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## **Assessing the impact of COVID-19 outbreak on the attitudes and practice of Italian oncologists towards breast cancer care and related research activities**

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## **KEY POINTS**

### **Question**

Does COVID-19 outbreak impact attitudes and practice of Italian oncologists towards breast cancer care and related research activities?

### **Findings**

This survey showed a radical change in attitudes and practice of the 165 respondents towards breast cancer care and related research activities during COVID-19 outbreak. Although many were reasonable responses to the current health care emergency without expected negative impact on patients' outcomes, potential alarming signals of undertreatment were observed.

### **Meaning**

Medical oncologists face many challenges in providing cancer care during COVID-19 outbreak. These data voice for developing cautious recommendations to help them ensuring continuous effective and safe cancer care.

## **ABSTRACT**

**IMPORTANCE** Coronavirus disease 2019 (COVID-19) outbreak is progressively changing the approach of medical oncologists to cancer management. However, the real impact of COVID-19 outbreak on cancer care and its potential negative consequences are currently unknown.

**OBJECTIVE** To investigate the impact of COVID-19 outbreak on oncologists' attitudes and practice towards breast cancer care and related research activities.

**DESIGN** A 29-question anonymous online survey.

**SETTING** The survey was sent by email to the members of the Italian Society of Medical Oncology (AIOM) and the Italian Breast Cancer Study Group (GIM) on April 3, 2020. One week was given for its completion.

**PARTICIPANTS** Only Italian medical oncologists (both those in training and specialists) were invited to complete the survey.

**MAIN OUTCOMES AND MEASURES** Oncologists' attitudes and practice before and during COVID-19 outbreak on three different relevant areas in breast cancer care: 1) (neo)adjuvant setting; 2) metastatic setting; 3) research activities.

**RESULTS** The survey was completed by 165 oncologists, of whom 121 (73.3%) worked in dedicated Breast Units.

In the (neo)adjuvant setting, as compared to before the emergency, a lower number of oncologists adopted during COVID-19 outbreak weekly paclitaxel (68.5% vs. 93.9%,  $p<0.001$ ) and the dose-dense schedule for anthracycline-based chemotherapy (43% vs. 58.8%,  $p<0.001$ ).

In the metastatic setting, as compared to before the emergency, a lower number of oncologists adopted during COVID-19 outbreak first-line weekly paclitaxel for HER2-positive disease (41.8% vs. 53.9%,  $p=0.002$ ) or CDK4/6 inhibitors for hormone receptor-positive tumors with less aggressive characteristics (55.8% vs. 80.0%,  $p<0.001$ ). A significant change was also observed in terms of delaying the timing for monitoring therapy with CDK4/6 inhibitors, assessing treatment response with imaging tests and flushing central venous devices.

During COVID-19 outbreak, clinical research and scientific activities were reduced in 73.9% and 73.3% of respondents, respectively.

**CONCLUSIONS AND RELEVANCE** Medical oncologists face many challenges in providing cancer care during COVID-19 outbreak. Although most of the changes in their attitudes and practice were reasonable responses to the current health care emergency without expected negative impact on patients' outcomes, potential alarming signals of undertreatment were observed. These data voice for developing cautious recommendations to help them ensuring continuous effective and safe cancer care.

**STUDY REGISTRATION** Not applicable.

## **MANUSCRIPT**

### **INTRODUCTION**

Since the end of 2019, a progressive escalation of cases infected by a novel coronavirus (named severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] or 2019 novel coronavirus [2019-nCoV]) have been reported, initially in China and then worldwide.<sup>1</sup> The rapid outbreak of the related syndrome (named coronavirus disease 2019 [COVID-19]) has led the World Health Organization (WHO) to declare it as a pandemic on March 11, 2020.<sup>2</sup> Italy has been the first European country facing this health care emergency and remains the second most affected country after the US as of April 15, 2020.<sup>3</sup> The northern part of the country and particularly the Lombardy region are the most affected areas.<sup>4</sup>

