

REVIEW

## COVID-19 infection in cancer patients: what has been the contribution of Associazione Italiana Oncologia Medica (AIOM) to oncological care since the beginning of the first pandemic wave?

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High mortality rates in elderly patients or in those with underlying chronic illnesses and/or a compromised immune system is a peculiar feature of COVID-19 infection. The possible coexistence of a cancer and COVID-19 infection in the same individual prompted concerns regarding their synergistic effect on prognosis. In order to balance patients' needs with the risks related to the infection, the question oncologists have asked from the beginning of the first wave of the pandemic has been: 'how can we deal with COVID-19 infection in cancer patients?' In pursuing its mission, the Associazione Italiana Oncologia Medica (AIOM) has made every possible effort to support cancer patients, health care professionals and institutions in the decision-making processes the pandemic has engendered within this scenario. The relevant documents as well as the educational and institutional initiatives the AIOM has taken are reported in this article.

**Key words:** COVID-19, AIOM, cancer, vaccination, treatment

### INTRODUCTION

On 11 March 2020, the World Health Organization (WHO) declared the outbreak of COVID-19 pneumonia cases, caused by the novel coronavirus SARS-CoV-2, a global pandemic.<sup>1</sup> Since the inception of the outbreak, frail patients were affected by high mortality rates, mostly elderly patients or those with underlying chronic illnesses and a compromised immune system.<sup>2</sup> The possible coexistence of cancer and COVID-19 infection in the same individual prompted concerns regarding their synergistic effect on prognosis. In order to balance patients' needs with the infection risks, the question oncologists have asked from the beginning of the first wave of the pandemic has been: 'how can we deal with COVID-19 infection in cancer patients?'<sup>3</sup> The international

oncology community began to propose health care strategies and recommendations with little evidence-based information to support clinical decision making.<sup>4-7</sup>

In Italy, according to the estimates of the Italian Association of Cancer Registries for 2019, about 1000 new cancers were diagnosed every day with an expected prevalence of cancer patients by 2020 equal to about 6% of the general population.<sup>8</sup>

In pursuing its mission,<sup>9</sup> the Associazione Italiana di Oncologia Medica (AIOM) with its various components (council, national board and regional chapters) has made every possible effort to support cancer patients, health care professionals and institutions in the decision-making processes despite the deep limitation due to the pandemic scenario. The relevant documents, as well as the educational and institutional initiatives AIOM has taken, are reported in this article.

### HOW HAS THE PANDEMIC CHANGED THE LIFE OF THE ASSOCIATION?

Under the restrictions to curb the spread of SARS-CoV-2 issued by Italy's National Health Authorities, all board

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meetings have been held in virtual mode since March 2020. AIOM's executive committee (consisting of the president, president-elect, secretary and treasurer) met remotely every evening during the first wave of the pandemic and, subsequently, twice a week. The objectives were to punctually assess the emergency, determine the initiatives to be proposed (related or not to the emergency) and manage decisions promptly.

### **AIOM national conference**

Several conference activities and training courses were canceled during the first wave of the pandemic. Most of the events were redesigned and held as webinars. The national congress was held from 30 October 2020 to 1 November 2020 with an average of 100 users per session (range: 16 to 241) and a total of 1001, 1089 and 782 participants on each of the 3 days, respectively. The online platform remained open to users for 6 weeks after the conference ended so that registered participants could continue to interact with the speakers over that period. Finally, compared with the 'standard' program of the previous years, a special session was dedicated to the management of cancer patients in the COVID-19 era.

### **AIOM CLOSE TO ONCOLOGISTS**

#### ***Risk of infection from coronavirus update of AIOM, Italian College of University Medical Oncologists and Italian College of Primary Hospital Medical Oncologists recommendations for oncology***

Aware of the lack of scientific evidence useful for daily oncological clinical practice, AIOM, the Italian College of University Medical Oncologists and the Italian College of Primary Hospital Medical Oncologists provided suggestions for the oncology community in a joint document on 13 March 2020, a few days after the WHO had declared a COVID-19 worldwide pandemic. The suggestions were the results of expert opinions and clinical common sense.<sup>10</sup> In November 2020, a more detailed document was drafted, adding specific indications to each activity related to the care of cancer patients<sup>11</sup> (Table 1).

