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Utilizing the latest data from ESMO 2020 to optimize the management of patients with HR+/HER2- breast cancer

Transcript from a touchCONGRESS Data Review

THE EXPERT

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INTRODUCTION

Hello, my name is Cathy Kelly. I'm an Associate Clinical Professor at University College Dublin and consultant medical oncologist in the Mater Hospital and I'm here today to talk about some of the data that emerged from ESMO 2020 on the management of patients with hormone-receptor-positive HER2-negative breast cancer.

The learning objectives are to apply this data in particular for CDK4/6 inhibitors in patients with hormone-receptor-positive HER2-negative early breast cancer and to our clinical practice and to look at the latest data on CDK4/6 inhibitors in patients, again, with hormone-receptor-positive HER2-negative breast cancer but advanced disease and how they might inform our clinical practice. And we'll also look at some data that was presented on the outcomes of patients with cancer who unfortunately developed COVID during the COVID pandemic.

LEARNING OBJECTIVES

After watching this touchCONGRESS webinar, you should be able to:

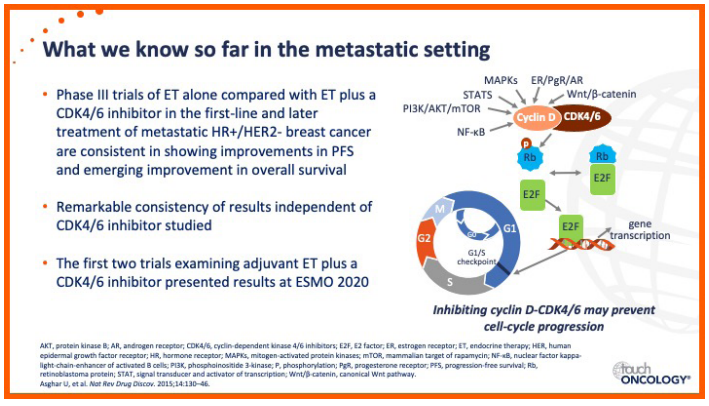
- Apply new and emerging data for CDK4/6 inhibitors in patients with HR+/HER2- early breast cancer in clinical practice
- Use the latest results for CDK4/6 inhibitors in patients with HR+/HER2- advanced breast cancer to inform treatment decisions in clinical practice
- Review emerging real-world data on the outcome of patients with active, or a history of, cancer who have developed COVID-19 during the COVID-19 pandemic

So we'll look at some new and emerging data for CDK4/6 inhibitors in patients with hormone-receptor-positive HER2-negative early breast cancer, then we'll move to the advanced setting and then we'll cover some emerging data on cancer patient outcomes during the COVID pandemic.

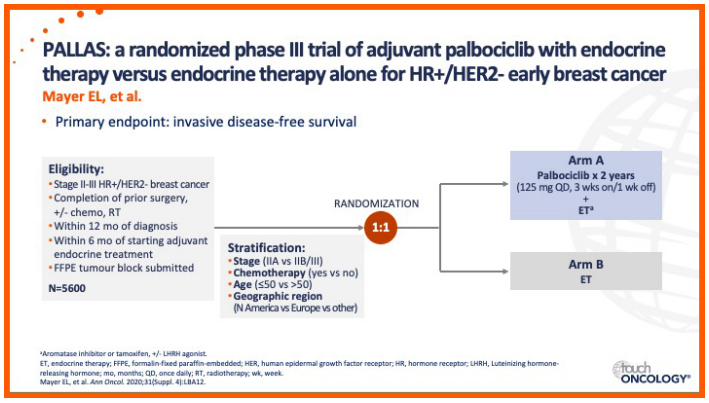
TOPICS DISCUSSED

- New and emerging data for CDK4/6 inhibitors in patients with HR+/HER2- early breast cancer
- CDK4/6 inhibitors in patients with HR+/HER2- advanced breast cancer
- Emerging data on the outcomes of patients with cancer during the COVID-19 pandemic

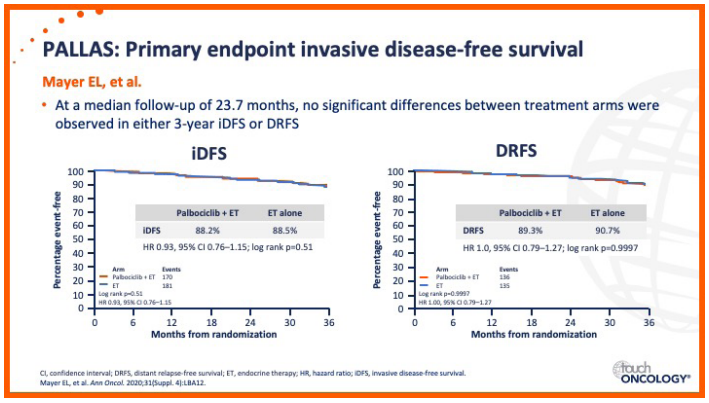
So what do we know so far in terms of hormone-receptor-positive HER2-negative metastatic breast cancer and CDK4/6 inhibitors? Well, really over the last five years CDK4/6 inhibitors have really been a game changer in our treatment in the first-line and later settings for patients with metastatic disease. We've seen remarkably consistent results over many first-line and beyond studies where endocrine treatment has been combined with the CDK4/6 inhibitors and they're quite remarkable in the consistency of the benefit we see. We were looking forward to ESMO because the first two early breast cancer studies using CDK4/6 inhibitors in combination with the endocrine therapy were presented. And, as you know, there are four studies. The NATALEE study is currently ongoing and the other three studies are completed. So PENELOPE, we hope will be presented later on this year. And so at ESMO we heard for the first time presentations on the PALLAS study and monarchE.