Elderly people and patients with underlying comorbidities are those with the highest risk of developing complications and the most severe consequences of COVID-19.<sup>5,6</sup> The current health care emergency is of particular concern in medical oncology considering the increased risk of infections and of their negative consequences in cancer patients, particularly in those receiving active treatments.<sup>7</sup> Preliminary series have shown that cancer patients may have higher chances of infection by SARS-CoV-2 as well as an increased risk of developing severe events related to COVID-19 as compared to the general population.<sup>8-10</sup> Several measures and recommendations to prevent and to reduce the risks of exposure to SARS-CoV-2 of cancer patients have been proposed and implemented worldwide.<sup>11-13</sup> For patient receiving active treatments, the Italian Association of Medical Oncology (AIOM) has invited oncologists to consider on a case-by-case basis the possibility of postponing treatment administration.<sup>12</sup> Their practical suggestions have been further developed by a panel of Italian oncologists suggesting treatment prioritization in specific settings including (neo)adjuvant and first-line treatments while delaying non-urgent therapies as well as imaging procedures to monitor treatment response.<sup>13</sup> However, notably, all these recommendations are not evidence-based.

Although medical oncologists worldwide are focused and committed to continue providing compassionate and safe care to patients, the current health care emergency is progressively changing the way medical oncologists approach cancer management. However, the real impact of the COVID-19 outbreak on cancer care and its potential negative consequences are currently unknown. To provide evidence on this regard, we conducted a survey among Italian medical oncologists exploring whether and how the COVID-19 outbreak has changed their attitudes and practice towards breast cancer care and related research activities. The decision to focus on a single disease was based on the need to have precise insights on specific issues that may be differently or not applicable to other malignancies.

## **MATERIAL AND METHODS**

A specific anonymous questionnaire (available as supplementary material) was developed to investigate the impact of COVID-19 outbreak on the attitudes and practice of Italian oncologists towards breast cancer care and related research activities.

The survey was sent by email to the members of AIOM and the Italian Breast Cancer Study Group (GIM) on April 3, 2020. One week was given to the oncologists for completing the survey. Only medical oncologists (both those in training and specialists) were invited to complete the questionnaire. To validate and send the survey, all the questions had to be answered.

### **Characteristics of survey**

The survey was composed of 29 questions that were divided into four different sections: a) demographic, medical training and employment information (Q1-8); b) attitudes and practice towards breast cancer care in the (neo)adjuvant setting before and during COVID-19 outbreak (Q 9-16); c) attitudes and practice towards breast cancer care in the metastatic setting before and during



COVID-19 outbreak (Q 17-27); attitudes and practice towards the scientific and research activity during COVID-19 outbreak (Q 28-29).

This survey was conceived by a team of medical oncologists who are specifically dedicated to the breast cancer care and deeply involved in research activities in this field. The survey was structured with multiple choice answers.

### **Study objectives**

The objectives of the current survey were to investigate the impact of the COVID-19 outbreak on the attitudes and practice of oncologists before and during COVID-19 outbreak on three different relevant areas in breast cancer care: 1) (neo)adjuvant setting; 2) metastatic setting; 3) research activities.

Most of the questions were repeated twice to investigate the attitudes and practice about the same issue before versus during COVID-19 outbreak. A minority of questions explored specific issues only during the current health care emergency.

### **Statistical analysis.**

Due to the exploratory nature of the survey, no sample size calculation was performed. However, approximately 150 respondents were auspicated in order to obtain sufficient precision in the estimate of the attitudes and practice of oncologists on the explored issues. Estimating a population of about 2,000 oncologists receiving the invitation to complete the survey, in the case of a 2-category grouping of answers, a number of 150 respondents would allow a margin of error in the estimate of the proportion of approximately  $\pm 7.70\%$  with a 95% confidence level.