#### ***Central venous catheter care***

Since the beginning of the pandemic, to reduce the number of hospital admissions, AIOM proposed modifying central venous catheter care. In compliance with several guidelines, many oncology institutions follow protocols with a 4-week maintenance flushing interval.<sup>12,13</sup> However, a phase II study showed that extending this interval to 3 months was not associated with higher complication rates than those reported in the relevant literature.<sup>14</sup> A similar conclusion was provided by two retrospective observational studies that considered intervals of 8 and 12 weeks, respectively.<sup>15,16</sup> In the light of these findings, AIOM recommended deferring port flushing to 8-12 weeks during the coronavirus pandemic emergency period,<sup>17</sup> pending randomized phase III studies.

### **Anti-influenza vaccination**

AIOM updated its recommendations for influenza vaccination<sup>18</sup> considering also the COVID-19 pandemic. Immunization, also against pneumococcal infections, is strongly recommended for patients undergoing active cancer treatment with chemotherapy or biological therapies including immunotherapy (in the light of the INVIDia study findings)<sup>19</sup> and for their families and caregivers.<sup>20</sup>

### **Clinical studies regarding COVID-19 in cancer patients**

AIOM supported the following studies related to the COVID-19 emergency in oncology:<sup>21</sup>

- OPICO trial: multicenter observational trial on cancer patients on immunotherapy during the COVID-19 outbreak; its primary objective is to evaluate the incidence of SARS-CoV-2 infection in cancer patients treated with immune checkpoint inhibitors (anti-cytotoxic T-lymphocyte-associated protein 4 and/or anti-programmed cell death protein 1/programmed death-ligand 1).
- INTENSIVE: InterNaTional rEgistry oN Sars-cov-2 posItive nEuroendocrine neoplasm patients; a retrospective/prospective international observational multicenter study of patients with neuroendocrine neoplasm and SARS-CoV-2 infection.
- Perceptions and opinions of cancer patients during the coronavirus epidemic in the most affected areas in Italy: a serial cross-sectional study; its aims are to explore the perceptions and opinions of cancer patients attending health care facilities for medical oncology treatment during the coronavirus epidemic in the most affected areas of the country.
- AIOM-L CORONA study: a multicenter cohort study; designed by AIOM Lombardia to assess the epidemiology and clinical course of COVID-19 infection in cancer patients.
- CO.I.ROS: clinical course of patients with castration-resistant prostate cancer infected with COVID 19.
- Clinical Psychology Service, working in collaboration with the Medical Oncology unit, to determine the psychological impact of the COVID-19 health emergency currently on Italian oncologists.
- TERAVOLT: Thoracic cancers international coVid 19 cOLlaboraTion (<http://teravolt-consortium.org/>).
- Hormone therapy and COVID-19 infection in cancer patients.

### ***ConFederazione degli Oncologi, Cardiologi e Ematologi: technical round table for oncology, onco-hematology and cardiology patients***

On 18 June 2020, following a proposal by Fondazione Insieme Contro il Cancro, a confederation of three scientific societies (AIOM, Società Italiana di Ematologia, and Società Italiana di Cardiologia) and two foundations (Insieme contro il Cancro and Cuore e Circolazione) called ConFederazione degli Oncologi, Cardiologi e Ematologi (FOCE) was

**Table 1. Risk of coronavirus infection—updated AIOM, COMU and CIPOMO recommendations for medical oncology (November 2020)**

