treatment includes horse antithymocyte globulin (hATG) and cyclosporin A (CsA). This summary investigated the results of standard immunosuppression treatment (Group A) versus standard immunosuppression treatment with a medication called eltrombopag (Group B) in participants with SAA and vSAA. Eltrombopag is a medicine that improves the blood **platelet** level and is taken by mouth (orally).

How to say (double click to play sound)...

- **Anemia :** uh·nee·mee·uh
- **Aplastic:** ay·pla·stuhk
- **Cyclosporin:** sai·kluh·spaw·ruhn
- **Eltrombopag:** el-TROM-boh-pag

What were the results of the study?
Compared to Group A, more participants in Group B showed increased blood cell level to a normal range without SAA or vSAA and faster treatment response. Side effects were similar in both groups even with the addition of eltrombopag for Group B. Participants in both groups reported feeling well after 6, 12 and 24 months. Differences in the participant-reported scores (overall health, physical, emotional, and social) between Group A and Group B were minimal.

What do the results of the study mean?
Immunosuppression treatment (hATG plus CsA) with eltrombopag benefited participants with SAA and vSAA and could be the new standard for SAA in persons who cannot undergo bone marrow transplant. At this time, eltrombopag is only approved in specific countries to treat the condition under study that is discussed in this summary.

Where can I find the original article on which this summary is based?

You can read the original article 'Eltrombopag Added to Immunosuppression in Severe Aplastic Anemia' published in the journal *The New England Journal of Medicine* for free at: https://www.nejm.org/doi/full/10.1056/NEJMoa2109965

Glossary

- **Bone marrow:** A soft spongy tissue found inside human bones that contains stem cells which produce new blood cells daily
- **Stem cells:** Special cells that can develop into other types of cells
- **Immunosuppression:** Lowering the activity of the body's immune system or the network of cells and organs that protects the body
- **Platelets:** Cells in the body that help stop bleeding

Future Medicine part of fsg

Who is this article for?

This plain language summary may be helpful for persons with severe aplastic anemia (SAA) and their family members and caregivers. General clinicians may find this article useful.

What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you to understand the findings from recent research. This summary reports the results of a single study. The results of this study may differ from those of other studies. Health professionals should make treatment decisions based on all available evidence, not on the results of a single study.

Who sponsored this study?

- The RACE study was sponsored by the European Society for Blood and Marrow Transplantation (EBMT). The study was funded by Novartis, Pfizer, a grant from Alexion Pharma, a grant (A22324) from Cancer Research UK, and grants (10024 and 14017) from Bloodwise UK (previously called Leukaemia and Lymphoma Research).
- Pfizer funded the development of this plain language summary.

Sponsor: A sponsor is a company or organization that oversees and pays for a clinical research study. The sponsor also collects and analyzes the information that was generated during the study.

What is aplastic anemia?

- Aplastic anemia is a rare blood disease of the bone marrow.
- Bone marrow is a soft spongy tissue found inside human bones that contains **stem cells**. Stem cells are special cells that can develop into other types of cells. Bone marrow produces new blood cells daily.
- In aplastic anemia, the bone marrow does not produce enough:
  - Red blood cells (cells that carry oxygen)
  - White blood cells (cells that help fight diseases)
  - Platelets (cells that help with stopping bleeding)
- Acquired aplastic anemia occurs when there is a problem in the immune system (a network of cells and organs that protect the body) where a trigger attacks the body's own stem cells.

What is severe or very severe aplastic anemia?

- The severity of the disease is based on the number of blood cells in the blood circulating throughout the body.
- SAA and very SAA (vSAA) involve specific decreases in blood cell levels in circulating blood compared with the normal range.
- Decreases are observed in at least two of the three cell types below:
  - Neutrophils (type of white blood cells that helps the body fight diseases)
  - Platelets
  - Reticulocytes (newly formed and still developing red blood cells)

What is the standard treatment for SAA?

- The initial treatment for SAA depends on the age of the person and if a donor for bone marrow transplant is available.
- Bone marrow transplant involves the transfer of healthy bone marrow containing stem cells from a donor to a person receiving the bone marrow stem cells that will later form into blood cells.
- The donor match for a bone marrow transplant could be a sibling or an unrelated person.