Analyses were mostly descriptive. In order to explore differences in paired proportions of categorical variables on the answers obtained for each specific topic before and during COVID-19 outbreak, a McNemar test was applied. Descriptive analyses were conducted to investigate potential differences in the answers obtained by oncologists practicing in Lombardy (the region suffering the most for COVID-19 outbreak) as compared to those working in the other parts of Italy.

All tests were two-sided, and  $p$  values  $<0.05$  were considered statistically significant. Statistical analyses were done with SPSS for Windows, Version 25.0.

## **RESULTS**

The survey was circulated to 1,909 and 210 oncologists through the AIOM and GIM mailing lists, respectively. A total of 165 oncologists implicated in breast cancer care completed the survey. Demographic, medical training and employment information of respondents is reported in Table 1. Median age was 52 years (interquartile range [IQR, 38.0-59.5]); most of the respondents were female ( $n=88$ , 53.3%), and worked in the north of Italy (65 [39.4%] outside and 21 [12.7%] in the Lombardy region). Among respondents, 138 worked in public hospitals (83.6%) and 121 (73.3%) in dedicated Breast Unit. Median years of clinical practice in Medical Oncology (including fellowship) were 23 years (IQR, 11.5-30.0).

### **(Neo)adjuvant setting**

Supplementary Table 1 reports all the responses of oncologists towards the explored issues in the (neo)adjuvant setting.

Oncologists' preference towards the neoadjuvant versus adjuvant approach in patients with clinical tumor size  $\geq 2$  cm and/or lymph nodal involvement was assessed in the case of triple-negative or HER2-positive disease. For triple-negative breast cancer, no significant changes during the current health care emergency ( $p=0.344$ ) were observed with the majority of respondents favoring the

neoadjuvant approach over upfront surgery followed by adjuvant treatment both before (n=159, 96.4%) and during (n=155, 93.9%) COVID-19 outbreak. Similarly, no significant changes were observed for HER2-positive breast cancer ( $p=0.289$ ), with most of respondents favoring neoadjuvant treatment both before (n=157, 95.2%) and during (n=153, 92.7%) COVID-19 outbreak.

The attitudes of oncologists towards the preferred type and schedule of taxane changed significantly during COVID-19 outbreak ( $p<0.001$ ; Figure 1A). Despite remaining the preferred regimen in the (neo)adjuvant setting, a lower number of oncologists adopted weekly paclitaxel during COVID-19 outbreak (n=113, 68.5%) as compared to before the emergency (n=155; 93.9%).

In terms of optimal schedule for administering anthracycline-based chemotherapy (dose-dense vs. standard-interval) in early breast cancer patients with aggressive features (e.g. node-positive and/or triple-negative disease), a significant change was observed during COVID-19 outbreak ( $p<0.001$ ; Figure 1B). A lower number of oncologists adopted the dose-dense schedule during COVID-19 outbreak (n=71, 43%) as compared to before the emergency (n=97, 58.8%).

No major differences in the attitudes of oncologists towards the explored issues in the (neo)adjuvant setting was observed according to region of practice (Supplementary Table 2).

### **Metastatic setting**

Supplementary Table 3 reports all the responses of oncologists towards the explored issues in the metastatic setting.

The COVID-19 outbreak significantly impacted the choice of the taxane used as first-line treatment with dual anti-HER2 blockade for patients with HER2-positive metastatic breast cancer ( $p=0.002$ ;

Figure 2A). A lower number of oncologists adopted weekly paclitaxel during COVID-19 outbreak (n=69, 41.8%) as compared to before the emergency (n=89, 53.9%) .

Oncologists' attitudes towards use of CDK4/6 inhibitors as first-line therapy for patients with hormone receptor-positive HER2-negative metastatic breast cancer and less aggressive characteristics (e.g, elderly and/or with only bone metastasis) changed significantly during COVID-19 outbreak ( $p<0.001$ ; Figure 2B). A lower number of oncologists added CDK4/6 inhibitors to endocrine therapy during COVID-19 outbreak (n=92, 55.8%) as compared to before the emergency (n=132, 80.0%). Similarly, in terms of monitoring blood tests during treatment with CDK4/6 inhibitors, a significant change in oncologists' attitudes was observed ( $p<0.001$ ; Figure 2C). A lower number of oncologists responded to monitor blood tests every two weeks for the first two cycles of treatment and monthly thereafter (as recommended by the drug technical sheet) during COVID-19 outbreak (n=116, 70.3%) as compared to before the emergency (n=146, 88.5%).