Activity	Recommendation
Separating teams working in ‘COVID-19 hospital units’ from those working in ‘non-COVID-19 hospital units’	In compliance with international recommendations, in order to guarantee the most suitable continuity of care and the greatest possible containment of COVID-19 transmission among patients, visitors and health care staff, it is appropriate to separate teams of health care workers (i.e. doctors, nurses) on duty in COVID-19 hospital units from those on duty in non-COVID-19 hospital units and avoid calling staff on duty in oncology facilities to cover shifts in COVID-19 hospital units.
Divisional outpatient clinics	It is suitable to continue to ensure divisional outpatient follow-up activities and resort to remote (online) modalities upon recommendation of the referring doctor when it is considered clinically appropriate and feasible. In this case, a standardized method will be used to record and report the health care services delivered or examinations carried out.
Access to day hospital, day service and/or ordinary inpatient areas	Before entering the Day Hospital, Day Service and ordinary inpatient areas of oncology units, it is advisable for patients to undergo nurse triage, including body temperature measurement, and complete a questionnaire regarding symptoms/signs of infection and other risk or risk-behavior items, in compliance with the current national, regional and local hospital procedures. Should a person present with fever and/or influenza-like symptoms (cough, sore throat, difficulty breathing), that person must not enter the Day Hospital and ordinary hospital areas without first being assessed by medical and/or nursing staff. Should oncology patients have such symptoms while at home, it is recommended that they inform the health care personnel by phone before getting to the oncology facility.
Access for caregivers	In order to avoid overcrowding in waiting rooms, holding areas, lounges, dressing or recovery rooms, etc. and rooms where chemotherapy and inpatient treatment are delivered, and in order to ensure the minimum recommended distance between people (at least 2 m), it is advisable not to allow access to caregivers to inpatient and Day Hospital areas. With the authorization of the Chief or the referring doctor, access by a single caregiver may be allowed for special clinical situations.
Use of personal protective equipment (PPE)	Given the extreme vulnerability of cancer patients and the need to protect them and their caregivers, the precautionary use of PPE (surgical masks) for cancer patients and their caregivers is appropriate. Additional PPE (rather than surgical masks) is appropriate for health care personnel. In particular, FFP2 masks plus eye protection are recommended when dealing with a patient who cannot wear a mask because he/she cannot tolerate it or because so required for the visit/treatment or procedure to be carried out. FFP3 masks plus eye protection should be worn when procedures that may generate aerosols are carried out. Additional PPE (e.g. latex gloves), proper hand hygiene and environmental hygiene measures (cleaning/disinfection/ventilation) are recommended based on specific indications and in compliance with the hospital’s protocols.
Pharmaceutical sales representatives and clinical trial monitoring	As a further preventive measure, in order to limit potential sources of contagion as far as possible, avoid face-to-face meetings and only meet online. In cases that cannot be postponed (meetings to start experimental protocols that provide a therapeutic opportunity for patients), meetings shall be held out outside the Day Hospital and/or inpatient area and participants shall wear appropriate PPE, in compliance with the hospital’s protocols and previous indications.
Swabs testing for staff	In order to protect patients and health care workers, a standardized protocol should be adopted nationwide whereby all the staff of oncology facilities periodically take swab tests (at least monthly or, if possible, fortnightly, unless otherwise specified). Such monitoring programs can be carried out in the facilities with rapid antigen tests rather than creating an excessive workload for laboratories. Swab testing is also of pivotal importance for contact tracing.
Staff on duty in oncology facilities	The rapid evolution of the current pandemic is creating more difficulties in cancer patient management. Cancer patients are among the most vulnerable categories and need to continue life-saving therapies in compliance with strict safety procedures, including telephone triage before getting to the hospital and nurse triage before entering Day Hospital and inpatient areas. In addition, the staff on duty will need to repeatedly interview patients and family members who are not allowed to be in the inpatient areas for patient safety. The extra workload calls for specially dedicated staff and hopefully a greater number of nursing staff to be employed in the facilities.
Seasonal influenza vaccination	As recommended by the AIOM, efforts are being made to increase influenza vaccination among patients, caregivers and medical staff.
COVID-19-positive cancer patients	Considering the current lack of studies, it is impossible to make recommendations for the initiation or continuation of cancer therapy in asymptomatic coronavirus-positive cancer patients. In most cases, a 2-week delay in starting treatment or repeating a cycle does not worsen the prognosis. The possibility of starting/continuing treatment shall be considered only in selected cases (patients with negative coronavirus test results at a given time from symptom onset), after a thorough interview with the patient and a multidisciplinary discussion.

Given the highly contagious nature of COVID-19, its lethality for frail patients and primarily cancer patients, and considering the special vulnerability of cancer patients who are often immunocompromised, affected by multiple diseases, elderly and undergoing life-saving therapies that can further lead to immunodepression, AIOM, COMU and CIPOMO have held in-depth discussions with the Italian Colleges of university and hospital oncology specialists. The meetings flagged up the need to better safeguard patients and workers in oncology facilities to reduce the possibility of COVID-19 transmission among patients, visitors and health care workers. AIOM, COMU and CIPOMO have thus proposed the following recommendations: Clinical records shall state that examinations and clinical procedures have been carried out with the due precautions and health care personnel and the patients have worn PPE, as per the current requirements.