- A person with SAA can be treated with options that lower the activity of their immune system (or immunosuppression) if:
  - There is no donor match
  - They are 40 years or older
- The standard immunosuppression treatment for persons with SAA is hATG (horse antithymocyte globulin; a medicine used to fight a type of white blood cell and is taken by infusion into a vein) plus CsA (cyclosporin A; another immunosuppression medicine that is taken by mouth).

What is eltrombopag?

- Eltrombopag is a medicine that works like a normal hormone (thrombopoietin) that the body makes.
- Eltrombopag stimulates bone marrow stem cells in the body to improve the blood platelet level.
- Eltrombopag is a medicine that is taken by mouth (orally).

Why was the RACE study conducted?

- Many studies in the past have shown that various methods did not improve the results of standard immunosuppression treatment.
- Early smaller studies of eltrombopag with hATG plus CsA showed it was effective in untreated participants with SAA or vSAA.
- Researchers in the RACE study wanted to understand if adding eltrombopag to the standard immunosuppression treatment (hATG plus CsA) can be a new standard treatment for persons with SAA or vSAA.
- This will provide another option when persons cannot undergo bone marrow transplant as an initial treatment.

How was the RACE study conducted?

Where and when was the study conducted?

The study was conducted at 24 hospitals in 6 countries in Europe between July 2015 and April 2019.

Who participated in the study?

There were a total of 197 participants in the study:
- All of them were 15 years of age or older
- All of them had a new diagnosis of SAA or vSAA
- None of them had a sibling donor for bone marrow transplant
- None of them were suitable for bone marrow transplant as their initial treatment
- None of them had other underlying serious diseases
- All of them were willing to be a part of the study and follow all requirements of the study

What was done in the study?

- Participants in the study were distributed by chance (randomized) into two groups:
  - Group A: hATG plus CsA or standard immunosuppression treatment
  - Group B: hATG plus CsA with eltrombopag
- Both doctors and participants were aware of the treatment being given in the study (open label).

197 participants in the study

Group A: hATG plus CsA
101 participants

Intravenous (infusion into a vein) hATG
- A fixed amount (dose) of 40 milligrams per kilogram of body weight given daily for 4 consecutive days

Oral (by mouth) CsA
- Day 1 to 12 months: 5 milligrams per kilogram of body weight given daily
- Months 13–24: dose gradually decreased and stopped by 24 months

Group B: hATG plus CsA with eltrombopag
96 participants

Intravenous (infusion into a vein) hATG
- A fixed amount (dose) of 40 milligrams per kilogram of body weight given daily for 4 consecutive days

Oral (by mouth) CsA
- Day 1 to 12 months: 5 milligrams per kilogram of body weight given daily
- Months 13–24: dose gradually decreased and stopped by 24 months

Oral (by mouth) eltrombopag
- Day 14 to 3 or 6 months: 150 milligrams given daily

If increase in blood cell level in the bone marrow to near normal at 3 months (complete response), then eltrombopag stopped at 3 months

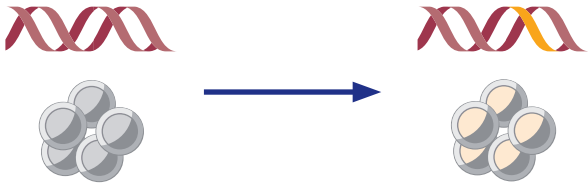
If increase in bone marrow blood cell level that no longer met the SAA and/or vSAA criteria at 3 months (partial response), then eltrombopag taken for 6 months

What were some features of participants in the study?

Age

Group A		Group B
15 years	Minimum age	**16** years
81 years	Maximum age	**77** years

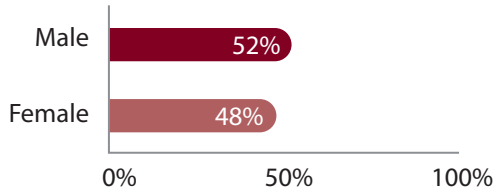
Genetic abnormalities in the bone marrow or acquired changes to the cells



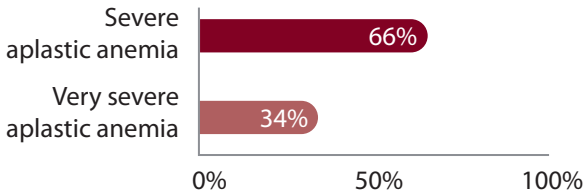
Changes to the cells developed over time due to change in genes (unit of information inside a cell that help the body work)