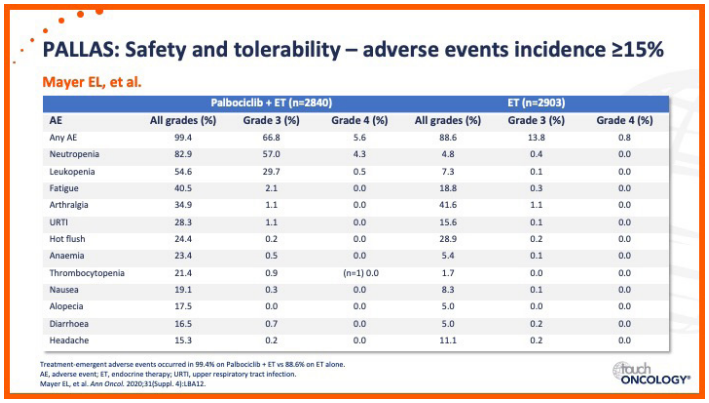
So if we look first at the PALLAS study, the PALLAS study is a randomised phase III trial of adjuvant palbociclib with endocrine therapy versus endocrine therapy alone in hormone-receptor-positive HER2 early breast cancer. And the primary end point of this trial was invasive disease-free survival. And to be eligible patients had to have stage II or III hormone-receptor-positive HER2-negative breast cancer, they had to have completed their adjuvant chemotherapy and radiation and to be within 12 months of their diagnosis or within 6 months of starting adjuvant endocrine treatment. And patients were randomised to palbociclib for two years at a starting dose of a 125mg daily for three weeks on and one week off combined with endocrine treatment compared to endocrine treatment alone; and endocrine treatment could be an aromatase inhibitor or tamoxifen plus or minus an LHRH agonist.



And what we saw was that a median follow-up of 23.7 months there was no significant difference in invasive disease in three-year invasive disease-free survival or distant recurrence-free survival. So if we look at invasive disease-free survival for the study arm it was 88.2% compared to 88.5%, so no difference. And in terms of distant recurrence-free survival it was exactly the same in both arms; 89.3 in the palbociclib arm versus 90.7 in the endocrine treatment alone arm. So this trial did not meet its end point and it was a negative study.

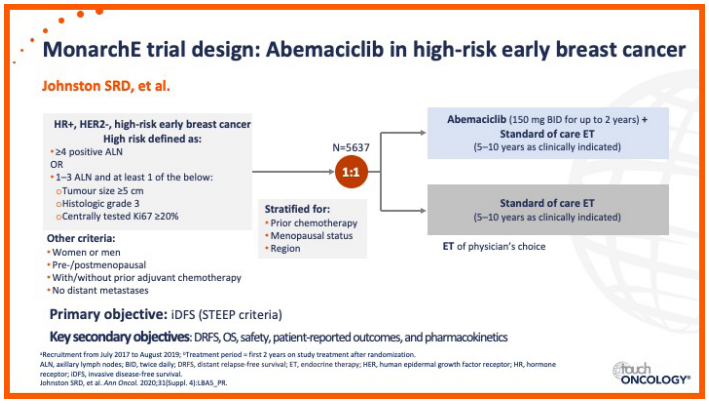


In terms of safety and tolerability we've all got a lot of experience now using palbociclib in the metastatic setting so there were no new safety signals or no new adverse events that we haven't already dealt with. So, as expected neutropenia, leukopenia and fatigue were the most common adverse advents.



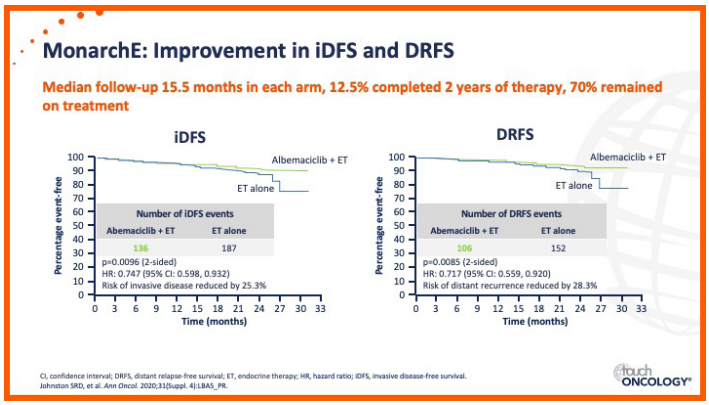
	Palbociclib + ET (n=2840)			ET (n=2903)		
AE	All grades (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade 3 (%)	Grade 4 (%)
Any AE	99.4	66.8	5.6	88.6	13.8	0.8
Neutropenia	82.9	57.0	4.3	4.8	0.4	0.0
Leukopenia	54.6	29.7	0.5	7.3	0.1	0.0
Fatigue	40.5	2.1	0.0	18.8	0.3	0.0
Arthralgia	34.9	1.1	0.0	41.6	1.1	0.0
URTI	28.3	1.1	0.0	15.6	0.1	0.0
Hot flush	24.4	0.2	0.0	28.9	0.2	0.0
Anaemia	23.4	0.5	0.0	5.4	0.1	0.0
Thrombocytopenia	21.4	0.9	(n=1) 0.0	1.7	0.0	0.0
Nausea	19.1	0.3	0.0	8.3	0.1	0.0
Alopecia	17.5	0.0	0.0	5.0	0.0	0.0
Diarrhoea	16.5	0.7	0.0	5.0	0.2	0.0
Headache	15.3	0.2	0.0	11.1	0.2	0.0