In terms of route of chemotherapy administration in patients with metastatic disease during COVID-19 outbreak (Figure 2D), oral treatments (n=139, 84.2%) were considered the preferred choice as compared to intravenous agents (n=26, 15.8%).

The attitudes of oncologists towards the timing for assessing treatment response with imaging tests in patients with metastatic breast cancer changed significantly during COVID-19 outbreak. In the case of triple-negative breast cancer ( $p<0.001$ ; Figure 3A), a higher number of respondents delayed imaging tests to every 4-6 months or more during COVID-19 outbreak (n=108, 65.5%) as compared to before the emergency (n=52, 31.5%). Similarly, for HER2-positive breast cancer ( $p<0.001$ ; Figure 3B), a higher number of respondents delayed imaging tests to every 4-6 months or more during COVID-19 outbreak (n=138, 83.6%) as compared to before the emergency (n=99, 60%). For hormone receptor-positive breast cancer ( $p<0.001$ ; Figure 3C), a higher number of respondents delayed imaging tests to every 6 months or more during COVID-19 outbreak (n=78, 47.3%) as compared to before the emergency (n=44, 26.7%).

The COVID-19 outbreak significantly impacted oncologists' attitudes towards the timing for flushing central venous devices ( $p<0.001$ ; Figure 3D). A higher number of respondents delayed the flushing intervals to every 2-3 months during COVID-19 outbreak (n=119, 72.1%) as compared to before the emergency (n=47, 28.5%).

No major differences in the attitudes of oncologists towards the explored issues in the metastatic setting was observed according region of practice, except for the preference of docetaxel as the taxane to be used as first-line treatment with dual anti-HER2 blockade during COVID-19 outbreak that was the highest for oncologists working in the Lombardy region (Supplementary Table 4).

### **Research setting**

Two questions explored the potential impact of COVID-19 outbreak on oncologists' attitudes towards clinical research and scientific activities (Supplementary Table 5).

A total of 122 respondents (73.9%) declared to have reduced their clinical research activities during COVID-19 outbreak in terms of participation and enrollment of patients in clinical trials, opening new clinical trials or recording information in study case report forms. Only 30 oncologists (18.2%) declared no changes in their clinical research activities (Figure 4A).

Similarly, 121 respondents (73.3%) declared to have reduced their scientific activities during COVID-19 outbreak in terms of writing research protocols, projects or papers and of applying for grants. Only 30 oncologists (18.2%) declared no changes in their scientific activities (Figure 4B).

No major differences in the attitudes of oncologists towards clinical research and scientific activities was observed according region of practice (Supplementary Table 6).

## **DISCUSSION**

To our knowledge, this is the first survey providing evidence on the impact of COVID-19 outbreak on breast cancer care and related research activities. We observed a radical change in the attitudes and practice of Italian medical oncologists towards the clinical management of breast cancer patients in both the (neo)adjuvant and metastatic settings. Although most of the changes in their attitudes and practice were reasonable responses to the current health care emergency without expected negative impact on patients' outcomes, potential alarming signals of undertreatment were observed. A significant reduction in all types of research activities was also observed.

In Italy and all the countries facing the most dramatic consequences of COVID-19 outbreak, optimizing cancer care has become a crucial and challenging issue. Up to now, the availability of general recommendations to reduce all non-urgent activities but without proper evidence-based indications makes the management of cancer patients difficult and uncertain.<sup>11-13</sup> Therefore, despite the strong recommendation to ensure continuity of care, a potential risk that a change in oncologists' attitudes and practice may negatively impact on patients' outcomes cannot be excluded. This survey was designed to specifically explore these possible issues.

