Data Structures and Sources to Compare Clinical Trials

INITIAL WORK ON JUNE 1-15

TEXT FROM WOLFF IN BLACK
OUR COMMENTS IN GREEN
COMPARISON SOURCES AND TABLES IN PURPLE

Breast cancer is the most prevalent type of malig- nant neoplasm worldwide, and estrogen-receptor (ER)–positive breast cancer is the most common phenotype. Outcomes continue to improve, but many patients present with advanced disease or have recurrence of disease that progressively becomes resistant to endocrine therapy. Efforts to enhance responsiveness to treatment and to overcome primary or acquired resistance through cotargeting of estrogen and cell proliferation– survival signaling pathways led to the recent approval of phosphatidylinositol 3-kinase–Akt–mammalian target of rapamycin (PI3K/Akt/mTOR) and cyclin-dependent kinase 4 and 6 (CDK4 and CDK6) inhibitors for the treatment of advanced ER-positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer.[1-3]

In this issue of the *Journal*, Finn et al.[4] report the results of PALOMA-2 (Palbociclib: Ongoing Trials in the Management of Breast Cancer–2). In a recent issue of the *Journal*, Hortobagyi et al.[5] also reported the interim analysis of the MONALEESA-2 (Mammary Oncology Assessment of LEE011's [Ribociclib's] Efficacy and Safety–2) trial. These studies had similar designs that included treatment of postmenopausal patients with the aromatase inhibitor letrozole plus a CDK4 and CDK6 inhibitor or placebo as first-line therapy for advanced disease.

STAGE 1: COMPARE DESIGN: Points out that they have "similar designs" in terms of similar intentions by both groups -- what does this mean:

- Patients are all postmenopausal -- Cohort inclusion criteria
    - Go to clinicaltrials.gov, look at the Study Design tab, go to the bottom to Eligibility Criteria section, and look at inclusion criteria
    - The inclusion criteria that are about the patient having cancer are not mentioned, the criteria about giving consent are not mentioned. So leave out criteria that have to do with cancer
        - so that leaves "postmenopausal women" and "*Adequate organ and marrow function"*
        - *How do we narrow it down to "postmenopausal women"*
- Treatment with letrozole + CDKI (CDK4 and CDK6 inhibitors) -- Trial treatment
    - Go to clinicaltrials.gov, look at the Study Design tab, look at Arms and Interventions
        - Extract the drug that is not the placebo: PD-0332991
        - You kind of have to know that PD-0332991 is an ORAL CDK 4/6 INHIBITOR
            - Could ask Wikidata (https://www.wikidata.org/wiki/Q15269707)
        - For MONALEESA-2, you need to know LEE011's is Ribociclib, which is also an inhibitor of cyclin D1/CDK4 and CDK6
            - https://www.wikidata.org/wiki/Q27088552

- Treatment for first-line therapy -- Trial treatment
    - Where do we get this information in clinicaltrials.org????
    - Patients have not had treatment before -- Cohort inclusion criteria
    - This is from the inclusion criteria, but WHY does Wolff consider this important????
- Placebo indicates randomized controlled trial -- Trial type (ie controlled experiment, vs randomized, vs double blind, etc)
    - Tabular View, see Descriptive Information: ALlocation = randomized

PALOMA-2 Inclusion Criteria:

- *Adult women with locoregionally recurrent or metastatic disease not amenable to curative therapy.*
- *Confirmed diagnosis of ER positive breast cancer*
- *No prior systemic anti-cancer therapy for advanced ER+ disease.*
- *Postmenopausal women*
- *Measurable disease as per Response Evaluation Criterion in Solid Tumors [RECIST] or bone-only disease*
- *Eastern Cooperative Oncology Group [ECOG] 0-2*
- *Adequate organ and marrow function*
- *Patient must agree to provide tumor tissue*

MONALEESA-2 Inclusion Criteria:

- *Women with advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy.*
- *Patient is postmenopausal. Postmenopausal status is defined either by:*
    - *Prior bilateral oophorectomy*
    - *Age ≥60*
    - *Age <60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression) and FSH and estradiol in the postmenopausal range per local normal range Note: For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol are needed to ensure postmenopausal status. Ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist (LH-RHa) (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression in this trial.*
- *No prior systemic anti-cancer therapy for advanced disease.*
- *Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive breast cancer by local laboratory.*
- *Patient has HER2-negative breast cancer defined as a negative in situ hybridization test or an IHC status of 0, 1+ or 2+. If IHC is 2+, a negative in situ hybridization (FISH, CISH, or SISH) test is required by local laboratory testing.*

- *Patient must have either:*

  • Measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria (Tumor lesions previously irradiated or subjected to other locoregional therapy will only be considered measurable if disease progression at the treated site after completion of therapy is clearly documented).

  OR

  • If no measurable disease is present, then at least one predominantly lytic bone lesion must be present (Patients with no measurable disease and only one predominantly lytic bone lesion that has been previously irradiated are eligible if there is documented evidence of disease progression of the bone lesion after irradiation).

- *Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1*

PALOMA-2 & MONALEESA-2 ideal structured assertions (2 COLUMNS)
may be provided when clinicaltrials.gov

PALOMA-2	MONALEESA-2	PALOMA-2 Paper	MONALEESA-2 Paper	WOLFF COMPARISON	Comment
Postmenopausal women ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/study/NCT01740427?cond=PALOMA-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 4)***	*Patient is postmenopausal. Postmenopausal status is defined either by:* • *Prior bilateral oophorectomy* • *Age ≥60* • *Age <60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression) and FSH and estradiol in*	Background line 2	Methods line 3	Both have postmenopausal women	

	the postmenopausal range per local normal range Note: For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol are needed to ensure postmenopausal status. Ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist (LH-RHa) (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression in this trial. ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/NCT01958021?cond=monaleesa-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 2)***				

Eastern Cooperative Oncology Group [ECOG] 0-2 ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/study/NCT01740427?cond=PALOMA-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 6)***	*Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1* ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/NCT01958021?cond=monaleesa-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 7)***	Table 1. Patient Demographic and Clinical Characteristics.	Table 1. Patient Demographic and Clinical Characteristics	**Not considered important to mention**	**Standard practice is to take in patients to clinical trials that have lower ECOG: 0: completely well the higher the worse**
Adult women with locoregionally recurrent or metastatic disease not amenable to curative therapy ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/study/NCT01740427?cond=PALOMA-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 1)***	*Women with advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy* ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/NCT01958021?cond=monaleesa-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 1)***	*Study Design, line 11*	*Methods, line 4*	*“many patients present with advanced disease or have recurrence of disease that progressively becomes resistant to endocrine therapy”*	
Confirmed diagnosis of ER positive breast cancer	*Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or*	*Background, line 3,4*	*Background, line 3*	*for the “treatment of advanced ER-positive, human epidermal growth factor re- ceptor 2 (HER2)–negative breast cancer”*	

(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/study/NCT01740427?cond=PALOMA-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 2)	*progesterone receptor positive breast cancer by local laboratory* *&* *Patient has HER2-negative breast cancer defined as a negative in situ hybridization test or an IHC status of 0, 1+ or 2+. If IHC is 2+, a negative in situ hybridization (FISH, CISH, or SISH) test is required by local laboratory testing* ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/NCT01958021?cond=monaleesa-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 4,5)***				
No prior systemic anti-cancer therapy for advanced ER+ disease ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/study/NCT01740427?***	*No prior systemic anti-cancer therapy for advanced disease* ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/NCT01958021?cond=monaleesa-***	*Methods, line 2,3*	*Methods, line 4*	*These studies had similar designs that included treatment of postmenopausal patients with the aromatase inhibitor letrozole plus a CDK4 and CDK6 inhibitor or placebo as first-line therapy for advanced disease.*	

cond=PALOMA-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 3)	***2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 3)***				
Measurable disease as per Response Evaluation Criterion in Solid Tumors [RECIST] or bone-only disease ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/study/NCT01740427?cond=PALOMA-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 5)***	*Patient must have either:* *• Measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria (Tumor lesions previously irradiated or subjected to other locoregional therapy will only be considered measurable if disease progression at the treated site after completion of therapy is clearly documented).* *OR* *• If no measurable disease is present, then at least one predominantly lytic bone lesion must be present (Patients with no measurable disease and only one predominantly lytic bone lesion that has been previously irradiated are eligible if there is documented*	**and mea-surable disease according to RECIST, version 1.1, or lesions only in the bone** **(*PROVENANCE:* Patients, line 26-28)**	**“Patients had either measurable disease (according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1)21 or at least one predominantly lytic bone lesion, along with** **an Eastern Cooperative Oncology Group perfor-mance status22 of 0 or 1 (on a 5-point scale on** **which a higher score indicates greater disability) and adequate bone marrow and organ function.”** **(*PROVENANCE: patients, line 5-12*)**	**Not considered important to mention**	

	evidence of disease progression of the bone lesion after irradiation) ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/NCT01958021?cond=monaleesa-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 6)***				
Adequate organ and marrow function ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/study/NCT01740427?cond=PALOMA-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 7)***	**Not considered important to mention**	**Patients, line 22**	**Patients line 12**	**Not considered important to mention**	
Patient must agree to provide tumor tissue ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/study/NCT01740427?cond=PALOMA-***	**Not considered important to mention**	**Not considered important to mention**	**Not considered important to mention**	**Not considered important to mention**	

2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 8)					

Approximately 80% of the patients were white, at least half had visceral disease, and half had received prior adjuvant chemotherapy. A third of the patients presented with advanced disease.