Group A: hATG plus CsA

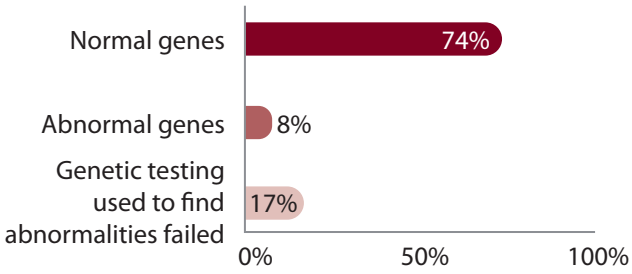
Sex



Severity of aplastic anemia

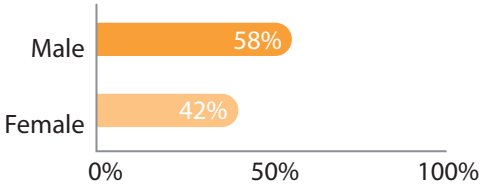


Genetic abnormalities of bone marrow or acquired changes to cells

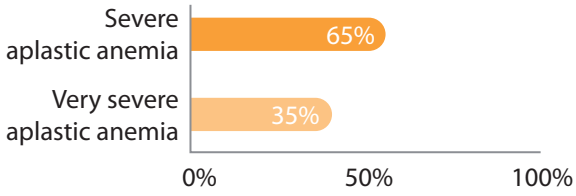


Group B: hATG plus CsA with eltrombopag

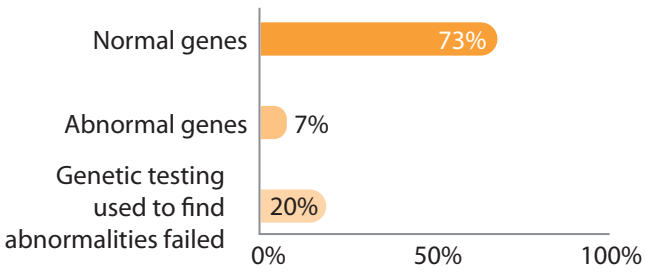
Sex



Severity of aplastic anemia



Genetic abnormalities of bone marrow or acquired changes to cells



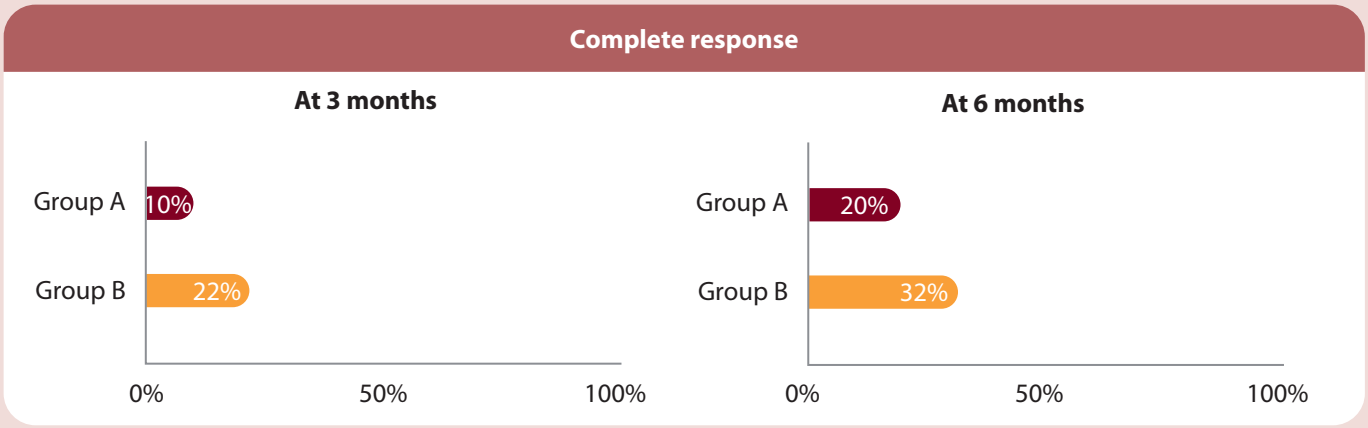
What indicators were measured in the RACE study?