And now moving onto the monarchE study, which is very similar in its design. Again, a very large phase III study; both of these studies with PALLAS and monarchE had over 5000 patients in them. And again this trial enrolled high risk early breast cancer patients with hormone-receptor-positive HER2-negative disease. High risk in this study was defined as having greater than or equal to four positive lymph nodes or else one to three positive lymph nodes but large tumours, so tumours over 5cm, grade III or high Ki-67, so greater than 20%. And patients in this study were randomised to abemaciclib at 150mg twice daily for up to two years or standard of care endocrine treatment for five to ten years as clinically indicated compared to standard of care endocrine treatment. And just like PALLAS endocrine treatment in both studies was commonly in AI, but patients could have had AI or tamoxifen plus or minus an LHRH agonist and both pre- and post-menopausal women were eligible for these studies. The primary end point was invasive disease free survival.

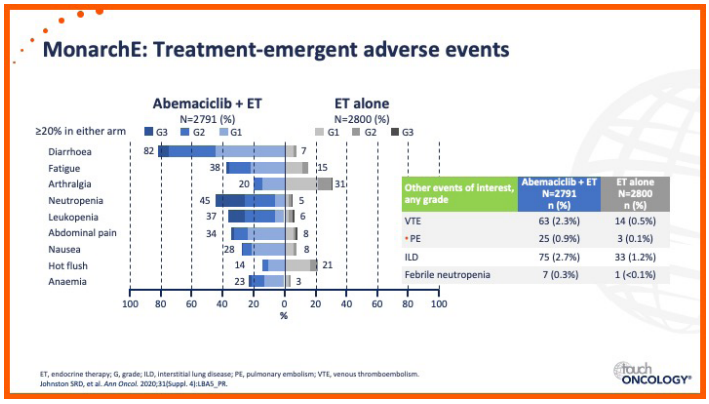


And in total contrast to the PALLAS study at a median follow-up of 15.5 months we saw an improvement in invasive disease-free survival and distant relapse-free survival emerge. And it's quite remarkable that only 12.5% of the patients on this study have actually completed their two years of therapy. So 70% remain on treatment yet at this early stage we've seen this improvement in both invasive disease free survival and distant relapse-free survival emerge.

And so what was the difference? So in absolute terms it amounts to about a 3.5% difference or a relative risk reduction of 25% in invasive disease free survival and about 28% or so for distant relapse-free survival. And we could see monarchE was published simultaneously with this presentation, so it's been published in the JCO with an excellent editorial by Antonio Wolff alongside it. And we can see in this study we have more detail. PALLAS, unfortunately we haven't seen it yet in publication form so we'll get a lot more detail hopefully in the coming weeks. But we can see in monarchE this benefit emerged very early on, somewhere between 9-12 months. So at ESMO and even prior to ESMO we were all wondering well, these are two very similar studies, why is one negative and one positive? We'll get to that in a second.

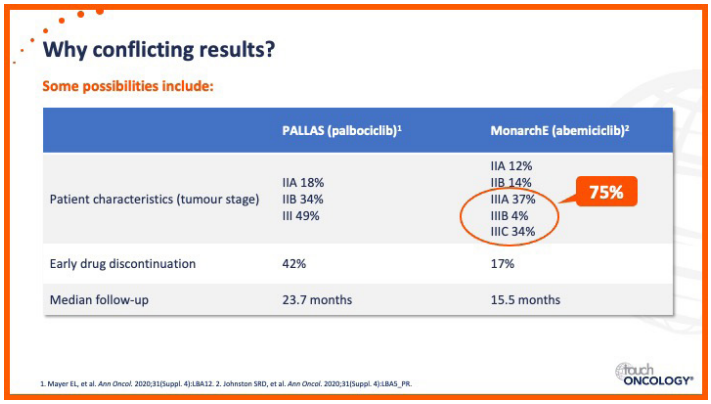


In terms of adverse events, as expected for abemaciclib diarrhoea was the most common adverse event particularly early on in the treatment but was manageable with loperamide. There were very few grade III adverse events for diarrhoea. In terms of events of interest venous thromboembolism was higher at 2.3% in the abemaciclib arm compared to the endocrine only arm, and interstitial lung disease at 2.7% compared to 1.2 %. Interestingly there were fewer hot flushes and arthralgia. There was less arthralgia and hot flushes reported in the abemaciclib arm, so that's interesting and something that we'll follow as time goes by.