STAGE 2: REFLECT ON ACCIDENTAL SIMILARITIES: Additional points of "similar designs" by coincidence:

- Most patients are white-- Cohort additional statistical properties
  - Not mentioned in both trials in clinicaltrials.gov, mentioned in papers, will check it later
- Half had visceral disease -- Cohort additional statistical properties
  - Mentioned in Exclusion criteria in PALOMA-2:
    - patients with advanced, symptomatic, visceral spread that are at risk of life threatening complication in the short term

  Comment: Why is it excluded in PALOMA-2 but included in Wolff's paper????
- Half received adjuvant chemo -- Cohort additional statistical properties
  - Mentioned in MONALEESA-2:
    - Inclusion Criteria:
      - *Age <60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression)*
    - Exclusion Criteria:
      - *Patient who received any prior systemic anti-cancer therapy (including hormonal therapy and chemotherapy) for advanced breast cancer*

  Comment: Conflict????
- A third had advanced disease -- Cohort additional statistical properties
  - See table above

PALOMA-2 Exclusion Criteria:

- *Confirmed diagnosis of HER2 positive disease*
- *Patients with advanced, symptomatic, visceral spread that are at risk of life threatening complication in the short term*
- *Known uncontrolled or symptomatic CNS metastases*
- *Prior (neo)adjuvant treatment with letrozole or anastrozole with DFI ≤ 12-months from completion of treatment.*
- *Prior treatment with any CDK 4/6 inhibitor.*

MONALEESA-2 Exclusion Criteria:

- *Patient who received any CDK4/6 inhibitor.*
- *Patient who received any prior systemic anti-cancer therapy (including hormonal therapy and chemotherapy) for advanced breast cancer*
  Note:
  - *Patients who received (neo) adjuvant therapy for breast cancer are eligible. If the prior neo (adjuvant) therapy included letrozole or anastrozole the disease free interval must be greater than 12 months from the completion of treatment until randomization.*
  - *Patients who received ≤ 14 days of letrozole or anastrozole for advanced disease prior to randomization are eligible.*
  - *Any prior (neo) adjuvant anti-cancer therapy must be stopped at least 5 half-lives or 7 days, whichever is longer, before randomization*
- *Patient is concurrently using other anti-cancer therapy.*
- *Patient has a concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer.*
- *Patient has active cardiac disease or a history of cardiac dysfunction including any of the following:*
  - *History of angina pectoris, symptomatic pericarditis, or myocardial infarction within 12 months prior to study entry*
  - *History of documented congestive heart failure (New York Heart Association functional classification III-IV)*
  - *Documented cardiomyopathy*
  - *Patient has a Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)*
  - *History of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality in the previous 12 months.*
  - *On screening, any of the following cardiac parameters:*
    - *bradycardia (heart rate < 50 at rest), tachycardia (heart rate > 90 at rest), PR interval > 220 msec, QRS interval >109 msec, or QTcF >450 msec.*
    - *Systolic blood pressure >160 or <90 mmHg*
- *Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior start if the treatment:*
  - *That are known strong inducers or inhibitors of CYP3A4.*
  - *That have a known risk to prolong the QT interval or induce Torsades de Pointes.*
  - *That have a narrow therapeutic window and are predominantly metabolized through CYP3A4.*
  - *Herbal preparations/medications*

PALOMA-2	MONALEESA-2	Comments

Confirmed diagnosis of HER2 positive disease	*N/A*	*Confirmed diagnosis of HER2 positive disease*
Patients with advanced, symptomatic, visceral spread that are at risk of life threatening complication in the short term	*N/A*	*Patients with* 1. *advanced spread that are at risk of life threatening complication in the short term* 2. *symptomatic spread that are at risk of life threatening complication in the short term* 3. *visceral spread that are at risk of life threatening complication in the short term*
Known uncontrolled or symptomatic CNS metastases	*N/A*	1. *uncontrolled CNS metastases* 2. *or symptomatic CNS metastases*
Prior (neo)adjuvant treatment with letrozole or anastrozole with DFI ≤ 12-months from completion of treatment.	*Patients who received (neo) adjuvant therapy for breast cancer are eligible. If the prior neo (adjuvant) therapy included letrozole or anastrozole the disease free interval must be greater than 12 months from the completion of treatment until randomization.* *Patients who received ≤ 14 days of letrozole or anastrozole for advanced disease prior to randomization are eligible.* *Any prior (neo) adjuvant anti-cancer therapy must be stopped at least 5 half-lives or 7 days, whichever is longer, before randomization*	1. *Prior (neo)adjuvant treatment* 2. *with letrozole* 3. *or with anastrozole* 4. *with DFI ≤ 12-months from completion of treatment* 5. *Any prior (neo) adjuvant anti-cancer therapy must be stopped at least 5 half-lives or 7 days, whichever is longer, before randomization*
Prior treatment with any CDK 4/6 inhibitor.	*Patient who received any CDK4/6 inhibitor.*	*Prior treatment with any CDK 4/6 inhibitor.*

N/A	*Patient is concurrently using other anti-cancer therapy*	*Patient is concurrently using other anti-cancer therapy*
N/A	*Patient has a concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer.*	1. *Patient has a concurrent malignancy* 2. *or malignancy within 3 years of randomization,* 3. *with the exception of adequately treated* 4. *basal cell carcinoma* 5. *or squamous cell carcinoma* 6. *non-melanomatous skin cancer* 7. *or curatively resected cervical cancer*
N/A	*Patient has active cardiac disease or a history of cardiac dysfunction including any of the following:* ○ *History of angina pectoris, symptomatic pericarditis, or myocardial infarction within 12 months prior to study entry* ○ *History of documented congestive heart failure (New York Heart Association functional classification III-IV)* ○ *Documented cardiomyopathy* ○ *Patient has a Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)* ○ *History of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality in the previous 12 months.* ○ *On screening, any of the following cardiac parameters:* ■ *bradycardia (heart rate < 50 at rest), tachycardia (heart rate > 90 at rest), PR interval > 220 msec, QRS interval >109 msec, or QTcF >450 msec.*	1. *History of angina pectoris within 12 months prior to study entry* 2. *symptomatic pericarditis within 12 months prior to study entry* 3. *or myocardial infarction within 12 months prior to study entry* 4. *History of documented congestive heart failure (New York Heart Association functional classification III-IV)* 5. *Documented cardiomyopathy* 6. *Patient has a Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan* 7. *or echocardiogram (ECHO)* 8. *History of any cardiac arrhythmias in the previous 12 months.* 9. *or conduction abnormality in the previous 12 months.* 10. *bradycardia (heart rate < 50 at rest),* 11. *tachycardia (heart rate > 90 at rest)* 12. *PR interval > 220 msec* 13. *QRS interval >109 msec,* 14. *or QTcF >450 msec* 15. *Systolic blood pressure >160* 16. *or Systolic blood pressure <90 mmHg*

	■ *Systolic blood pressure >160 or <90 mmHg*	
N/A	*Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior start if the treatment:* ○ *That are known strong inducers or inhibitors of CYP3A4.* ○ *That have a known risk to prolong the QT interval or induce Torsades de Pointes.* ○ *That have a narrow therapeutic window and are predominantly metabolized through CYP3A4.* ○ *Herbal preparations/medications*	1. *That are known strong inducers or inhibitors of CYP3A4.* 2. *That have a known risk to prolong the QT interval* 3. *or have induce Torsades de Pointes.* 4. *That have a narrow therapeutic window.* 5. *and are predominantly metabolized through CYP3A4* 6. *Herbal preparations/medications*

Information from the papers, from the "Patient Demographics and Clinical Characteristics" table:
(above 50%)
add page number

PALOMA-2	MONALEESA-2	WOLFF COMPARISON	Comment
From paper table 1: 77.5%	*From paper table 1: 80.5% and 83.8%*	Approximately 80% of the patients were white	
From paper table 1: 48.2% and 49.5%	*From paper table 1: 59% and 58.7%*	Approximately at least half had visceral disease (the sites of metastatic spread)	*In cancer it is important to distinguish visceral vs bone vs neither*
From paper table 1: 48% and 49.1%	*From paper table 1: 43.7% and 43.4%*	Approximately half had received prior adjuvant chemotherapy	

Patients: *line 14-15* *"37.2% had newly diagnosed advanced breast cancer"*	*patient characteristics:* *line 11-13* *"A total of 227 patients (34.0%) had newly diagnosed advanced or metastatic disease"*	*A third had advanced disease*	
Disease stage, *Disease-free interval* *Disease site* *No. of disease sites*	*Disease stage,* *Disease-free interval* *Metastatic sites*	*Patient demographics table has many entries that are not mentioned in Wolff*	*Other entries not mentioned*

Information from clinicaltrials.gov under, find the Study Design tab, go to the bottom to Eligibility Criteria section, and look at exclusion criteria:

Advanced disease here is not the same as "a third had advanced disease". See table above

PALOMA-2	MONALEESA-2	WOLFF COMPARISON	Comment
advanced disease	*advanced disease*	*A third had advanced disease*	*Advanced disease mentioned in both study details→ study design, but Wolff mentioned only a third with advanced disease.* *????*

The observed efficacy and toxicity outcomes in PALOMA-2 and MONALEESA-2 suggest a drug- class–specific effect.