In the early breast cancer setting, neoadjuvant treatment is the preferred approach for the majority of patients with triple-negative and HER2-positive disease, also considering the possibility to adapt the adjuvant approach based on the pathological results at the time of surgery.<sup>14</sup> As recommended by current guidelines,<sup>15</sup> almost all responding oncologists favored the neoadjuvant approach in these patients with no changes observed during COVID-19 outbreak.

On the contrary, the current health care emergency significantly modified oncologists' attitudes and practice towards the type and scheduling of chemotherapy administration in the early setting. Specifically, a reduction in the preference for weekly paclitaxel over 3-weekly docetaxel and of dose-dense over standard-interval anthracycline-based chemotherapy was observed. In order to reduce as much as possible the number of visits at the hospital and considering the similar efficacy

between the two taxane-based regimens,<sup>16</sup> an increased preference for 3-weekly docetaxel appears reasonable in this situation. On the contrary, the reasons for reducing the indications to dose-dense anthracycline-based chemotherapy in high-risk patients remain less clear. They are characterized by similar frequency of hospital visits than with the 3-weekly schedule. Dose-dense chemotherapy has clearly shown to significantly improve patients' outcomes.<sup>17</sup> In addition, considering that the use of granulocyte colony-stimulating factors is mandatory when anthracycline-based chemotherapy is administered in a dose-dense schedule,<sup>18,19</sup> the risk of grade 3-4 neutropenia and neutropenic sepsis is lower than with 3-weekly regimens.<sup>17</sup> This could be potentially considered an advantage to favor the dose-dense schedule during COVID-19 outbreak.

In the metastatic setting, similar findings as for (neo)adjuvant therapy were observed in terms of choice of taxane as first-line treatment in patients with HER2-positive disease, with a reduction in the preference for weekly paclitaxel during COVID-19 outbreak, particularly for oncologists working in the Lombardy region. The combination of single agent taxane with dual anti-HER2-blockade trastuzumab plus trastuzumab is the current first-line treatment in these patients.<sup>20,21</sup> Although 3-weekly docetaxel was the chemotherapy agent used in the registration CLEOPATRA trial,<sup>22</sup> the feasibility of administering the same regimen with weekly paclitaxel was subsequently demonstrated.<sup>23,24</sup> However, despite being better tolerated, weekly access to the hospital is needed with the use of paclitaxel, making a reasonable choice the preference for docetaxel during COVID-19 outbreak.

In patients with hormone receptor-positive metastatic breast cancer, the recent development and approval of CDK4/6 inhibitors in combination with endocrine therapy represents a major milestone in the treatment landscape of this disease.<sup>25</sup> In patients with both endocrine-sensitive and endocrine-resistant disease, a significant improvement in progression-free survival<sup>26</sup> and overall survival<sup>27-30</sup> has been shown with this combination. Notably, so far, no clinicopathological subgroup of patients appears to not derive benefit from a treatment that include a CDK4/6 inhibitor.<sup>26</sup> Therefore, this

combination is now considered standard of care in all patients with hormone receptor-positive metastatic breast cancer.<sup>21</sup> Nevertheless, although 80% of responding oncologists declared to use these treatments as first-line therapy in all patients including those with less aggressive characteristics (e.g. elderly and/or with only bone metastasis), one third of them did not recommend this combination during COVID-19 outbreak. The risk of hematological toxicities,<sup>31-33</sup> and the need to additional monitoring (e.g. blood tests, cardiological evaluation) may be possible explanations for these findings. However, denying such an effective treatment without clear contraindications should be considered with cautious. Similarly, although 30% of responding oncologists suggested to reduce treatment monitoring with blood tests as compared to what suggested in the drug technical sheets of all available CDK4/6 inhibitors, such approach may not be appropriate particularly for the assessment of neutropenia during COVID-19 outbreak. To overcome these potential limitations, alternative ways of monitoring should be implemented including blood tests in external laboratories, phone calls with patients and drug shipment to limit the number of visits at the hospital.