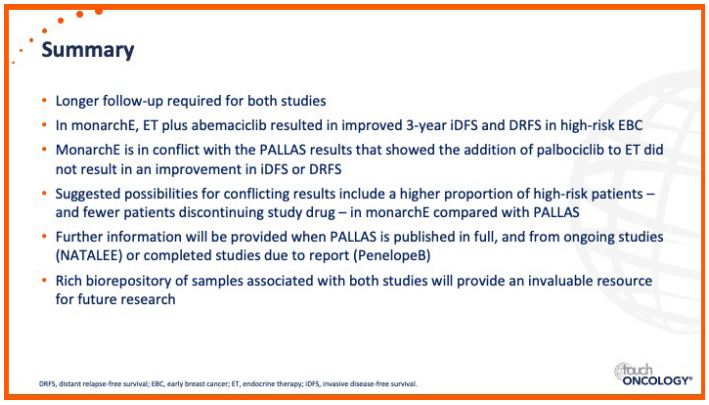


So why were these results conflicting? And at the presidential session where the monarchE study was presented the discussant George Sledge gave a really nice summary of both studies and his thoughts on them. But basically some of the possibilities for the conflict in these two studies would be one, the patient characteristics, and it looks like monarchE really is weighted towards those more high risk patients. So there were more stage II patients in PALLAS compared to monarchE, and then if you look at those very high risk stage III patients about 49% were stage III in PALLAS. And then when you look at the breakdown in the JCO publication from monarchE about 75% are stage III, so a higher risk population in monarchE and also some selection not only based on anatomical stage but biology. And then quite dramatically, and this again will be something that will be delved into in more detail over the coming weeks, is really the difference in the early drug discontinuation rates. So 42% of patients in PALLAS discontinued the

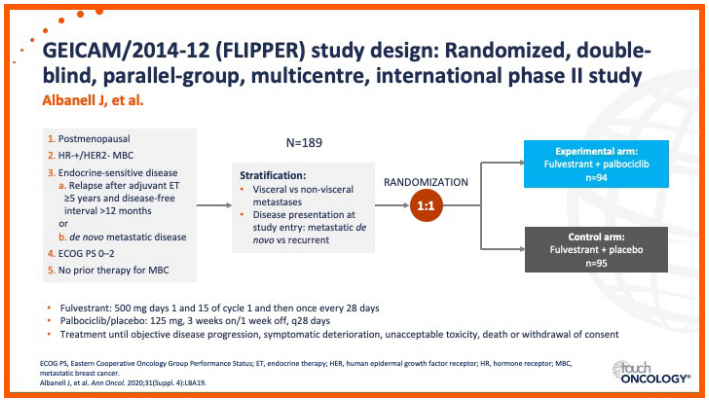
drug before the two year mark, and in comparison about 17% in the monarchE study. So quite a big difference there and probably is one of the reasons why these trials are conflicting. Also and very notable is we know, especially for these high risk women, that they're at high risk both early on and at risk of later relapse, so beyond five years, and really for this group of patients with this type of disease, hormone-receptor-positive disease, longer follow-up is essential to see how these women do and whether there'll be an impact of CDK4/6 inhibitors on late relapse. So longer follow-up definitely is required and we'll all be watching this very closely.



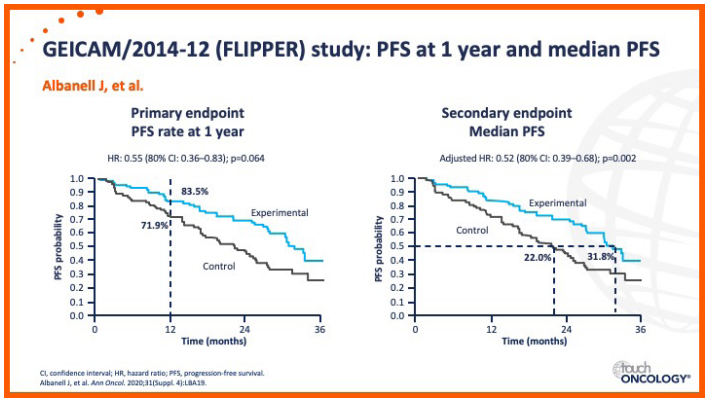
In terms of the monarchE study it met its end point and improved three year invasive disease-free survival and distant recurrence-free survival for these high risk women. The trial is in conflict with PALLAS but possibly this is due to the higher proportion of patients with more high risk disease and the authors of this study say they were particularly trying to target those high risk women who have endocrine resistance, who are going to relapse and we see they are going to relapse in the first year or so. Another reason that they haven't put on the slide but suggested also, or highlighted also, in the associated editorial for monarchE, is that imaging prior to eligibility on this trial was not mandated in the protocols. So Antonio Wolff who wrote the associated editorial alongside the monarchE study suggests that maybe there are some patients in here who have asymptomatic subclinical metastatic disease, and again that's a possibility. So we'll get further information over the coming weeks with PALLAS when it's published in full and then I'm certainly looking forward to the PENELOPE study results. And you'll remember that the PENELOPE study randomised women who had residual disease, post neoadjuvant chemotherapy to palbociclib plus a hormone versus standard of care hormone treatment, and patients were given palbociclib for one year. So that will be interesting and that was a double blind placebo controlled study that will be hopefully presented at San Antonio. And then for both studies there's a rich biorepository of tissue samples that are going to be an invaluable resource for future research.