STAGE 3: COMPARE TRIAL OUTCOMES: Analyze if they had "similar outcomes":

- Drug-class-specific effect
    - Effect is "comparable" -- Generalization of trial outcomes

- Primary Outcome: Progression Free Survival (PFS)
- Secondary outcome: see table below
  - Drug used is in same class -- Generalization of trial outcomes to the drug class (they both used CDKI, one used Palbociclib and the ther used Ribociclib)

PFS comparison: from clinicaltrials.gov

PALOMA-2	MONALEESA-2	PALOMA-2 paper	MONALEESA-2 paper	WOLFF	NOTES
TREATMENT GROUP: Participants received letrozole 2.5 milligram (mg) orally QD (once daily) combined with palbociclib 125 mg QD for 21 days of every-28-day cycle, followed by 7 days off treatment.	TREATMENT GROUP: LEE011 (ribociclib) oral (3 weeks on/ 1 week off) in combination with oral once daily letrozole. 600mg LEE011 QD + 2.5 mg letrozole QD	Study design. line 1-6	Methods: line 5-7		How do we infer “drug-class-specific effect” from the notes on the left
CONTROL GROUP: Participants received letrozole 2.5 mg orally QD combined with placebo QD for 21 days of every-28-day cycle, followed by 7 days off treatment.	Matching ribociclib placebo, control drug administered orally (3 weeks on/ 1 week off) in combination with oral once daily letrozole. 600mg LEE011 placebo QD + 2.5 mg letrozole	Study design line 1-6	Methods: line 5-7		
TREATMENT GROUP TOTAL: 444	TREATMENT GROUP TOTAL: 334	Table 1	Table 1		

CONTROL GROUP TOTAL: 222	CONTROL GROUP TOTAL: 334	Table 1	Table 1		
Median FOR TREATMENT GROUP: 24.8 [1]	Median FOR TREATMENT GROUP: NA [1] (19.3 to NA)	Results, line 1	Efficacy of Ribociclib plus Letrozole, line 9		
Median FOR CONTROL GROUP: 14.5 (12.9 to 17.1)	Median FOR CONTROL GROUP: 14.7 (13.0 to 16.5)	Results, line 3	Efficacy of Ribociclib plus Letrozole, line 10		

Secondary outcome comparison:

Comments: Since MONALEESA-2 Outcome Measure Data are Not Reported on clinicaltrials.gov, maybe the most useful effect so far is the primary outcome: PFS. I still listed and compared these two trials' secondary outcomes for reference in the future:

PALOMA-2	MONALEESA-2	Wolff's paper	Comment: Similarity	Comment: Difference	
Objective Response as Assessed by the Investigator	Overall Response Rate (ORR) as Per Investigator Assessment	Not considered important to mention	Both defined as overall complete response (CR) or partial response (PR) according to the RECIST v1.1. Both mentioned All target nodes must decrease to normal size (short axis <10mm). PR(partial response): ≥30%	Time frame: PALOMA-2: From randomization until end of treatment (up to approximately 2.5 years) for PALOMA-2 and MONALEESA-2: Up to approximately 20 months	
Objective Response: Patients With Measurable Disease at	Not mentioned		N/A	PALOMA-2: analysis population description are	Important ???

Baseline as Assessed by the Investigator				different for the two ORs: First:ITT population or full analysis set included all participants who were randomized, with study medication, regardless of whether participants received study medication or received a different drug from that to which they were randomized. Second: Patients who had measurable disease at baseline. A total of 338 and 171 patients had measurable disease at baseline in the palbociclib plus letrozole and placebo plus letrozole arms, respectively.	
Duration of Response (DR)	Overall Survival (OS)		Both mention the time from the first documentation of objective tumor response (CR or PR) to death due to any cause	PALOMA-2 also mention time from the first documentation of objective tumor response (CR or PR) to the first documentation of disease progression or to death due to any cause, whichever occurs first	
Disease Control (DC)/Clinical Benefit Response (CBR)	Clinical Benefit Rate (CBR)		defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR) or stable disease (SD) lasting more than 24 weeks as defined in RECIST 1.1.		
Not mentioned	Time to Definitive		N/A	N/A	

	Deterioration of ECOG Performance Status in One Category of the Score				
Not mentioned	Safety and Tolerability of LEE011		N/A	N/A	
Not mentioned	Time to Definitive 10% Deterioration in the Global Health Status/Quality of Life (QOL) Scale Score of the EORTC QLQ-C30		N/A	N/A	
Tumor Tissue Biomarkers, Including Genes (eg, Copy Numbers of CCND1, CDKN2A), Proteins (eg, Ki67, pRb), and RNA Expression (eg, cdk4, cdk6): Protein Biomarker Analyses by Using Immunohistochemistry Are Presented	Not mentioned		N/A	N/A	
Corrected QT Interval (QTc) Time-matched Change From Baseline on Cycle 1 Day 14	Not mentioned		N/A	N/A	
Corrected QT Interval (QTc)	QTc Interval		Both talked about the QT interval	PALOMA-2: Corrected QT Interval (QTc) Time-matched Change From Baseline on Cycle 1 Day 14 MONALEESA-2: Time between the start of the Q wave and the end of the T wave corrected for heart rate	
Observed Plasma Trough Concentration (Ctrough) at Steady-State	Not mentioned		N/A	N/A	

Change From Baseline Between Treatment Comparison in Euro Quality of Life (EQ-5D) Index	Not mentioned		N/A	N/A	
Change From Baseline Between Treatment Comparison in Functional Assessment of Cancer Therapy -Breast (FACT-B)	Not mentioned		N/A	N/A	
Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs; All Causalities)	Not mentioned		N/A	N/A	

The addition of palbociclib to letrozole in PALOMA-2 resulted in longer median progression-free survival than progression-free survival with letrozole plus placebo (24.8 months vs. 14.5 months; hazard ratio for disease progression or death, 0.58; 95% confidence inter- val [CI], 0.46 to 0.72). In the MONALEESA-2 trial, the addition of ribociclib to letrozole resulted in a higher rate of progression-free survival at 18 months than the rate with letrozole and placebo (63.0% vs. 42.2%; hazard ratio for disease progression or death, 0.56; 95% CI, 0.43 to 0.72).

- More detailed comparison of outcomes in terms of “effect”
  - Compares how survival was measured
    - PALOMA-2 reports the median survival (which is the usual thing to report) of 24.8 months vs 14.5 months
      - Can find on clinicaltrials.gov, under study results tab, primary outcome
    - MONALEESA-2 has progression-free survival at 18 months is 63% with Ribociclib treatment vs 42% placebo group [Ribociclib never reaches 50% so cannot report median]
      - survival rate with Ribociclib: 19.3 months- NA(N/A = not estimable as median PFS was not reached in the ribociclib arm)
      - survival rate with placebo: median 14.7 months
  - Hazard ratio is 0.58 vs 0.56 -- almost the same
    - Can find both under study results tab, primary outcome, statistical analysis 1: 0.576 vs 0.556
  - Confidence is 95% 0.46-0.72 and 95% 0.43-0.72 -- almost the same
    - Can find both under study results tab, primary outcome, statistical analysis 1: 95% 0.463 to 0.718 and 95% 0.429 to 0.720

PALOMA-2	MONALEESA-2	PALOMA-2 paper	MONALEESA-2 paper	WOLFF	NOTES
Median FOR TREATMENT GROUP: 24.8 [1] Median FOR CONTROL GROUP: 14.5 (12.9 to 17.1) *(PROVENANCE: https://clinicaltrials.gov/ct2/show/results/NCT01740427?cond=PALOMA-2&draw=2&rank=1&view=results* *Study Results, Primary Outcome*	Median FOR TREATMENT GROUP: NA [1] (19.3 to NA) Median FOR CONTROL GROUP: 14.7 (13.0 to 16.5) *(PROVENANCE: https://clinicaltrials.gov/ct2/show/results/NCT01958021?cond=monaleesa-2&draw=2&rank=1* *Study Results, Primary Outcome*	Results, line 1,3	Efficacy of Ribociclib plus Letrozole, line 9,10 Figure 1, comparison of PFS at month=18	"PALOMA-2 resulted in longer median progression-free survival than progression-free survival with letrozole plus placebo (24.8 months vs. 14.5 months;" " In the MONALEESA-2 trial, the addition of ribociclib to letrozole resulted in a higher rate of progression-free survival at 18 months than the rate with letrozole and placebo (63.0% vs. 42.2%; "	
Hazard Ratio: 0.576 *(PROVENANCE: https://clinicaltrials.gov/ct2/show/results/NCT01740427?cond=PALOMA-2&draw=2&rank=1&view=results* *Study Results, Primary Outcome, Statistical Analysis*	Hazard Ratio: 0.556 *(PROVENANCE: https://clinicaltrials.gov/ct2/show/results/NCT01958021?cond=monaleesa-2&draw=2&rank=1* *Study Results, Primary Outcome, Statistical Analysis*	Results, line 4	Methods, line 11	PALOMA-2: "hazard ratio for disease progression or death, 0.58;" MONALEEASA-2: "hazard ratio for disease progression or death, 0.56; "	

(2-Sided) 95% 0.463 to 0.718 *(PROVENANCE: https://clinicaltrials.gov/ct2/show/results/NCT01740427?cond=PALOMA-2&draw=2&rank=1&view=results* *Study Results,* *Primary Outcome,* *Statistical Analysis*	(2-Sided) 95% 0.429 to 0.720 *(PROVENANCE: https://clinicaltrials.gov/ct2/show/results/NCT01958021?cond=monaleesa-2&draw=2&rank=1* *Study Results,* *Primary Outcome,* *Statistical Analysis*	Results, line 4	Results, line 4,5	PALOMA-2:"95% confidence inter- val [CI], 0.46 to 0.72)" MONALEESA-2: "95% CI, 0.43 to 0.72)."	

The data are also striking because approximately half the patients had also received prior adjuvant endocrine therapy (with a disease-free interval of at least 12 months); approximately 80% of these patients had received tamoxifen and approximately 55% had received an aromatase inhibitor.

comparison in table

STAGE 4: REFLECT ON OUTCOMES

UNCLEAR HOW TO INTERPRET WHAT HE IS SAYING HERE

- Seems to point out that both drugs had similar outcomes even if the patient pools were so different among the two trials (unclear if he is doing this based on quantitative similarity, or cohorts diversity?):
  - "Striking" that results are so close in values? -- Compare effects quantitatively
    - Check table under stage 3 about primary outcome
  - "Striking" that the patient pool was so different in prior treatments? -- Cohort additional statistical properties
    - Comments: from the criteria comparison from clinicaltrials.gov, not very different
  - "Striking" indicates that he concludes that these are good things?
    - Comments: probably because the hazard ratio is less than 1?

Comments: so different probably because of their dose difference and time frame??????
Create a table containing all results from stages before and find what Wolff thinks striking.
Please see table above

The PALOMA-2 and MONALEESA-2 trials remain blinded, and overall survival has not been reported.

Comments: PALOMA-2 has already reported PFS but MONALEESA-2 didn't report PFS for patients who received ribociclib.