AIOM, COMU and CIPOMO also suggest that the above recommendations be reviewed periodically in the light of changing contingent circumstances. AIOM, Associazione Italiana di Oncologia Medica; CIPOMO, Collegio Italiano Primari Oncologi Medici Ospedalieri; COMU, Collegio Oncologi Medici Universitari.

founded.<sup>22</sup> The confederation is the first technical round table in the world that brings together experts from the fields of oncology, cardiology and hematology. In Italy these three medical areas account for major diseases affecting >11 million Italians. The Confederation has focused on the critical issues encountered by patients with cancer, heart or

blood disorders/diseases during the COVID-19 public health emergency.

After the members of the relevant scientific associations met with the president of Italy’s Higher Health Council (Consiglio Superiore di Sanità) the Technical Round Table has worked on standardizing care pathways by

identifying guidelines and protocols. In its final report, the section regarding cancer patient management highlighted the greater risks and vulnerability of patients with tumors and heart diseases given that the COVID-19 epidemic had undermined their treatment opportunities. Treatments had been suspended, surgeries and visits canceled while other serious inconveniences require immediate attention. The issues experienced are well illustrated in the introduction to the chapter on cancer patients. The report points out that it is essential to promptly draw up guidelines and treatment protocols for these categories of patients and to streamline procedure standardization throughout the country to avoid regional disparities.

### **Anti-COVID-19 vaccination for cancer patients**

A recent review of 28 clinical trials reporting the mortality rates of cancer patients with COVID-19 showed that subjects with active oncological diseases should be considered for priority access to anti-COVID-19 vaccination.<sup>23</sup> This is mainly true for onco-hematology patients but seems to be just as valid for patients previously diagnosed with cancer but currently free of disease or long-term survivors.<sup>24</sup> Considering the requests of FOCE, AIOM has forcefully recommended that the country's authorities include oncology and onco-hematology patients in the high priority groups, together with health care workers and elderly people in nursing homes, to protect them from high mortality infection.<sup>25</sup> It is not clear whether this recommendation should apply to cancer survivors as they may be considered at the same risk as other people of similar age and with other risk factors (Table 2). Similarly, international oncology societies released recommendations concerning this topic.<sup>26,27</sup>

### **Extending continuity of care outside hospitals and activating regional oncology networks**

The adoption of preventive measures in almost all countries to curb the spread of Sars-CoV2 has re-proposed the long-debated question of whether or not general practitioners should take part in the management of cancer patients. AIOM has addressed this issue on several occasions and has considered the results presented at the European Society for Medical Oncology Virtual Congress 2020 regarding the Cancer Fast-track Programme.<sup>28</sup> In particular, during the critical phase of the COVID-19 emergency, efforts were made to transfer mainly oral therapy management to community-based services. However, it soon became clear that long-term survivors could especially benefit from out-of-hospital management of their follow-up. AIOM has therefore proposed to roll out oncology expertise in the community setting, also by training community doctors specialized in oncology. A joint document of AIOM and Federazione delle Associazioni di Volontariato in Oncologia, Associazione Italiana Radioterapia e Oncologia clinica, Società Italiana di Chirurgia Oncologica, Società Italiana di

Psico-Oncologia and Federazione Nazionale Ordini Professioni Infermieristiche presented during the 15th Cancer Patients Day stated that: 'the pandemic should be an opportunity to strengthen and innovate community health-care organizational models to ensure better management of cancer patients, including those receiving palliative care, by integrating and simplifying care pathways as well as ensuring proximity and continuity of care'.<sup>29</sup>

AIOM has often declared that health care pathways need to be completed to achieve all benefits so that regional oncology networks can immediately start operating throughout the country. With the networks, patients would have access to treatments based on shared medical recommendations and migration of patients for health care purposes would be limited.

In this scenario, 'telemedicine' represented an effective and satisfactory alternative for the care of cancer patients during the first phase of the pandemic. In the USA, oncological and hematological patients were visited via web through the Houston Methodist MyChart platform, registering an 83.8% adherence (dropouts were mainly among elderly patients and lower-income residents), most of whom (92.6%) said they were satisfied with the system.<sup>30</sup> AIOM has supported this option, highlighting its valuable potential also in the post-COVID-19 'new normal' setting, especially during follow-up or for patients receiving oral therapies.<sup>31</sup> Clearly, there is no claim that telephone and telematic contacts can aptly replace face-to-face visits, but they do allow intermediate checks and a timely discussion of laboratory tests and other examinations, as well as any signs and symptoms related to the disease or its treatments. AIOM has stressed that the formal and legal recognition of telemedicine as well as ensuring reimbursement of any related services are essential.