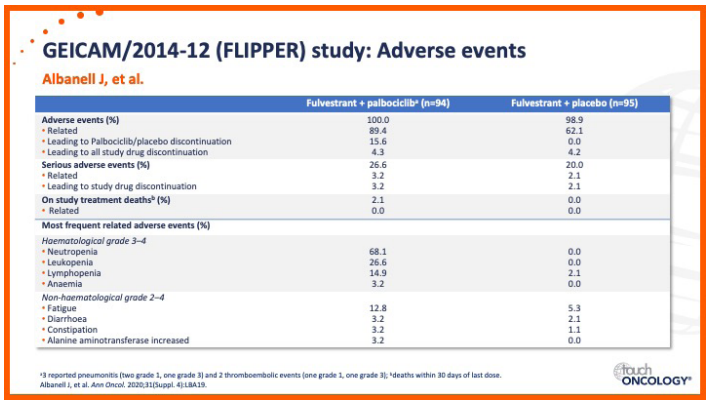
So we move on now to the advanced breast cancer setting and we know we've had PALOMA, the MONALEESA and the MONARCH family of studies all showing quite dramatic improvements in progression free survival in first-line hormone-receptor-positive metastatic disease and also, as I said, some of these trials showing improvements in overall survival. So we had another study in the first-line setting for a hormone sensitive advanced breast cancer hormone-receptor-positive HER2-negative, and this was the FLIPPER study that was conducted by the Spanish group in collaboration with Cancer Trials Ireland. So this is a phase II study and this was the first analysis of the results from this study. Post-menopausal patients were randomised to fulvestrant plus placebo versus fulvestrant plus palbociclib. The primary end point of this study was progression-free survival at one year and also medium progression-free survival was a secondary end point.



So consistent with previous studies the progression-free survival at one year favoured the addition of palbociclib to fulvestrant and that was 83.5% compared to 71.9%. And in terms of median progression-free survival the improvement was approximately 10 months at 22 in the control arm of fulvestrant placebo versus almost 32 months in the fulvestrant palbociclib arm. So hazard ratios there for both the primary end point and the secondary end point of about 0.55 and 0.52 respectively.



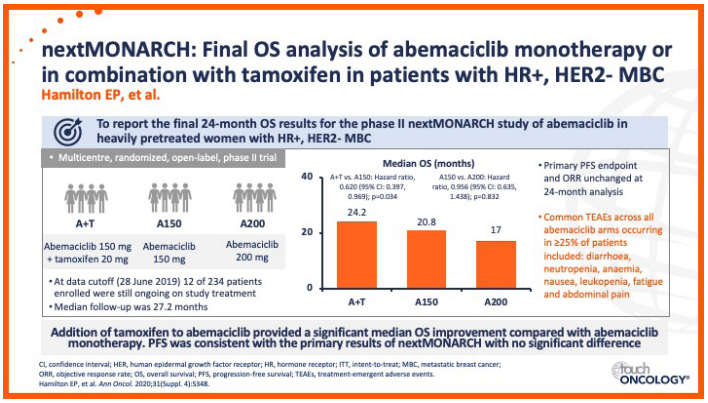
In terms of adverse events they're very consistent with what we've seen previously in neutropenia and leukopenia and some fatigue.



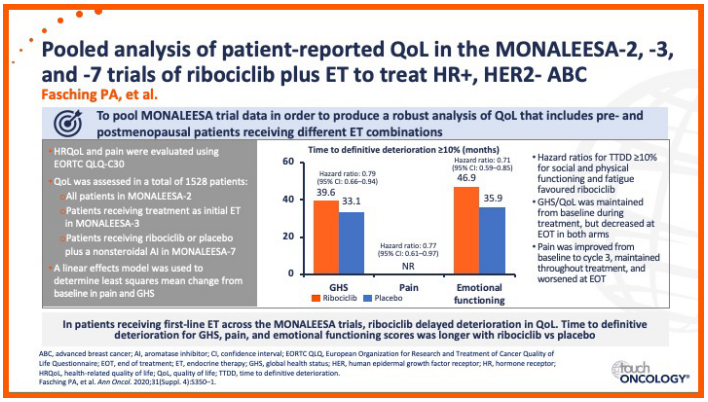
	Fulvestrant + palbociclib[a] (n=94)	Fulvestrant + placebo (n=95)
Adverse events (%)	100.0	98.9
• Related	89.4	62.1
• Leading to Palbociclib/placebo discontinuation	15.6	0.0
• Leading to all study drug discontinuation	4.3	4.2
Serious adverse events (%)	26.6	20.0
• Related	3.2	2.1
• Leading to study drug discontinuation	3.2	2.1
On study treatment deaths[b] (%)	2.1	0.0
• Related	0.0	0.0
Most frequent related adverse events (%)		
Haematological grade 3–4		
• Neutropenia	68.1	0.0
• Leukopenia	26.6	0.0
• Lymphopenia	14.9	2.1
• Anaemia	3.2	0.0
Non-haematological grade 2–4		
• Fatigue	12.8	5.3
• Diarrhoea	3.2	2.1
• Constipation	3.2	1.1
• Alanine aminotransferase increased	3.2	0.0

[a]3 reported pneumonitis (two grade 1, one grade 3) and 2 thromboembolic events (one grade 1, one grade 3); [b]deaths within 30 days of last dose.
Albanell J, et al. *Ann Oncol.* 2020;31(Suppl. 4):LBA19.