- Response to treatment based on improvement in the blood cell level in the circulating blood:
  - Complete response: Percentage of participants who had an increase in blood cell levels to near normal. Complete response was checked at 3 months and 6 months
  - Overall response: Percentage of participants who had a complete or partial (an increase in blood cell level such that it no longer met the SAA and/or vSAA criteria) response. Overall response was checked at 3 months and 6 months
  - Time taken to respond to treatment including the actual time till the first response to treatment and the actual time between the start and end of treatment to achieve the best response to treatment
- Factors that affect the response to treatment
- Side effects of treatment (unwanted reactions to the treatment)
- Quality of life (one's perception of overall well-being) results reported by participants
  - Quality of life related to daily activities was measured using surveys completed by participants. Survey questions covered overall health, physical health, emotional health, fatigue (e.g., do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?), pain, and financial difficulties due to treatment or illness (e.g., during the past week, has your physical condition or medical treatment caused you financial difficulties?)

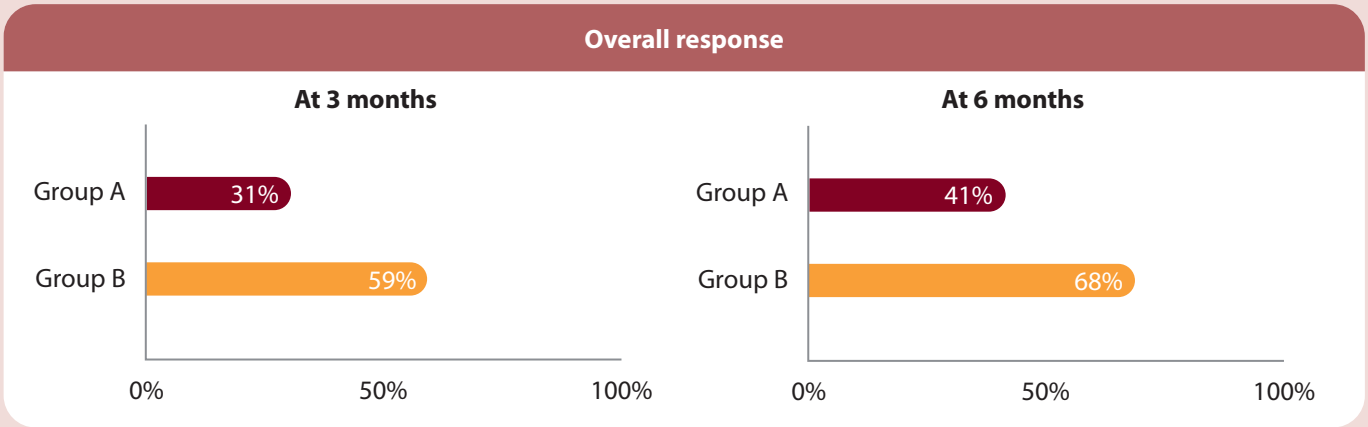
- Genetic abnormalities in the bone marrow or acquired changes to the cells on treatment
- Long-term results of treatment:
  - 2-year overall survival: Percentage of participants who remained alive at 2 years after starting treatment
  - 18-month relapse: Percentage of participants who had SAA and/or vSAA return 18 months after responding to the treatment
  - 2-year hemolytic paroxysmal nocturnal hemoglobinuria (PNH): This is a rare blood disease where a part of the body's immune system (or the complement system) attacks the red blood cells and platelets
  - 2-year event-free survival: Percentage of participants who remained free from complications of SAA and/or vSAA for an increased length of time since the start of treatment

What were the main findings of the RACE study?