## **AIOM CLOSE TO PATIENTS AND HEALTH INSTITUTIONS**

### **AIOM news: special number on COVID-19**

Starting 14 May 2020, AIOM has published a weekly newsletter to offer citizens, patients, journalists and government officials some direction amidst the COVID-19 situation.<sup>32</sup> The newsletter gathers contributions from patients' associations, in-depth analyses of pertinent clinical studies, interviews with government officials and news regarding local initiatives. A total of 32 issues have been published up to now, with a reach of >60 000 persons.

AIOM has also organized numerous webinars with several patient organizations for the same outreach purposes.

### **COVID-19 and fake news**

In view of the significant and sometimes contradictory amount of information that has appeared to be potentially capable of hiding many pitfalls for patients and their families and caregivers, the AIOM Foundation has created a dedicated area on its website in which it invites the utmost caution in verifying the reliability of information.<sup>33</sup>

Must Covid-19 vaccination be offered to patients with a cancer diagnosis?	Currently, it is mandatory to offer cancer patients SARS-CoV-2 vaccination provided there are no contraindications (similar to those for the general population: reported or known allergies to specific vaccine components or other contraindications). However, the current International Recommendations <sup>a</sup> do not refer to the oncological population but to immunocompromised patients, stating: 'Immunocompromised patients may still receive SARS-CoV-2 vaccination if there are no contraindications to vaccination. However, they should be informed about the current lack of data regarding the safety profile of the vaccine and its efficacy in immune-compromised populations, as well as the potential for reduced immune responses and the need to continue to follow all current guidelines to protect themselves against COVID-19'. <sup>b</sup> On the other hand, even if cancer patients were not included in the studies demonstrating the efficacy of the vaccine, the possible benefits of protection against COVID-19 appear to reasonably outweigh the risks, the latter being associated with possible reduced efficacy rather than a reduced safety profile. Vaccination does not counteract a previous infection with COVID-19, but rather enhances its immunological memory, so testing before vaccination is not useful.
Should people undergoing active cancer treatment be offered vaccination against COVID-19?	Patients under active treatment of cancer disease must be offered SARS-CoV-2 vaccination if there are no contraindications. Whenever possible, vaccines should be administered before starting cancer therapy. In patients who have already started chemotherapy, existing data do not indicate a specific timing for vaccine administration. <sup>c</sup> Experience with the administration of influenza and pneumococcal vaccines in patients undergoing active oncological treatment, such as chemotherapy, has shown that there is no need for specific timing.
Should long-term survivors in cancer follow-up be offered vaccination?	The answer is yes when there are no contraindications.
Are there patients that must not be vaccinated against COVID-19?	Based on current data, it is preferable not to administer the vaccine only to patients presenting contraindications because of a specific component of the proposed vaccine (similar to the general population).
Are there data available regarding the interactions between the vaccines and cancer treatments?	Although there are no known safety issues, the fact that no cancer patients were included in trials demonstrating the efficacy and safety of vaccines means that no specific data can be produced regarding the interaction of vaccines with antineoplastic therapies or the preference of a specific vaccine technology for cancer patients. Furthermore, availability of the vaccine will make it possible to collect data regarding the efficacy and toxicity through trials, post-trials and monitoring procedures in specific registries.
Conclusions and final recommendations	The data collected so far in the cancer population currently undergoing active treatment point to an increased mortality risk after COVID-19 infection. Therefore, it is recommended that cancer patients undergoing active treatment be considered for priority access to Sars-Cov-2 vaccination. It is unclear whether priority should be extended to patients with a previously diagnosed cancer and not currently undergoing active treatment, since long-term survivors may have the same risk factors as other persons in their same age brackets and with other risk factors.

(i) If a patient has had a severe allergic reaction to any of the excipients of a SARS-CoV-2 vaccine, it is recommended not to administer that specific vaccine.

(ii) If a patient has had a severe allergic reaction to other vaccines or injectable therapies, that reaction needs to be flagged up and discussed with a physician competent in allergy and immunology.