- Compares if the outcomes are reported as final or interim results:
    - Notes that the trials are still ongoing and we should look at the information with that in mind
        - "Remain blinded" means that the patients still don't know what they got. If it was unblinded, the patients would know and so they may make decisions that influence the ultimate outcomes (eg if they don't get the experimental therapy they may quit the trial)
            - (BTW MONALEESA-2 is double blinded)
            - Both of the two trials are double-blinded from description on clinicaltrials.gov. Study Design tab, study design, official tab
        - "Unreported survival" means that we have progression data but not final data.

However, it is notable that 70% of the patients in both studies had a response or had prolonged stable disease with letrozole alone, as compared with 80 to 85% of patients who were treated with a CDK4 and CDK6 inhibitor.

- Compares the details of the interim results reported by both
    - Despite no final reporting yet, we still see efficacy and that is notable
        - Control group (letrozole alone) is 70% for both studies vs case group (Letrozole + CDKI) that is 80-85% across trials -- Compare case and control, points out 10-15% difference between case and control in both trials already demonstrates some efficacy

The findings of PALOMA-2 affirm the decision by the Food and Drug Administration (FDA) to grant accelerated approval for palbociclib, which was based on the results of PALOMA-1,[6] and the findings of PALOMA-3 led to the recent approval of palbociclib in combination with fulvestrant for the treatment of patients who had disease progression during endocrine therapy.[7]

- Reflects on different variants of the trial and their efficacy:
    - That efficacy result has been reproduced across both PALOMA-2 and MONAL-2 , leading to:
        - PALOMA-1 led to FDA accelerated approval,
        - PALOMA-2 affirmed that decision, and
    - PALOMA-3 led to the approval of a second-line treatment with the drug plus fulvestrant.

NOTE: fulvestrant and letrozole are in the same drug class (HRT)

A third of the patients in the PALOMA-2 and MONALEESA-2 trials required one or two dose reductions (usually early in the treatment period). Infection, fatigue, alopecia, and gastrointestinal symptoms including stomatitis were common and resembled mild effects of chemotherapy.

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WEEK OF JUNE 15, 2020: DESIGN THE PROPERTIES THAT WE WILL USE TO DESCRIBE THE CLINICAL TRIALS

Types of reasoning:

Type I: Properties that have simple values/functions

Type II: entities with structure of some features

Type III: entities with more complicated structure with more features

Cohort Ontology: https://docs.google.com/document/d/1OkheUVnzp0s75Tk6nGnJBZW85NWWmLxCBRWTA8Y5UIs/edit

(resistant to endocrine therapy?
curative: only for non-metastatic patients)

stage was defined at initially diagnose, it won't change even get worse

PALOMA-2	MONALEESA-2	Wolff's comments	Type	Property

Postmenopausal women ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/study/NCT01740427?cond=PALOMA-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 4)***	*Patient is postmenopausal. Postmenopausal status is defined either by:* • *Prior bilateral oophorectomy* • *Age ≥60* • *Age <60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression) and FSH and estradiol in the postmenopausal range per local normal range Note: For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol are needed to ensure postmenopausal status. Ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist (LH-RHa) (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression in this trial.* ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/NCT01958021?cond=monaleesa-2&draw=2&rank=1, Study Details,***	Both have postmenopausal women	Type I : postmenopausal? 1	CT/cohort/demographic: postmenopausal? 1

	Eligibility, Criteria, Inclusion Criteria, Bullet 2)			
Eastern Cooperative Oncology Group [ECOG] 0-2 ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/study/NCT01740427?cond=PALOMA-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 6)***	*Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1* ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/NCT01958021?cond=monaleesa-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 7)***	**Not considered important to mention**	**Type I :** *[ECOG]: 0-2*	CT/cohort/demographic: ECOG status: 0-2
Adult women with locoregionally recurrent or metastatic disease not amenable to curative therapy ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/study/NCT01740427?cond=PALOMA-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 1)***	*Women with advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy* ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/NCT01958021?cond=monaleesa-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 1)***	*"many patients present with advanced disease or have recurrence of disease that progressively becomes resistant to endocrine therapy"* *RECIST: 1. tumor shrink* *2. change of therapy*	Type II : Patients with: 1. *advanced disease or recurrence disease* 2. *this disease progressively becomes resistant to endocrine therapy*	CT/cohort/disease: breast cancer 1. metastatic? (1. newly diagnosed 2. progressed to) 2. locoregionally recurrent?
Confirmed diagnosis of ER positive breast cancer ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/***	*Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive breast cancer by local laboratory*	*for the "treatment of advanced ER-positive, human epidermal growth factor re- ceptor 2 (HER2)–negative breast cancer"*	Type II: ER positive, HER2 negative	CT/cohort/disease: breast cancer 1. ER positive or negative? 2. HER2 positive or negative?

study/NCT01740427?cond=PALOMA-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 2)	*&* *Patient has HER2-negative breast cancer defined as a negative in situ hybridization test or an IHC status of 0, 1+ or 2+. If IHC is 2+, a negative in situ hybridization (FISH, CISH, or SISH) test is required by local laboratory testing* ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/NCT01958021?cond=monaleesa-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 4,5)***			
No prior systemic anti-cancer therapy for advanced ER+ disease ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/study/NCT01740427?cond=PALOMA-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 3)***	*No prior systemic anti-cancer therapy for advanced disease* ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/NCT01958021?cond=monaleesa-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 3)***	*These studies had similar designs that included treatment of postmenopausal patients with the aromatase inhibitor letrozole plus a CDK4 and CDK6 inhibitor or placebo as first-line therapy for advanced disease.*	Type II: 1. No prior systemic therapy 2. use CDK4 and CDK6 as first-line therapy	CT/cohort/patient history: 1. prior systemic anti-cancer therapy for advanced disease? (is advanced disease = advanced ER+ disease?) - No == first-line
Measurable disease as per Response Evaluation Criterion in Solid Tumors [RECIST] or bone-only disease	*Patient must have either:* *• Measurable disease, i.e., at least one measurable lesion as per*	**Not considered important to mention**	Type II: 1. Measurable disease	CT/cohort/disease:breast cancer RECIST measurable (property of breast cancer)

(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/study/NCT01740427?cond=PALOMA-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 5)	*RECIST 1.1 criteria (Tumor lesions previously irradiated or subjected to other locoregional therapy will only be considered measurable if disease progression at the treated site after completion of therapy is clearly documented).* *OR* *• If no measurable disease is present, then at least one predominantly lytic bone lesion must be present (Patients with no measurable disease and only one predominantly lytic bone lesion that has been previously irradiated are eligible if there is documented evidence of disease progression of the bone lesion after irradiation)* ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/NCT01958021?cond=monaleesa-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 6)***		2. *or at least one predominantly lytic bone lesion must be present*	
Adequate organ and marrow function ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/study/NCT01740427?cond=PALO***	**Not considered important to mention**	**Not considered important to mention**	Type II: *Adequate organ and marrow function*	CT/cohort/disease: 1. adequate organ function? 2. adequate marrow function?

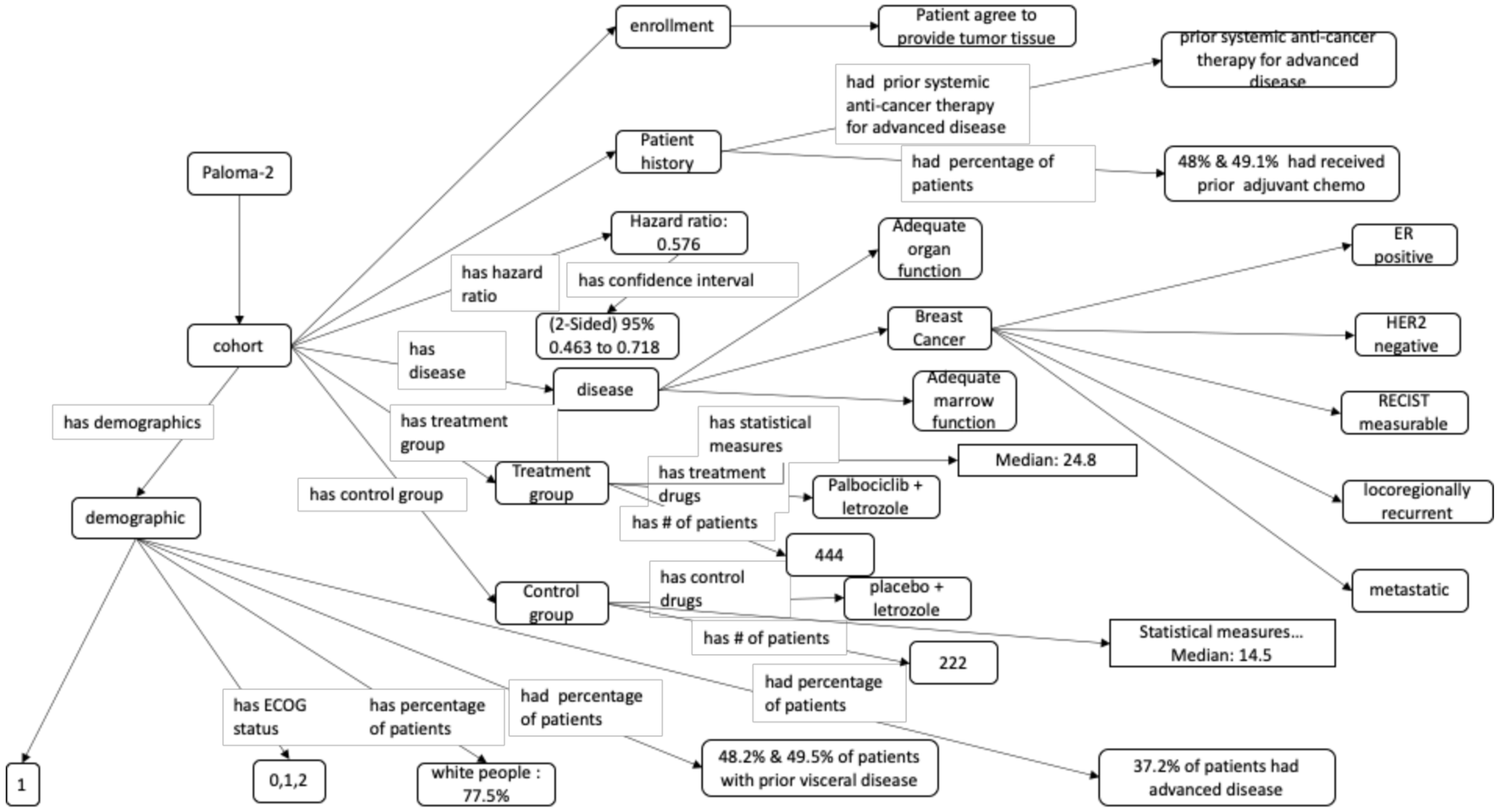
MA-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 7)				
Patient must agree to provide tumor tissue ***(PROVENANCE: clincatrials,gov, https://clinicaltrials.gov/ct2/show/study/NCT01740427?cond=PALOMA-2&draw=2&rank=1, Study Details, Eligibility, Criteria, Inclusion Criteria, Bullet 8)***	**Not considered important to mention**	**Not considered important to mention**	Type I: Patients agree? 1	CT/cohort/enrollment FDA doesn't require tumor tissue
Patients Statistics from papers table 1			Type III: Many characteristics of patients from both trials	subject characteristics
From paper table 1: 77.5% *(Provenance:* *paper table 1* *pg 1928)*	*From paper table 1: 80.5% and 83.8%* *(Provenance:* *paper table 1* *pg 1742)*	Approximately 80% of the patients were white	Type I: White Patients: ~80%	CT/cohort/demographics: percentage of white?
From paper table 1: 48.2% and 49.5% *(Provenance:* *paper table 1*	*From paper table 1: 59% and 58.7%* *(Provenance:*	Approximately at least half had visceral disease (the sites of metastatic spread) (visceral is part of metastatic)	Type I Patients have visceral disease: >=50%	CT/cohort/disease or demographics? percentage of patients with prior visceral disease?