- As a reminder, treatment for participants in Group A was hATG plus CsA or standard immunosuppression treatment, and treatment for participants in Group B was hATG plus CsA (standard immunosuppression treatment) with eltrombopag
- Response to treatment based on improvement in the blood cell level in the circulating blood:
  - Responses (complete and overall) at 3 months and 6 months were higher in participants in Group B compared with those in Group A
  - Complete response at both 3 and 6 months was higher in participants from Group B

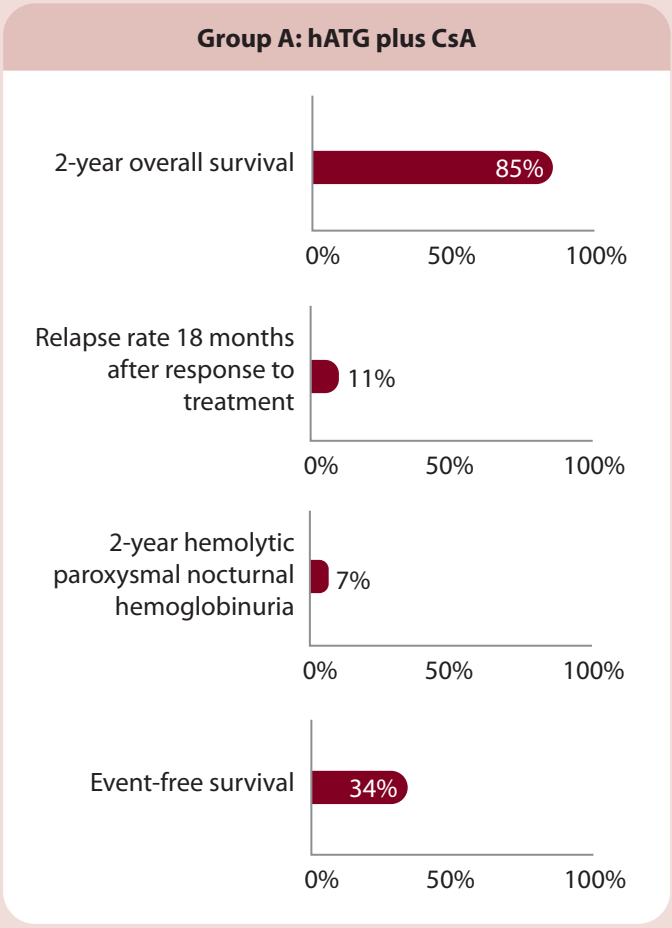


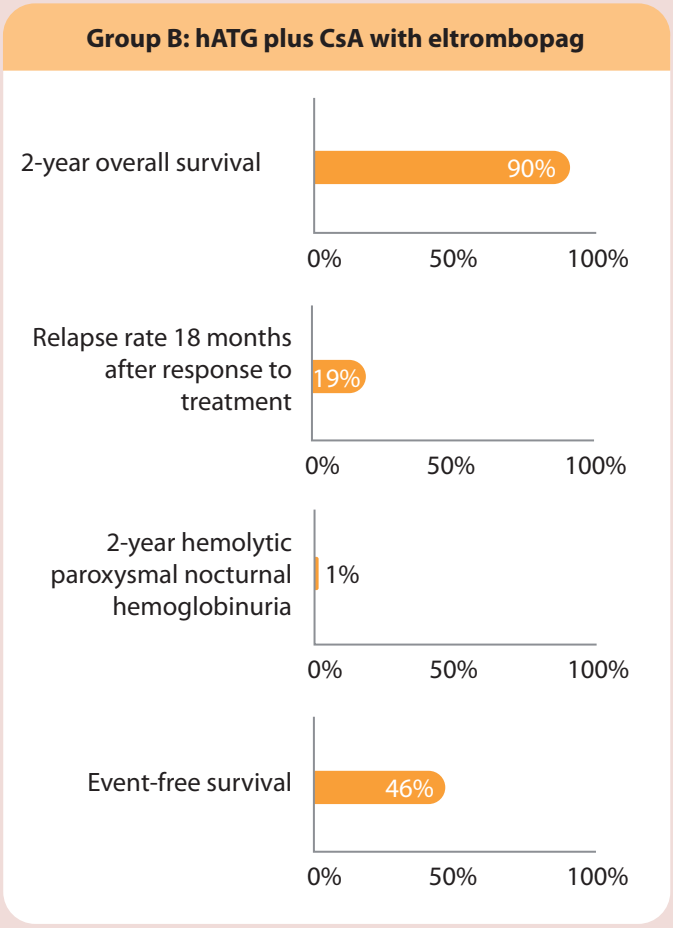
  - Overall response at both 3 and 6 months was higher in participants from Group B



  - Participants in Group B responded faster to treatment (half the participants achieved first response at 3 months) compared with participants in Group A (half the participants achieved first response at about 9 months)
  - Median (middle or halfway) time to achieve best response was longer in participants in Group A (9 months) compared with Group B (4 months)