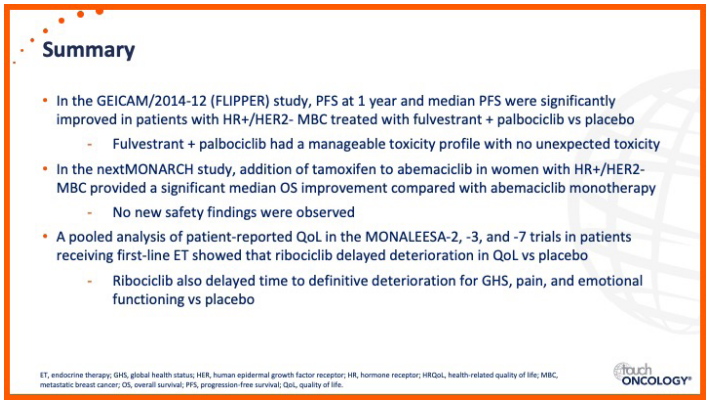
NextMONARCH was another study presented at ESMO 2020 and we saw the final overall survival analysis of abemaciclib monotherapy or in combination with tamoxifen in patients with hormone-receptor-positive HER2-negative metastatic breast cancer. And in this multicentre randomised open-label phase II trial patients were randomised to abemaciclib plus tamoxifen and abemaciclib at 150mg to abemaciclib 150mg or else abemaciclib 200mg. The median follow-up now is 27.2 months. The primary end point of this study was progression-free survival and objective response rates, and they're unchanged in this 24-month analysis. But what we are seeing in terms of median overall survival is that there is an improvement in median and overall survival for abemaciclib plus tamoxifen compared to tamoxifen at 200mg. It's important to note that this study was not powered for overall survival but it was one of the pre-planned analyses. So the addition of tamoxifen to abemaciclib provided a significant median overall survival improvement compared with the abemaciclib monotherapy. In terms of what does this mean, the results are consistent with prior studies. Abemaciclib has single agent activity but certainly activity improves in combination with tamoxifen and the benefit we saw for progression-free survival appears to be carried through now with an overall survival benefit that was consistent across all subgroups including patients with liver metastases and those who've received prior tamoxifen for advanced disease.



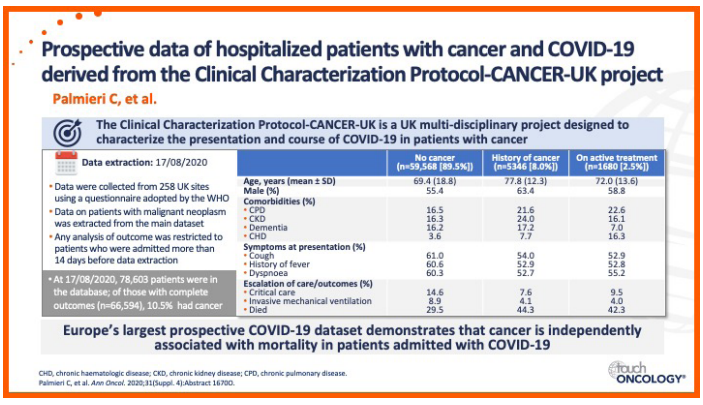
There was a study by Fasching and colleagues, a pooled analysis of patient reported quality of life outcomes in the MONALEESA studies, so MONALEESA 2, 3 and 7 and trials of abemaciclib plus endocrine treatment to patients with hormone-receptor-positive HER2-negative advanced breast cancer and this was presented by Fasching on behalf of his colleagues. And basically the objective was to pool MONALEESA trial data in order to produce a robust analysis of quality of life that includes pre and post menopausal women receiving different endocrine therapy combinations. And so they were interested in obviously quality of life and pain as evaluated by EORTC QLQ-C30 questionnaires. Quality of life was assessed in over 1500 patients: all patients in MONALEESA-2, patients receiving endocrine therapy in MONALEESA-3 and patients receiving ribociclib or placebo plus a nonsteroidal AI in MONALEESA-7.



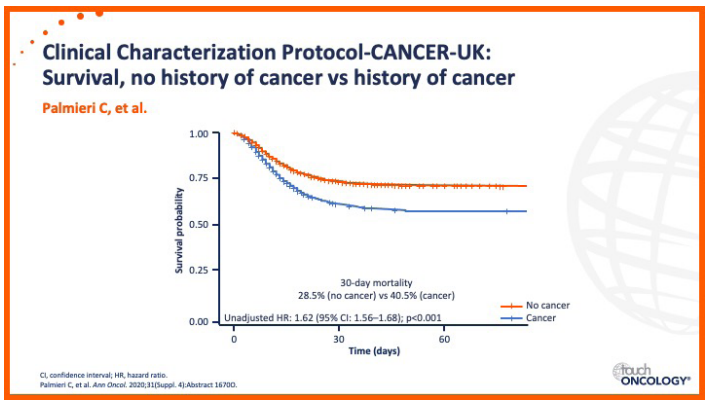
And what they saw: delay to definitive deterioration, favoured all of the ribociclib arms in these studies. So, global health status, for example, emotional functioning, social and physical functioning all favoured ribociclib. So in patients receiving first-line endocrine therapy across the MONALEESA trials ribociclib delayed deterioration in quality of life, time to definitive deterioration in global health status and emotional functioning scores were longer with ribociclib compared to placebo. And there was a very nice discussion session with Professor Leslie Fallowfield on how we're measuring quality of life and are we getting it right. And she made a very important point and encouraged the use of PRO-CTCAE as a measure of quality of life, in other words getting patients to report or grade their symptoms. So there was a nice discussion if you get a chance to look at that discussion.