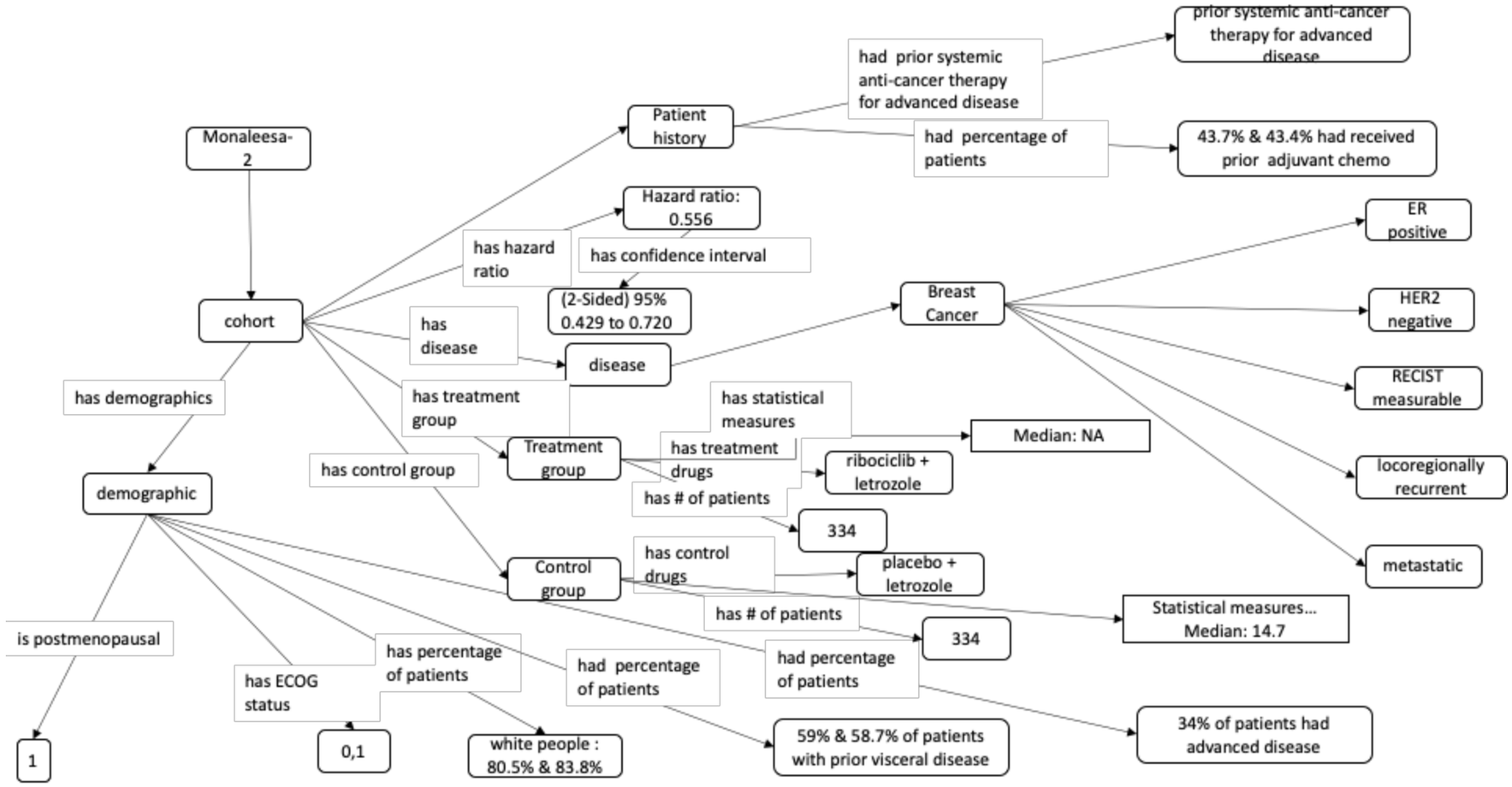
pg 1928)	*paper table 1* *pg 1742)*			
From paper table 1: 48% and 49.1% *(Provenance:* *paper table 1* *pg 1928)*	*From paper table 1: 43.7% and 43.4%* *(Provenance:* *paper table 1* *pg 1742)*	Approximately half had received prior adjuvant chemotherapy	Type I Patients have received prior adjuvant chemotherapy: 50%	CT/cohort/demographic or patient history? percentage of patients who had received prior adjuvant chemo?
"37.2% had newly diagnosed advanced breast cancer" *(Provenance:* *Paper pg 1927* *Patients:* *line 14-15)*	*"A total of 227 patients (34.0%) had newly diagnosed advanced or metastatic disease"* *(Provenance:* *paper pg 1741* *patient characteristics:* *line 11-13)*	*A third had advanced disease*	Type I Patients had advanced disease: 1/3	CT/cohort/disease or demographics? percentage of patients who had advanced disease?
Disease stage, *Disease-free interval* *Disease site* *No. of disease sites* *(Provenance:* *paper table 1*	*Disease stage,* *Disease-free interval* *Metastatic sites* *(Provenance:* *paper table 1* *pg 1742)*	*Patient demographics table has many entries that are not mentioned in Wolff*	Type I *Disease stage,* *Disease-free interval* *Disease site* *No. of disease sites*	CT/cohort/disease or demographics?

pg 1928)				
TREATMENT GROUP: Participants received letrozole 2.5 milligram (mg) orally QD (once daily) combined with palbociclib 125 mg QD for 21 days of every-28-day cycle, followed by 7 days off treatment. *(PROVENANCE: https://clinicaltrials.gov/ct2/show/results/NCT01740427?cond=PALOMA-2&draw=2&rank=1&view=results Study Results, Primary Outcome, Outcome measure data)*	TREATMENT GROUP: LEE011 (ribociclib) oral (3 weeks on/ 1 week off) in combination with oral once daily letrozole. 600mg LEE011 QD + 2.5 mg letrozole QD *(PROVENANCE: https://clinicaltrials.gov/ct2/show/results/NCT01958021?cond=monaleesa-2&draw=2&rank=1 Study Results, Primary Outcome, Outcome measure data)*	Not mentioned in Wolff's paper	Type III: more sophisticated analysis, to generalize the type of drugs Note: Initially we won't consider the dosage and time frame	CT/cohort: has diagnostic group/treatment group: 1. treatment: drugs: letrozole + palbociclib letrozole + ribociclib
CONTROL GROUP: Participants received letrozole 2.5 mg orally QD combined with placebo QD for 21 days of every-28-day cycle, followed by 7 days off treatment. *(PROVENANCE: https://clinicaltrials.gov/ct2/show/results/NCT01740427?cond=PALOMA-2&draw=2&rank=1&view=results Study Results, Primary Outcome, Outcome measure data)*	Matching ribociclib placebo, control drug administered orally (3 weeks on/ 1 week off) in combination with oral once daily letrozole. 600mg LEE011 placebo QD + 2.5 mg letrozole *(PROVENANCE: https://clinicaltrials.gov/ct2/show/results/NCT01958021?cond=monaleesa-2&draw=2&rank=1 Study Results, Primary Outcome, Outcome measure data)*	Not mentioned in Wolff's paper	Type III Note: Initially we won't consider the dosage and time frame	CT/cohort: has diagnostic group/control group: 1. treatment: drugs: letrozole + placebo
TREATMENT GROUP TOTAL: 444 *(PROVENANCE:*	TREATMENT GROUP TOTAL: 334 *(PROVENANCE:*	Not mentioned in Wolff's paper	Type I	CT/cohort/treatment group