- Factors that affect the response to treatment:
  - Disease severity (vSAA versus SAA) had an adverse impact on the complete response at 3 months and overall response at 6 months
  - Participants over the age of 40 years had a reduced response compared to those below the age of 40 years
- Side effects of treatment:
  - The frequency of side effects was mostly similar in both groups, and the most common side effects in both groups were stomach-related issues (Group A: 306 incidents of side effects; Group B: 273) and infections (Group A: 215; Group B: 177)
  - Infectious and liver-related complications were similar in both groups (Group A: 100 incidents of side effects; Group B: 96)
- Quality of life results reported by participants:
  - Participants reported feeling well in both groups after 6, 12, and 24 months
  - There were minimal differences in the participant-reported scores (overall health, physical, emotional, and social) between both groups
- Genetic abnormalities in the bone marrow or acquired changes to the cells:
  - Increased genetic changes were observed after 6 months from the start of treatment in both groups
  - These changes did not appear to affect the response to treatment and overall survival
- Long-term results of treatment:
  - The 2-year overall survival was similar in Group A and Group B
  - The relapse rate 18 months after response to treatment was lower in Group A
  - PNH was observed at 24 months in more participants in Group A
  - The event-free survival in Group B was higher





  - The risk of treatment failure among participants in Group B was reduced in the first 6 months
  - Older age and severity of aplastic anemia were risk factors for treatment failure

What do the results of this study mean?

- Standard immunosuppression treatment (hATG plus CsA) with eltrombopag (Group B) was more beneficial for participants with SAA and vSAA compared with standard immunosuppression treatment (Group A).
- The response in participants with SAA after the addition of eltrombopag to standard immunosuppression treatment was faster and of higher quality. Adding eltrombopag to standard immunosuppression treatment did not cause more side effects.
- Participants with less severe disease and those under 40 years of age showed a higher response to treatment.
- Participants in both groups reported similar overall health and physical, emotional, and social well-being related to their daily activities.
- This information on a new standard treatment for SAA and/or vSAA when persons do not have a suitable donor for bone marrow transplant is important for persons with SAA or vSAA and their family members and caregivers.
- These findings can help doctors consider adding eltrombopag to the standard immunosuppression treatment (hATG plus CsA) for persons who cannot undergo bone marrow transplant as initial treatment.

Where can readers find more information on this study?

- This plain language summary is based on the original article titled 'Eltrombopag Added to Immunosuppression in Severe Aplastic Anemia', which was published in *The New England Journal of Medicine*
- You can read the full article here: https://www.nejm.org/doi/full/10.1056/NEJMoa2109965
- The citation for the original article is: Peffault de Latour R, Kulasekararaj A, Iacobelli S *et al.*; Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation. Eltrombopag added to immunosuppression in severe aplastic anemia. *N. Engl. J. Med.* 386(1), 11–23 (2022)
- Clinical trial identifier: ClinicalTrials.gov number, NCT02099747; EudraCT number, 2014-000363-40

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Competing interests disclosure

R Peffault de Latour has received honoraria and been a consultant for Alexion Pharmaceuticals, Amgen Inc., Apellis Pharmaceuticals, Novartis, Pfizer, and Sobi Inc.; and received research funding and grants from Alexion Pharmaceuticals, Amgen Inc., Novartis and Pfizer. A Kulasekararaj has been on the advisory board and a consultant for Alexion Pharmaceuticals, Amgen Inc., BioCryst Pharmaceuticals, Celgene Corporation, F Hoffman-La Roche and Novartis; and received funding for travel from Alexion Pharmaceuticals and Novartis. M Griffin is on the advisory board of Alexion, Amgen, BioCryst Pharmaceuticals and Novartis; consultant for BioCryst Pharmaceuticals and Regeneron; and received lecture fees/honoraria from Alexion, Novartis and Sobi Inc. C Dufour has been a consultant for BioCryst Pharmaceuticals, Inc. and Novartis. AM Risitano received grants from Achillion, Alexion Pharmaceuticals, Alnylam Pharmaceuticals, BioCryst Pharmaceuticals, Novartis, Pfizer, RA Pharmaceuticals, Roche and Samsung; and is on the advisory board and received lecture fees from Apellis. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

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