(iii) The Centers for Disease Control and Prevention recommends that people with a history of severe allergic reactions not related to vaccines or injectable drugs, such as allergies to food, pets, poison, the environment or latex, should still be vaccinated.

(iv) People with a history of allergies to oral drugs or a family history of severe allergic reactions, or those who may have a milder allergy to vaccines (no anaphylaxis), may still be vaccinated.

(v) If a patient has a severe allergic reaction after receiving the first dose of the vaccine, he/she should not be given the second dose.

Given the scarcity of data regarding interactions between cancer treatments and SARS-CoV-2 vaccination, AIOM encourages healthcare professionals, industry sponsors, regulatory bodies and academics to rapidly collect and report new data regarding vaccination-related aspects in actively treated cancer patients. Chemotherapy and especially immunotherapy could have a positive or negative impact on the efficacy and safety of SARS-CoV-2 vaccination.

Ongoing data collection and research will help fill these gaps to further define optimal protocols for SARS-CoV-2 vaccination in cancer patients undergoing immunotherapy or chemo-immunotherapy. Critical aspects that need to be further explored include among others:

- The optimal sequencing of SARS-CoV-2 vaccination and chemo- and immunotherapy treatment to preserve efficacy and safety in both situations.
- Determination of the effective dosage of SARS-CoV-2 vaccine for patients undergoing treatment.
- Monitoring of SARS-CoV-2 antibody and cellular immune response in patients receiving immunotherapy after SARS-CoV-2 vaccination.
- Impact and reporting of SARS-CoV-2 vaccination on immune-related adverse events and regulatory considerations for adverse event attribution in immunotherapy clinical trials.

<sup>a</sup> <https://www.cdc.gov/coronavirus/2019-ncov/index.html>, last read on 25 December 2020.

<sup>b</sup> <https://www.asco.org/asco-coronavirus-resources/covid-19-patient-care-information/covid-19-vaccine-patients-cancer>, last read on 25 December 2020.

<sup>c</sup> <https://www.esmo.org/covid-19-and-cancer/covid-19-vaccination?hit=some>, last read on 25 December 2020.

## CONCLUSIONS

The storm triggered by the COVID-19 pandemic has forced each of us into unfamiliar, life-threatening situations as health systems have been overwhelmed even in the most advanced countries. From the very start, AIOM has been aware of its role in promoting all the necessary initiatives. The added value of these initiatives is that AIOM has involved and has provided support to health professionals, patients and institutions during a public health crisis that has impacted the activity of medical oncologists and other specialties, primarily surgery.<sup>34,35</sup> The actions carried out by AIOM in this scenario have also been made available to other European scientific oncology societies that have

requested to share AIOM's documents in their own countries. We still have a long road ahead of us, as both individuals and institutions, in tackling the changes and developments of a pandemic, the end of which may be in sight as safe and effective vaccines are rolled out.

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## DISCLOSURE

NS has served as a consultant for Celgene and Isheo; MDM has served as a consultant for AstraZeneca, Takeda, Pfizer, Novartis, Roche, Janssen, Astellas, Eisai; UDG has served as a consultant for Janssen, Astellas Pharma, Sanofi, Bayer, Pfizer, Bristol-Myers Squibb (BMS), Novartis, Ipsen, and Merck Sharp & Dohme (MSD); MT has served as a consultant for Janssen, Astellas Pharma, Sanofi, Bayer, Pfizer, Novartis; DG has served as a consultant for Pfizer, Ipsen, Novartis, Merck; RC has served as a consultant for Novartis, Pfizer, Roche, Takeda, AstraZeneca, BMS, MSD; NLV has served as a consultant for Novartis, Pfizer, Roche, Gentili, Celgene, Eisai, MSD; LDM has served as a consultant for Roche, Novartis, Eli Lilly, Pfizer, MSD, Ipsen, Takeda, Celgene, Eisai, Genomic Health, General Electric, Amgen, Pierre Fabre, Daiichi Sankyo, AstraZeneca; FP has served as consultant for Roche, Bayer, AstraZeneca, Pierre Fabre, Janssen Cilag, Ipsen; SC has served as consultant for Eli Lilly; GB has served as consultant for Roche, Servier, Celgene, Ipsen, Sanofi, Merck Serono. AR has declared no conflicts of interest.

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