https://clinicaltrials.gov/ct2/show/results/NCT01740427?cond=PALOMA-2&draw=2&rank=1&view=results *Study Results,* *Primary Outcome,* *Outcome measure data)*	*https://clinicaltrials.gov/ct2/show/results/NCT01958021?cond=monaleesa-2&draw=2&rank=1* *Study Results,* *Primary Outcome,* *Outcome measure data)*			
CONTROL GROUP TOTAL: 222 *(PROVENANCE:* *https://clinicaltrials.gov/ct2/show/results/NCT01740427?cond=PALOMA-2&draw=2&rank=1&view=results* *Study Results,* *Primary Outcome,* *Outcome measure data)*	CONTROL GROUP TOTAL: 334 *(PROVENANCE:* *https://clinicaltrials.gov/ct2/show/results/NCT01958021?cond=monaleesa-2&draw=2&rank=1* *Study Results,* *Primary Outcome,* *Outcome measure data)*	Not mentioned in Wolff's paper	Type I	CT/cohort/control group
Median FOR TREATMENT GROUP: 24.8 [1] Median FOR CONTROL GROUP: 14.5 (12.9 to 17.1) *(PROVENANCE:* *https://clinicaltrials.gov/ct2/show/results/NCT01740427?cond=PALOMA-2&draw=2&rank=1&view=results* *Study Results,* *Primary Outcome,* *Outcome measure data)*	Median FOR TREATMENT GROUP: NA [1] (19.3 to NA) Median FOR CONTROL GROUP: 14.7 (13.0 to 16.5) *(PROVENANCE:* *https://clinicaltrials.gov/ct2/show/results/NCT01958021?cond=monaleesa-2&draw=2&rank=1* *Study Results,* *Primary Outcome,* *Outcome measure data)*	"PALOMA-2 resulted in longer median progression-free survival than progression-free survival with letrozole plus placebo (24.8 months vs. 14.5 months;" " In the MONALEESA-2 trial, the addition of ribociclib to letrozole resulted in a higher rate of progression-free survival at 18 months than the rate with letrozole and placebo (63.0% vs. 42.2%; "	Type II	CT/cohort/treatment group/statistical measure CT/cohort/control group/statistical measure
Hazard Ratio: 0.576	Hazard Ratio: 0.556	PALOMA-2: "hazard ratio for disease progression or death, 0.58;"	Type I	CT/cohort/hazard ratio/value

(PROVENANCE: https://clinicaltrials.gov/ct2/show/results/NCT01740427?cond=PALOMA-2&draw=2&rank=1&view=results Study Results, Primary Outcome, Statistical Analysis	*(PROVENANCE: https://clinicaltrials.gov/ct2/show/results/NCT01958021?cond=monaleesa-2&draw=2&rank=1 Study Results, Primary Outcome, Statistical Analysis*	MONALEEASA-2: “hazard ratio for disease progression or death, 0.56; ”		
(2-Sided) 95% 0.463 to 0.718 *(PROVENANCE: https://clinicaltrials.gov/ct2/show/results/NCT01740427?cond=PALOMA-2&draw=2&rank=1&view=results Study Results, Primary Outcome, Statistical Analysis*	(2-Sided) 95% 0.429 to 0.720 *(PROVENANCE: https://clinicaltrials.gov/ct2/show/results/NCT01958021?cond=monaleesa-2&draw=2&rank=1 Study Results, Primary Outcome, Statistical Analysis*	PALOMA-2:“95% confidence interval [CI], 0.46 to 0.72)” MONALEESA-2: “95% CI, 0.43 to 0.72).”	Type I	CT/cohort/hazard ratio/confidence interval


Paloma-2
cohort
has demographics
demographic
1
has ECOG status
0,1,2
has percentage of patients
white people : 77.5%
had percentage of patients
48.2% & 49.5% of patients with prior visceral disease
had percentage of patients
37.2% of patients had advanced disease
has control group
Control group
has control drugs
placebo + letrozole
has # of patients
222
Statistical measures... Median: 14.5
has treatment group
Treatment group
has treatment drugs
Palbociclib + letrozole
has # of patients
444
has statistical measures
Median: 24.8
has disease
disease
Adequate organ function
Adequate marrow function
has hazard ratio
Hazard ratio: 0.576
has confidence interval
(2-Sided) 95% 0.463 to 0.718
enrollment
Patient agree to provide tumor tissue
Patient history
had prior systemic anti-cancer therapy for advanced disease
prior systemic anti-cancer therapy for advanced disease
had percentage of patients
48% & 49.1% had received prior adjuvant chemo
Breast Cancer
ER positive
HER2 negative
RECIST measurable
locoregionally recurrent
metastatic


Monaleesa-2
cohort
has demographics
demographic
is postmenopausal
1
has ECOG status
0,1
has percentage of patients
white people : 80.5% & 83.8%
had percentage of patients
59% & 58.7% of patients with prior visceral disease
had percentage of patients
34% of patients had advanced disease
Patient history
had prior systemic anti-cancer therapy for advanced disease
prior systemic anti-cancer therapy for advanced disease
had percentage of patients
43.7% & 43.4% had received prior adjuvant chemo
has hazard ratio
Hazard ratio: 0.556
has confidence interval
(2-Sided) 95% 0.429 to 0.720
has disease
disease
Breast Cancer
ER positive
HER2 negative
RECIST measurable
locoregionally recurrent
metastatic
has treatment group
Treatment group
has statistical measures
Median: NA
has treatment drugs
ribociclib + letrozole
has # of patients
334
has control group
Control group
has control drugs
placebo + letrozole
has # of patients
334
Statistical measures... Median: 14.7

STAGE 5: REFLECT ON SIDE EFFECTS

- Seems to be linking side-effects to other things he has seen before (eg chemo) based on his own knowledge:
    - He knows that dose reductions are done because of toxicity
    - Points out negative side effects that are common to chemotherapy (unclear of the side effects occurred in both, or if he lists here any side effects that occurred in either)

Despite frequent neutropenia, febrile neutropenia was rare owing to the reversible pharmacologic quiescence of hematopoietic progenitors caused by CDK4 and CDK6 inhibitors, with no cytotoxic effects.

- Points out negative side effects that were due to the CDKI proper
- Points out that no cytotoxic effects means that it is not linked to chemotherapy
- So he is separating the neutropenia side-effect from the chemo side-effects.
    - Why is this significant to point out?

Patients also maintained good quality of life owing to the improved progression-free survival; frequent dose reductions in PALOMA-3 appeared not to affect progression-free survival.[8] A small number of drug-related deaths occurred, and ribociclib can prolong a QT interval.

???

A third CDK4 and CDK6 inhibitor, abemaciclib, also has FDA “breakthrough therapy” designation, and studies similar to PALOMA are ongoing with fulvestrant (ClinicalTrials.gov number, NCT02107703) and nonsteroidal aromatase inhibitors (NCT02246621). Abemaciclib is less myelo-suppressive than palbociclib and ribociclib and has reported single-agent activity.

Serious Adverse Events comparison:

Blanks means N/A for the trial

Leave out for now

PALOMA-2	MONALEESA-2
Blood and lymphatic system disorders	Blood and lymphatic system disorders
Anaemia	ANAEMIA
Febrile	FEBRILE NEUTROPENIA

	LEUKOCYTOSIS
	LEUKOPENIA
	NEUTROPENIA
	PANCYTOPENIA
	THROMBOCYTOPENIA
Cardiac disorders	Cardiac disorders
Acute	ARRHYTHMIA
Aortic	ATRIAL FIBRILLATION
Atrial	CARDIAC FAILURE CONGESTIVE
Atrioventricular	CARDIOMYOPATHY
Cardiac	CORONARY ARTERY DISEASE
Cardiogenic	
Cardiopulmonary	
Cardiovascular	
Myocardial	
Pericardial	
Endocrine disorders	
Hypercalcaemia	
Hyperthyroidism	
Eye disorders	Eye disorders
Cataract	GLAUCOMA
Gastrointestinal disorders	Gastrointestinal disorders
Abdominal	ABDOMINAL DISTENSION

Colitis	ABDOMINAL INCARCERATED HERNIA
Constipation	ABDOMINAL PAIN
Diarrhoea	ABDOMINAL PAIN LOWER
Gastrooesophageal	ABDOMINAL PAIN UPPER
Haemorrhoids	ASCITES
Intestinal	CONSTIPATION
Large	DIARRHOEA
Mechanical	DUODENAL OBSTRUCTION
Nausea	DUODENAL PERFORATION
Pancreatitis	DYSPEPSIA
Pancreatitis	FLATULENCE
Small	GASTRIC ANTRAL VASCULAR ECTASIA
Vomiting	GASTROINTESTINAL WALL THICKENING
	GASTROOESOPHAGEAL REFLUX DISEASE
	HAEMATEMESIS
	INGUINAL HERNIA
	NAUSEA
	OBSTRUCTION GASTRIC
	VOMITING
General disorders	General disorders
Chest	GENERAL PHYSICAL HEALTH DETERIORATION

Death	MALAISE
Device	NON-CARDIAC CHEST PAIN
Disease	PYREXIA
General	SUDDEN DEATH
Non-cardiac	
Pain	
Puncture	
Pyrexia	
Hepatobiliary disorders	Hepatobiliary disorders
Bile	AUTOIMMUNE HEPATITIS
Biliary	CHOLECYSTITIS
	CHOLECYSTITIS ACUTE
	HEPATIC FAILURE
	HEPATOCELLULAR INJURY
	HEPATOTOXICITY
Infections and infestations	Infections and infestations
Appendicitis	BRONCHITIS
Breast	CELLULITIS
Bronchiolitis	CLOSTRIDIUM DIFFICILE INFECTION
Bronchitis	ERYSIPELAS
Cellulitis	PNEUMONIA
Clostridium	PYELONEPHRITIS
Cystitis	PYELONEPHRITIS ACUTE

Diverticulitis	RETROPERITONEAL ABSCESS
Erysipelas	SEPSIS
Influenza	SKIN INFECTION
Lower	URINARY TRACT INFECTION
Lower	UROSEPSIS
Peritonitis	
Pharyngitis	
Pneumonia	
Pyelonephritis	
Respiratory	
Sepsis	
Staphylococcal	
Tracheobronchitis	
Urinary	
Urosepsis	
Injury, poisoning and procedural complications	Injury, poisoning and procedural complications
Ankle	FEMORAL NECK FRACTURE
Fall	FEMUR FRACTURE
Femoral	HIP FRACTURE
Femur	HUMERUS FRACTURE
Foot	INFLAMMATION OF WOUND
Fracture	OVERDOSE
Gastroenteritis	RADIUS FRACTURE