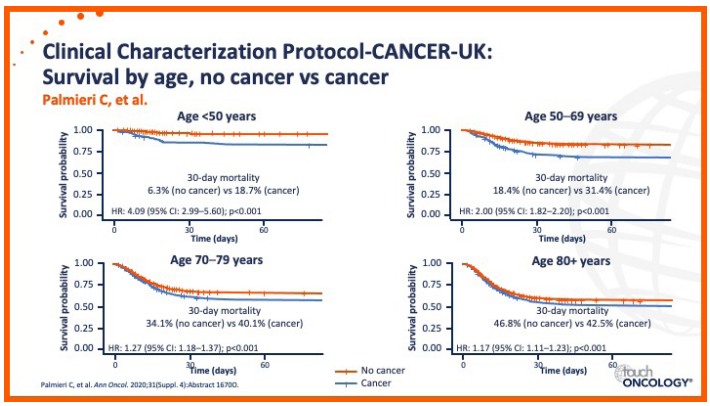
Now, moving on, there were some very nice studies from both the US and the UK looking at patients with a history of cancer or patients with active cancer who contracted COVID-19 over the recent months. So one study presented by Carlo Palmieri from Clatterbridge Cancer Centre in Liverpool looked at prospective data of hospitalised patients with cancer and COVID-19 derived from the Clinical Characterisation Protocol Cancer UK project. And so they looked at patients with a history of cancer, no history of cancer, or patients on active treatment. They looked at co-morbidities and in terms of patients with no history of cancer compared to patients with a history of cancer or on active treatment. There were slightly higher incidences of chronic pulmonary disease and chronic kidney disease in those patients either on active or a history of cancer and then dementia was lower in those patients on active treatment, as you might expect. In terms of the presentation of symptoms there was no clinically significant difference in terms of symptoms at presentation between people with no history of cancer compared to those with a history or on active treatments. What was quite dramatic was in terms of escalation of care and outcomes. And certainly there were more patients with no history of cancer likely to have their treatment escalated to the critical care setting compared with those patients with a history of cancer or on active treatment. So, for example, 14.6% of people with no history of cancer compared to only 7.6% of patients with a history of cancer or 9.5% on active treatment had their care escalated to the critical care setting. And in terms of invasive mechanical ventilation 8.9% of patients with no history of cancer who developed COVID accessed invasive mechanical ventilation compared to only about 4% in those with a history or active cancer. In terms of deaths: about 30% in patients with no history of cancer, but much higher at 44% and 42% of patients with a history of cancer or an active treatment respectively.



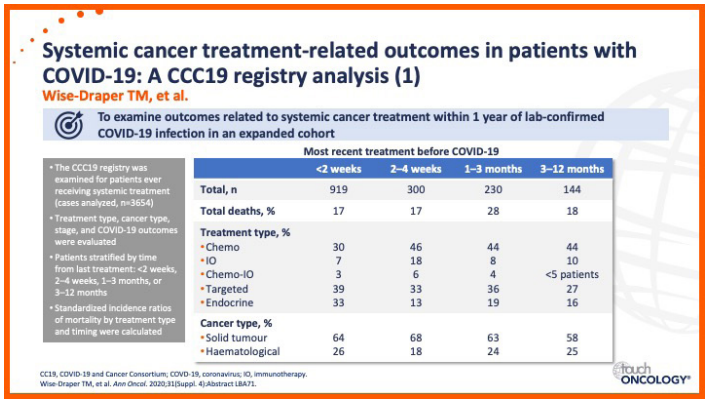
And Dr Palmieri presented some nice, unadjusted however, data on probability of survival for patients with COVID with a history of cancer compared to no cancer history, and there was quite a dramatic difference in terms of 30-day mortality. It was 28.5% if you had no history of cancer compared to 40.5% for those with cancer, so a 30-day mortality, much higher for our patients with cancer who developed COVID.



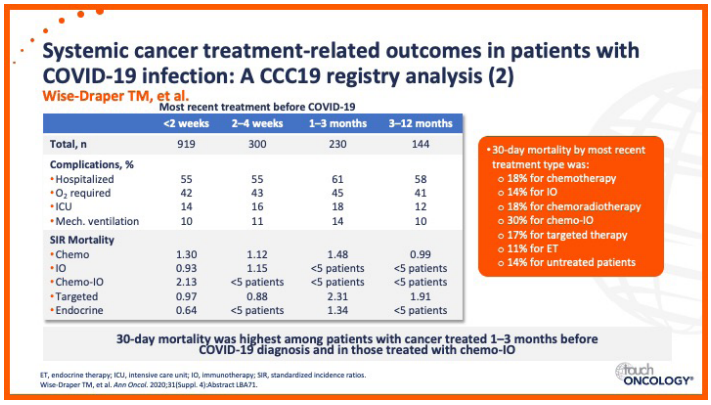
And in terms of breaking it down by age group this was quite dramatic for those very elderly patients, so over eighty, although there was a slight difference in 30-day mortality, both whether you had cancer or not, if you were over 80, 30-day mortality was high at 46.8% if you had a history of cancer versus 42.5% if you had no history of cancer, so 30-day mortality high there regardless of cancer mostly driven by age. But when you look at those patients under 50, that was where there was actually a very significant difference in 30-day mortality. So for patients under 50 with no cancer there was a 30-day mortality of 6.3% compared to 18.7% if they had a history or active cancer, so a very dramatic difference there.