Similarly, considering the more predictable and manageable toxicity, when patients with metastatic breast cancer are candidates to chemotherapy, the oral formulation should be prioritized whenever possible during COVID-19 outbreak. As recommended by the European Society of Medical Oncology (ESMO) guidelines for breast cancer during COVID-19 outbreak,<sup>34</sup> it was the preferred choice for almost 85% of responding oncologists.

The COVID-19 outbreak showed to influence also the timing for performing imaging procedures to monitor treatment response and for flushing central venous devices. Many oncologists suggested to postpone these activities as compared to their practice before the health care emergency. Despite the lack of proper evidence to counsel patients on this regard, these can be considered reasonable approaches for reducing the access of patients to the hospital.<sup>13,35</sup>



Cancer research represents a key stone in the oncology field. Special guidance for the conduction of this activity has been provided by Food & Drug Administration, European Medicines Agency and “Agenzia Italiana del Farmaco”.<sup>36-38</sup> However, as expected, the COVID-19 outbreak has shown to hamper also cancer research by reducing both clinical research and scientific activities in almost three quarters of responding oncologists. Special attention should be given to safely maintain the care of patients enrolled in clinical trials, including to avoid potential issues in drug supply.<sup>13</sup>

### **Limitations**

This survey focused only on oncologists’ attitudes and practice towards specific issues in breast cancer care. It was shared with all Italian oncologists working in different regions with heterogeneous hospital organization and burden of COVID-19 outbreak. A relatively limited number of oncologists responded the survey. Hence, these results cannot be generalized to the international oncology community. Nevertheless, the lack of clear differences in the attitudes and practice between oncologists working in the Lombardy region and other Italian areas (except for the choice of taxane as first-line treatment in patients with HER2-positive disease) highlights the global impact of this health care emergency irrespective of the actual burden of COVID-19 outbreak. Notably, the great majority of respondents worked within a Breast Unit, and the response rate was higher than expected allowing the collection of an adequate number of responses to have a representative picture of the attitudes and practice of Italian oncologists, specifically focused on breast cancer care, towards the explored issues.

### **Conclusions**

This survey provides the first evidence on the actual impact of COVID-19 outbreak on breast cancer care and related research activities among Italian oncologists. The majority of the observed changes in their attitudes and practice are reasonable responses to the current health care emergency without expected negative impact on patients’ outcomes. However, some potential alarming signals

of undertreatment emerged. These data may help to better understand the challenges faced by oncologists in providing cancer care during COVID-19 outbreak, and voice for the development of cautious recommendations to help them ensuring continuous effective and safe cancer care.

## ARTICLE INFORMATION

**Author Affiliations:** Author affiliations are listed in the Title Page.

**Author Contributions:** Dr. Poggio, Dr. Tagliamento, Dr. Di Maio and Dr. Lambertini had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Concept and design:* Poggio, Tagliamento, Del Mastro, Lambertini.

*Acquisition, analysis, or interpretation of data:* Poggio, Tagliamento, Di Maio, Martelli, De Maria, Barisione, Grosso, Boccardo, Pronzato, Del Mastro, Lambertini.

*Drafting of the manuscript:* Poggio, Lambertini.

*Critical revision of the manuscript for important intellectual content:* Tagliamento, Di Maio, Martelli, De Maria, Barisione, Grosso, Boccardo, Pronzato, Del Mastro.

*Statistical analysis:* Tagliamento, Di Maio.

*Administrative, technical, or material support:* Poggio, Tagliamento, Di Maio, Martelli, De Maria, Barisione, Grosso, Boccardo, Pronzato, Del Mastro, Lambertini.