Lower	SPINAL COMPRESSION FRACTURE
Meniscus	SPINAL FRACTURE
Pelvic	
Spinal	
Wound	
Investigations	Investigations
Alanine	ALANINE AMINOTRANSFERASE INCREASED
Aspartate	ASPARTATE AMINOTRANSFERASE INCREASED
Neutrophil	BLOOD BILIRUBIN INCREASED
	BLOOD CREATININE INCREASED
	BLOOD THYROID STIMULATING HORMONE DECREASED
	LYMPHOCYTE COUNT DECREASED
	NEUTROPHIL COUNT DECREASED
	TRANSAMINASES INCREASED
	WAIST CIRCUMFERENCE INCREASED
	WEIGHT DECREASED
	WHITE BLOOD CELL COUNT DECREASED
Metabolism and nutrition disorders	Metabolism and nutrition disorders

Decreased	DECREASED APPETITE
Hyperglycaemia	DEHYDRATION
	ELECTROLYTE IMBALANCE
	HYPERCALCAEMIA
	HYPOGLYCAEMIA
	HYPOKALAEMIA
	HYPOPHOSPHATAEMIA
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorders
Bone	ARTHRALGIA
Pain	BACK PAIN
Pathological	BONE PAIN
	HAEMARTHROSIS
	PATHOLOGICAL FRACTURE
	SPINAL PAIN
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Acute	BASAL CELL CARCINOMA
Basal	BLADDER CANCER
Cervix	MALIGNANT MELANOMA IN SITU
Endometrial	MENINGIOMA
Malignant	METASTASES TO CENTRAL NERVOUS SYSTEM
Ovarian	METASTASES TO MENINGES
Papillary	ONCOCYTOMA

	SQUAMOUS CELL CARCINOMA
	TUMOUR PAIN
	UTERINE LEIOMYOMA
Nervous system disorders	Nervous system disorders
Cauda	DEPRESSED LEVEL OF CONSCIOUSNESS
Cerebral	DIZZINESS
Cerebrovascular	EPILEPSY
Headache	HAEMORRHAGE INTRACRANIAL
Hemiparesis	HEADACHE
Paraesthesia	MIGRAINE
Seizure	PARAESTHESIA
Syncope	SPINAL CORD COMPRESSION
Thrombotic	SYNCOPE
Psychiatric disorders	Psychiatric disorders
Depression	CONFUSIONAL STATE
	MENTAL STATUS CHANGES
Renal and urinary disorders	Renal and urinary disorders
Acute	ACUTE KIDNEY INJURY
Hydronephrosis	RENAL FAILURE
Renal	
Stag	
Urinary	
Reproductive system and breast	

disorders	
Breast	
Uterovaginal	
Respiratory, thoracic and mediastinal disorders	Respiratory, thoracic and mediastinal disorders
Chronic	ASTHMA
Dyspnoea	DYSPNOEA
Interstitial	HYPOXIA
Pleural	PLEURAL EFFUSION
Pneumonitis	PLEURAL FIBROSIS
Pulmonary embolism	PNEUMOTHORAX
Respiratory	PULMONARY EMBOLISM
Tracheomalacia	PULMONARY HAEMORRHAGE
	PULMONARY OEDEMA
Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders
Dermatitis	ERYTHEMA
Rash	
Vascular disorders	Vascular disorders
Deep	HYPERTENSION
	HYPOTENSION
	ORTHOSTATIC HYPOTENSION
	SUBCLAVIAN VEIN THROMBOSIS

Other Adverse Events comparison:

PALOMA-2	MONALEESA-2
Blood and lymphatic system disorders	Blood and lymphatic system disorders
Anaemia	ANAEMIA
Leukopenia	LEUKOPENIA
Neutropenia	NEUTROPENIA
Thrombocytopenia	THROMBOCYTOPENIA
	Ear and labyrinth disorders
	VERTIGO
Eye disorders	Eye disorders
Lacrimation increased	DRY EYE
	LACRIMATION INCREASED
Gastrointestinal disorders	Gastrointestinal disorders
Abdominal distension	ABDOMINAL PAIN
Abdominal pain	ABDOMINAL PAIN UPPER
Abdominal pain upper	CONSTIPATION
Constipation	DIARRHOEA
Diarrhoea	DRY MOUTH
Dry mouth	DYSPEPSIA
Dyspepsia	NAUSEA
Gastrooesophageal reflux disease	STOMATITIS

Nausea	VOMITING
Stomatitis	
Vomiting	
General disorders	General disorders
Asthenia	ASTHENIA
Fatigue	FATIGUE
Influenza like illness	INFLUENZA LIKE ILLNESS
Mucosal inflammation	NON-CARDIAC CHEST PAIN
Oedema peripheral	OEDEMA PERIPHERAL
Pain	PYREXIA
Pyrexia	
Infections and infestations	Infections and infestations
Nasopharyngitis	INFLUENZA
Oral herpes	NASOPHARYNGITIS
Sinusitis	UPPER RESPIRATORY TRACT INFECTION
Upper respiratory tract infection	URINARY TRACT INFECTION
Urinary tract infection	
Injury, poisoning and procedural complications	
Fall	
Investigations	Investigations
Alanine aminotransferase increased	ALANINE AMINOTRANSFERASE INCREASED
Aspartate aminotransferase increased	ASPARTATE AMINOTRANSFERASE INCREASED

Neutrophil count decreased	BLOOD ALKALINE PHOSPHATASE INCREASED
Platelet count decreased	BLOOD CREATININE INCREASED
Weight decreased	LYMPHOCYTE COUNT DECREASED
White blood cell count decreased	NEUTROPHIL COUNT DECREASED
	WEIGHT DECREASED
	WHITE BLOOD CELL COUNT DECREASED
Metabolism and nutrition disorders	Metabolism and nutrition disorders
Decreased appetite	DECREASED APPETITE
	HYPERGLYCAEMIA
	HYPOCALCAEMIA
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorders
Arthralgia	ARTHRALGIA
Back pain	BACK PAIN
Bone pain	BONE PAIN
Muscle spasms	MUSCLE SPASMS
Musculoskeletal chest pain	MUSCULOSKELETAL CHEST PAIN
Musculoskeletal pain	MUSCULOSKELETAL PAIN
Myalgia	MYALGIA
Neck pain	PAIN IN EXTREMITY
Pain in extremity	
Nervous system disorders	Nervous system disorders

Dizziness	DIZZINESS
Dysgeusia	DYSGEUSIA
Headache	HEADACHE
Psychiatric disorders	Psychiatric disorders
Anxiety	ANXIETY
Depression	DEPRESSION
Insomnia	INSOMNIA
	Reproductive system and breast disorders
	BREAST PAIN
Respiratory, thoracic and mediastinal disorders	Respiratory, thoracic and mediastinal disorders
Cough	COUGH
Dyspnoea	DYSPNOEA
Epistaxis	OROPHARYNGEAL PAIN
Oropharyngeal pain	
Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders
Alopecia	ALOPECIA
Dry skin	DRY SKIN
Pruritus	PRURITUS
Rash	RASH
Vascular disorders	Vascular disorders
Hot flush	HOT FLUSH
Hypertension	HYPERTENSION

STAGE 6: FIND OTHER RELEVANT CLINICAL TRIALS AND STUDIES

- Additional relevant clinical trials found for a third and fourth drugs -- search is based on drugs that are in the same class

Adjuvant trials of palbociclib have begun. The Palbociclib Collaborative Adjuvant Study (PALLAS, NCT02513394, involving 4600 patients) will evaluate invasive disease–free survival with the addition of 2 years of palbociclib therapy to at least 5 years of endocrine therapy among patients with stage II (stage IIa was limited to 1000 patients) or stage III ER-positive–HER2-negative disease.

- Additional relevant clinical trials -- using same drugs with other treatment conditions

PENELOPE-B (NCT01864746, involving 1100 patients) will evaluate invasive disease–free survival with a year of palbociclib therapy among women treated with neoadjuvant chemotherapy who remain at high risk for future recurrence. The side-effect profile associated with extended adjuvant administration may become an issue in healthy patients, and data from an ongoing feasibility trial (NCT02040857) may be infor- mative.

- Additional relevant clinical trials -- using same drugs with other cohorts inclusion criteria

The Palbociclib Collaborative Adjuvant Study (PALLAS, NCT02513394, involving 4600 patients):

Inclusion Criteria: (similar criteria as PALOMA-2 and MONALEESA-2 are underlined)

- *Signed informed consent prior to study specific procedures.*
- *Age ≥18 years (or per national guidelines).*
- *Pre- and postmenopausal women or men with Stage II (Stage IIA limited to max. 1000 patients) or Stage III early invasive breast cancer*
- *Patients with multicentric and/or multifocal and/or bilateral early invasive breast cancer are eligible if all histopathologically examined tumors meet pathologic criteria for ER+ and/or PR+ and HER2-.*
- *Patients must have histologically confirmed ER+ and/or PR+, HER2-, early invasive breast cancer.*
- *Patients must have undergone adequate (definitive) breast surgery for the current malignancy.*
- *FFPE tumor tissue block must be confirmed to be received at the central sample repository prior to randomization.*
- *ECOG performance status 0-1.*
- *Patients must be able and willing to swallow and retain oral medication.*
- *Serum or urine pregnancy test must be negative in premenopausal women within 14 days of randomization, or in women with amenorrhea of less than 12 months at time of randomization.*
- *Patients who received neo/adjuvant therapy must be after last dose of chemotherapy and/or biologic therapy and must have sufficient resolution of side effects.*
- *Patients who received breast/axilla/post-mastectomy chest wall radiotherapy must be after last dose of radiotherapy and must have sufficient resolution of side effects.*
- *Patients must have sufficient resolution of any surgical side effects (no active wound healing complications).*