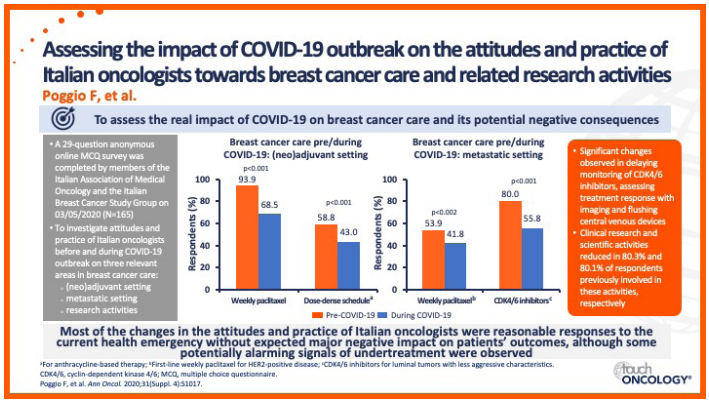
So in terms of their conclusions, so their data came from a large prospective UK series, 10% of hospitalised patients with COVID-19 had a history of cancer. In terms of presenting symptoms there was no difference between whether you had a history or active cancer compared to no cancer. There were significant differences observed in admissions to critical care and access to invasive mechanical ventilation between patients with or without cancer. Patients with a reported history of cancer had a worse survival than those without cancer, and while the absolute survival was worse in older cancer patients the impact of cancer on survival was the greatest in those cancer patients under 50. Obviously like all studies like this there was some missing data, in particular lack of information around cancer type, stage and treatments, but I think this group will publish this data and delve more deeply into it so it's a very important data set. Another study that came from Cincinnati Cancer Centre presented by Wise-Draper looked at a US data set and looked at systemic cancer treatment related outcomes in patients with COVID-19 infection and their objective was to correlate COVID complications and mortality, I think it was 30-day mortality, in patients with cancer and to correlate that with the timing of their cancer treatments. And so they looked at cancer treatment types, so chemotherapy and immunotherapy, targeted treatments and endocrine treatments and they broke it up into less than two weeks of the patient being diagnosed with COVID; two to four weeks from when the patient was diagnosed with COVID; or if the patient was diagnosed with COVID and had to have treatment one to three months prior or three to twelve months prior. And so chemotherapy was by far the most common anti-cancer therapy used with about 30% of patients who had COVID receiving it within two weeks of their treatment; targeted therapy at 39%; and endocrine treatment at 33%. And basically patients with both solid and haematological cancers were included in the study.



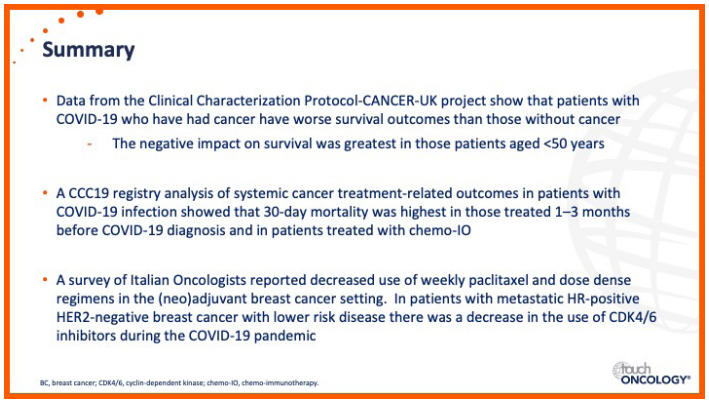
Complications were high across the board regardless of when the patient had their treatment, so hospitalisations of about 55-60%; high in terms of those requiring oxygen: over 40%. In terms of ICU admission it was slightly higher for the 1–3 month group, and mechanical ventilation ranged from 10-14%. In terms of standardised mortality ratios, for those patients who had received treatment within two weeks of developing COVID-19 the standardised mortality ratio was highest for those who received chemotherapy in combination with immunotherapy, so chemoimmunotherapy, with a standardised mortality ratio of 2.13, so higher, it seems to be. In terms of the standardised mortality ratio for endocrine treatment it was 0.64. And what was noted by the presenter was for the patients at one to three months the highest standardised mortality ratio appeared in those patients who received targeted therapies, and that was a hazard ratio of 2.31. And they delved a little bit more into this and it seems to be driven by those patients who received anti-CD20 antibodies, so may be associated with B cell depletion, which would be expected to happen at about that period. So those patients seemed to fair the worst. Now if you look at 30-day mortality by most treatment type it was 30%, so highest for those chemotherapy/immunotherapy group and ranged from 11%, which was the lowest for those on endocrine treatment, or 18% for example for chemotherapy; 14% for immunotherapy alone.



There were some nice studies, this is an Italian study, that looked at how Italian medical oncologists treating breast cancer patients had maybe altered their chemotherapy prescribing during COVID. And so they compared prescribing patterns pre- and post-COVID. So this was a questionnaire they did and they asked medical oncologists, gave them a series of questions and asked how things had changed during COVID.



And so interestingly for those oncologists prescribing weekly paclitaxel at pre-COVID was at 93.9% and that dropped to 68.5% indicating that medical oncologists were trying to, I suppose, keep patients out of the hospital and increasing the intervals between giving chemotherapy. Similarly the number of patients getting dose dense treatment fell. In terms of the metastatic setting, again weekly paclitaxel use fell. But also, particularly for those patients with metastatic disease but lower burdens of disease or those very hormone sensitive luminal tumours with less aggressive characteristics, prescribing CD4K/6 inhibitors for that particular group fell during the COVID surge.



Thank you very much for listening and I hope you're all staying well during COVID and hopefully our next cancer meeting we will be able to meet together in person. Thank you.

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