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## References

1. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061. doi:10.1001/jama.2020.1585
2. WHO Director-General’s opening remarks at the media briefing on COVID-19 - 11 March 2020. <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020>.
3. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *The Lancet*. 2020;395(10231):1225-1228. doi:10.1016/S0140-6736(20)30627-9
4. Grasselli G, Pesenti A, Cecconi M. Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response. *JAMA*. March 2020. doi:10.1001/jama.2020.4031
5. Murthy S, Gomersall CD, Fowler RA. Care for Critically Ill Patients With COVID-19. *JAMA*. March 2020. doi:10.1001/jama.2020.3633
6. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239. doi:10.1001/jama.2020.2648
7. Rolston KVI. Infections in Cancer Patients with Solid Tumors: A Review. *Infect Dis Ther*. 2017;6(1):69-83. doi:10.1007/s40121-017-0146-1
8. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21(3):335-337. doi:10.1016/S1470-2045(20)30096-6
9. Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. *Ann Oncol*. March 2020:S0923753420363833. doi:10.1016/j.annonc.2020.03.296
10. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 Transmission in Patients With Cancer at

- a Tertiary Care Hospital in Wuhan, China. *JAMA Oncol.* March 2020.  
doi:10.1001/jamaoncol.2020.0980
11. Ueda M, Martins R, Hendrie PC, et al. Managing Cancer Care During the COVID-19 Pandemic: Agility and Collaboration Toward a Common Goal. *J Natl Compr Canc Netw.* 2020;18(4):366-369. doi:10.6004/jnccn.2020.7560
  12. Beretta DG, Cinieri DS, Blasi DL, Cipomo P, Aglietta M, Comu P. Rischio infettivo da Coronavirus COVID-19: indicazioni per l'oncologia. Associazione Italiana di Oncologia Medica (AIOM); March 13 2020. Available at: [https://www.aiom.it/wp-content/uploads/2020/03/20200313\\_COVID-19\\_indicazioni\\_AIOM-CIPOMO-COMU.pdf](https://www.aiom.it/wp-content/uploads/2020/03/20200313_COVID-19_indicazioni_AIOM-CIPOMO-COMU.pdf). :2.
  13. Lambertini M, Toss A, Passaro A, et al. Cancer care during the spread of coronavirus disease 2019 (COVID-19) in Italy: young oncologists' perspective. *ESMO Open.* 2020;5(2):e000759. doi:10.1136/esmoopen-2020-000759
  14. Caparica R, Lambertini M, Pondé N, Fumagalli D, de Azambuja E, Piccart M. Post-neoadjuvant treatment and the management of residual disease in breast cancer: state of the art and perspectives. *Ther Adv Med Oncol.* 2019;11:175883591982771. doi:10.1177/1758835919827714
  15. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol Off J Eur Soc Med Oncol.* 2019;30(8):1194-1220. doi:10.1093/annonc/mdz173
  16. Sparano JA, Zhao F, Martino S, et al. Long-Term Follow-Up of the E1199 Phase III Trial Evaluating the Role of Taxane and Schedule in Operable Breast Cancer. *J Clin Oncol.* 2015;33(21):2353-2360. doi:10.1200/JCO.2015.60.9271
  17. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. *Lancet Lond Engl.* 2019;393(10179):1440-1452. doi:10.1016/S0140-6736(18)33137-4
  18. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth

- Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212. doi:10.1200/JCO.2015.62.3488
19. Klastersky J, de Naurois J, Rolston K, et al. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2016;27:v111-v118. doi:10.1093/annonc/mdw325
  20. Giordano SH, Temin S, Chandarlapaty S, et al. Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36(26):2736-2740. doi:10.1200/JCO.2018.79.2697
  21. Cardoso F, Senkus E, Costa A, et al. 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. *Ann Oncol*. 2018;29(8):1634-1657. doi:10.1093/annonc/mdy192
  22. Swain SM, Miles D, Kim S-B, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020;21(4):519-530. doi:10.1016/S1470-2045(19)30863-0
  23. Dang C, Iyengar N, Datko F, et al. Phase II Study of Paclitaxel Given Once per Week Along With Trastuzumab and Pertuzumab in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer. *J Clin Oncol*. 2015;33(5):442-447. doi:10.1200/JCO.2014.57.1745
  24. Bachelot T, Ciruelos E, Schneeweiss A, et al. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for HER2-positive locally recurrent or metastatic breast cancer (PERUSE). *Ann Oncol*. 2019;30(5):766-773. doi:10.1093/annonc/mdz061
  25. Spring LM, Wander SA, Andre F, Moy B, Turner NC, Bardia A. Cyclin-dependent kinase 4 and 6 inhibitors for hormone receptor-positive breast cancer: past, present, and future. *The Lancet*. 2020;395(10226):817-827. doi:10.1016/S0140-6736(20)30165-3
  26. Gao JJ, Cheng J, Bloomquist E, et al. CDK4/6 inhibitor treatment for patients with hormone receptor-positive, HER2-negative, advanced or metastatic breast cancer: a US Food and Drug