- *Patients must either be initiating or have already started adjuvant hormonal treatment. -Patients who already received neo/adjuvant endocrine therapy are eligible as long as they are enrolled within 12 months of initial histological diagnosis and after completing no more than 6 months of adjuvant endocrine therapy.*
- *Absolute neutrophil count ≥ 1,500/µL*
- *Platelets ≥ 100,000/ mm3*
- *Hemoglobin ≥ 10g/dL*
- *Total serum bilirubin ≤ ULN; or total bilirubin ≤ 3.0 × ULN with direct bilirubin within normal range in patients with documented Gilbert's Syndrome.*
- *Aspartate amino transferase (AST or SGOT) and alanine amino transferase (ALT or SGPT) ≤ 1.5 × institutional ULN.*
- *Serum creatinine below the upper limit of the institutional normal range (ULN) or creatinine clearance ≥ 60 mL/min/1.73 m2 for patients with serum creatinine levels above institutional ULN.*

PENELOPE-B (NCT01864746, involving 1100 patients)

Inclusion Criteria

1. *Written informed consent prior to beginning specific protocol procedures, including expected cooperation of the patients for the treatment and follow-up, must be obtained and documented according to the local regulatory requirements.*
2. *Willingness and ability to provide archived formalin fixed paraffin embedded tissue block or a partial block from surgery after neoadjuvant chemotherapy and from core-biopsy before start of neoadjuvant chemotherapy, which will be used for centralized retrospective confirmation of hormone- and HER2-status and to evaluate correlation between genes, proteins, and mRNAs relevant to the endocrine and cell cycle pathways and sensitivity/resistance to the investigational agents. In case of bilateral breast cancer, tumor tissue of both sides needs to be assessable.*
3. *Histologically confirmed unilateral or bilateral primary invasive carcinoma of the breast.*
4. *Residual invasive disease post-neoadjuvant either in the breast or as residual nodal invasion.*
5. *Centrally confirmed hormone-receptor-positive (≥1% ER and/or PR positive stained cells) and HER2-normal (IHC score 0-1 or FISH negative (in-situ hybridization (ISH) ratio) <2.0 status) assessed preferably on tissue from post-neoadjuvant residual invasive disease or core biopsy of the breast, or if no other tissue is available the residual tumor of the lymphnode*

can be assessed.

In case of bilateral breast cancer hormonreceptor positivity and HER2-normal status has to be centrally confirmed for both sides.

6. *Centrally assessed Ki-67, pRB, and Cyclin D1 status assessed preferably on post-neoadjuvant residual invasive disease of the breast, or if not possible, of residual nodal invasion or core biopsy. In case of bilateral breast cancer, tumor tissue of both sides needs to be assessable.*
7. *Patients must have received neoadjuvant chemotherapy of at least 16 weeks. This period must include 6 weeks of a taxane -containing neoadjuvant therapy (Exception: For patients with progressive disease that occurred after at least 6 weeks of taxane-containing neoadjuvant treatment, a total treatment period of less than 16 weeks is also eligible).*
8. *Adequate surgical treatment including resection of all clinically evident disease and ipsilateral axillary lymph node dissection. Histologically complete resection (R0) of the invasive and ductal in situ tumor is required in case of breast conserving surgery as the final treatment. No evidence of gross residual disease (R2) is required after total mastectomy (R1 resection is acceptable). Axillary dissection is not required in patients with a negative sentinel-node biopsy before (pN0, pN+(mic)) or after (ypN0, ypN+(mic) neoadjuvant chemotherapy.*
9. *Less than 16 weeks interval since the date of final surgery or less than 10 weeks from completing radiotherapy (whichever occurs last) at date of randomization.*
10. *Completion of adjuvant radiotherapy according to standard guidelines (e.g. AGO Mamma, NCCN) is strongly recommended. If radiotherapy is not performed the reason for this needs to be documented in the eCRF.*
11. *No clinical evidence for locoregional or distant relapse during or after preoperative chemotherapy. Local progression during chemotherapy is not an exclusion criterion.*
12. *A clinical-pathologic stage - estrogen/grade (CPS-EG) score of ≥3, or score 2 if nodal status at surgery is ypN+, calculated using local estrogen receptor status and grade assessed on either core biopsies taken before start of neoadjuvant treatment or surgical specimen (see chapter 21.1).*
13. *Age at diagnosis at least 18 years.*
14. *Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 (see Appendix 21.2).*
15. *Resolution of all acute toxic effects of prior anti cancer therapy or surgical procedures to NCI CTCAE version 4.0 Grade ≤1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).*
16. *Estimated life expectancy of at least 5 years irrespective of the diagnosis of breast cancer.*
17. *The patient must be accessible for scheduled visits, treatment and follow-up. Patients registered on this trial must be treated at the participating center which could be the Principal or a Co- investigator's site.*

PALLAS	PENELOPE-B	Wolff	Comment
Pre- and postmenopausal women or men with Stage II (Stage IIA limited to max. 1000 patients) or Stage III early invasive breast cancer	*pre- and postmenopausal women* *(PROVENANCE: Study Details, Study Description, Brief summary)*	PALOMA-2 and MONALEESA-2 only considered postmenopausal women	Patients selection are wider
Patients must have histologically confirmed ER+ and/or PR+, HER2-, early invasive breast cancer.	*Centrally confirmed hormone-receptor-positive (≥1% ER and/or PR positive stained cells) and HER2-normal (IHC score 0-1 or FISH negative (in-situ hybridization (ISH) ratio) <2.0 status) assessed preferably on tissue from post-neoadjuvant residual invasive disease or core biopsy of the breast, or if no other tissue is available the residual tumor of the lymphnode can be assessed.*	PALOMA-2 and MONALEESA-2 considered ER+, HER2-	*PENELOPE-B applied on different type (HER2 normal)*

Patients with multicentric and/or multifocal and/or bilateral early invasive breast cancer are eligible if all histopathologically examined tumors meet pathologic criteria for ER+ and/or PR+ and HER2-.	*Centrally assessed Ki-67, pRB, and Cyclin D1 status assessed preferably on post-neoadjuvant residual invasive disease of the breast, or if not possible, of residual nodal invasion or core biopsy. In case of bilateral breast cancer, tumor tissue of both sides needs to be assessable.*	Not mentioned in Wolff's paper	*Not mentioned in both PALOMA-2 and MONALEESA-2*
Patients must either be initiating or have already started adjuvant hormonal treatment. - Patients who already received neo/adjuvant endocrine therapy are eligible as long as they are enrolled within 12 months of initial histological diagnosis and after completing no more than 6 months of adjuvant endocrine therapy.	*Patients must have received neoadjuvant chemotherapy of at least 16 weeks. This period must include 6 weeks of a taxane - containing neoadjuvant therapy (Exception: For patients with progressive disease that occurred after at least 6 weeks of taxane-containing neoadjuvant treatment, a total treatment period of less than 16 weeks is also eligible)*	*half received adjuvant chemotherapy, half received adjuvant endocrine therapy*	*PALLAS needs prior adjuvant hormonal treatment while PENELOPE-B requires prior neoadjuvant chemotherapy* *Wolff's paper mixed both therapies. And he feels striking when consider "half received adjuvant endocrine therapy"*

Subset analyses in the PALOMA-2 and MONALEESA-2 trials thus far have not identified subgroups of patients who would not be expected to benefit from CDK4 and CDK6 inhibition. The ER-positive phenotype is in essence the only biomarker. However, low-estrogen environments associated with exposure to aromatase inhibitors favor selection for activating mutations in *ESR1*, the gene encoding ER, and ligand-independent ER activity may result. Hence, although tumors with *ESR1* mutation have a greater response to fulvestrant than to aromatase inhibitors, it is unknown whether these tumors respond further to palbociclib. It is also unknown whether exposure to palbociclib favors emergence of *ESR1* mutations. Controlled trials are also needed to test the benefit associated with continuing CDK4 and CDK6 inhibition when the patient is switched to a new antiestrogen drug after disease progression during palbociclib therapy.

STAGE 7: REFLECT ON POTENTIAL PATIENT SUBGROUPS WITH YET UNPROVEN EFFECTS

- ER-positive phenotype is confirmed biomarker
- Tumors with ESR1 is unknown
- Tumors with ESR1 mutations are unknown
- If disease progresses with palbociclib, then unknown if patient should switch to anti estrogen drug

decision tree

Trials of CDK4 and CDK6 inhibitors followed rational development. Luminal ER-positive breast- cancer cell lines (including those that also had amplification of *HER2*) were more sensitive to inhibition with palbociclib than other cell lines.[10] CDK4 and CDK6 inhibitors prevent G1–S progression through reduced phosphorylation of the retinoblastoma protein encoded by the gene *RB1*. *RB1* is infrequently lost in ER-positive tumors, but the lack of association between loss of $p16^{INK4a}$ or amplification of cyclin D1 with clinical activity suggests that markers of ER-independent proliferation are possible predictors of a response to palbociclib. These potential associations will be further evaluated in PALOMA-2. Abemaciclib may also have preclinical in vitro activity in some triple-negative breast-cancer subtypes.

STAGE 8: REFLECT ON BIOLOGICAL PATHWAYS

- Justifies the reasons for prior clinical trials:
    - Prevent G1-S progression through reduced phosphorylation
    - Lack of association
    - Etc

Ongoing studies are investigating the combination of CDK4 and CDK6 inhibitors and inhibitors of signaling pathways, such as those interfering with PI3K/Akt/mTOR and HER2 pathways. Other therapies remain of interest in ER-positive breast cancer, such as the combination of the steroidal aromatase inhibitor exemestane with the histone deacetylase inhibitor entinostat (another FDA breakthrough therapy), before or after exposure to palbociclib or another CDK4 and CDK6 inhibitor (ECOG–ACRIN 2112, NCT02115282).

- Justifies and explains the reasons for ongoing clinical trials

Palbociclib is approved in the United States. The European Medicines Agency recently recommended marketing authorization in the European Union, and member states of the European Union will make decisions regarding price and reimbursement within the context of each national health system. CDK4 and CDK6 inhibition in combination with antiestrogens is clearly a new standard for

the treatment of advanced ER- positive breast cancer. However, palbociclib is costly and has some toxic effects. Some patients derive strong clinical benefit with antiestrogens alone as first-line therapy, and we must learn to identify those patients so that we can apply CDK4 and CDK6 inhibition in those who will benefit the most.