- Administration pooled analysis. *Lancet Oncol.* 2020;21(2):250-260. doi:10.1016/S1470-2045(19)30804-6
27. Turner NC, Slamon DJ, Ro J, et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. *N Engl J Med.* 2018;379(20):1926-1936. doi:10.1056/NEJMoa1810527
28. Slamon DJ, Neven P, Chia S, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. *N Engl J Med.* 2020;382(6):514-524. doi:10.1056/NEJMoa1911149
29. Im S-A, Lu Y-S, Bardia A, et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. *N Engl J Med.* 2019;381(4):307-316. doi:10.1056/NEJMoa1903765
30. Sledge GW, Toi M, Neven P, et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor–Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy—MONARCH 2: A Randomized Clinical Trial. *JAMA Oncol.* 2020;6(1):116. doi:10.1001/jamaoncol.2019.4782
31. Martel S, Bruzzone M, Ceppi M, et al. Risk of adverse events with the addition of targeted agents to endocrine therapy in patients with hormone receptor-positive metastatic breast cancer: A systematic review and meta-analysis. *Cancer Treat Rev.* 2018;62:123-132. doi:10.1016/j.ctrv.2017.09.009
32. Kassem L, Shohdy KS, Lasheen S, Abdel-Rahman O, Bachelot T. Hematological adverse effects in breast cancer patients treated with cyclin-dependent kinase 4 and 6 inhibitors: a systematic review and meta-analysis. *Breast Cancer.* 2018;25(1):17-27. doi:10.1007/s12282-017-0818-4
33. Diéras V, Rugo HS, Schnell P, et al. Long-term Pooled Safety Analysis of Palbociclib in Combination With Endocrine Therapy for HR+/HER2- Advanced Breast Cancer. *JNCI J Natl Cancer Inst.* 2019;111(4):419-430. doi:10.1093/jnci/djy109
34. ESMO management and treatment adapted recommendations in the COVID-19 era; breast cancer. Available at: <https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/breast-cancer-in-the-covid-19-era>.



35. Raccomandazioni per la gestione di CVC durante l'emergenza COVID-19. Associazione Italiana di Oncologia Medica (AIOM); March 30 2020. Available at: [http://media.aiom.it/mailling/files/doc/lettera\\_manutenzione\\_%20accessi\\_%20venosi\\_%20centrali\\_%20tipo\\_%20Port.pdf](http://media.aiom.it/mailling/files/doc/lettera_manutenzione_%20accessi_%20venosi_%20centrali_%20tipo_%20Port.pdf).
36. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards. :16.
37. Guidance to sponsors on how to manage clinical trials during the COVID-19 pandemic. European Medicines Agency (EMA); March 20 2020. Available at: <https://www.ema.europa.eu/en/news/guidance-sponsors-how-manage-clinical-trials-during-covid-19-pandemic>. :2.
38. Clinical trials' management in Italy during the COVID-19 (coronavirus disease 19) emergency. Agenzia Italiana del Farmaco (AIFA); March 12 2020. Available at <https://www.aifa.gov.it/web/guest/-/gestione-degli-studi-clinici-in-italia-in-corso-di-emergenza-covid-19-coronavirus-disease-19->. :4.