Targeted treatments

Introduction

Here we will present novel therapies and the evidence that supports them. Firstly, in ER+ disease CDK4/6 therapy is historically and contemporaneously used . Then biomarkers used in ER+ disease and how these have been incorporated into the latest trials in ER+ disease, and finally novel agents as per ESMO that are mainly relevant in Metastatic ER+ disease. Then we will cover the novel therapies for TN disease. HER2 is discussed separately.

There is a great overview on CDK4/6 and biomarkers on vimeo: https://vimeo.com/714026715/d0c821c54a

CDK 4/6 Inhibitors overview and current use

Overview

- The CDK4/6 proteins, found both in healthy cells and cancer cells, control how quickly cells grow and divide
- In metastatic breast cancer, these proteins can become overactive and cause the cells to grow and divide uncontrollably
- CDK4/6 inhibitors are cytostatic, not cytocidal. They work to control the growth and division of cancer cells. They block phosphorylation of the Rb protein, blocking the progression from G1 to S phase of the cell cycle. By inhibiting DNA synthesis, cell cycle arrest is induced, and cell proliferation and tumour growth is suppressed.
- Commonest SE is diarrhoea but only 5% discontinue as most are mild to moderately affected.
- Also more VTE events and Interstitial lung disease (see MonarchE)
- Can be given orally rather than IV

Evidence

Initially, as commonly the case, these were trialled in the metastatic context with **MONALESSA- 2 (2018)** (Ribociclib + letrozole versus placebo + letrozole post-menopausal), **PALOMA -3 (2018)** (Palbociclib + fulvestrant versus placebo +fulvestrant), **MONARCH-2** and **MONARCH-3** (abemaciclib). All showed an improvement in progression free survival or overall survival. This formed the basis for CDK4/6 approval for ER+ HER2- metastatic disease in the UK.

*** PALOMA-2 (2016) postmenopausal women with ER-positive, HER2-negative breast cancer, who had not had prior treatment for advanced disease, to receive palbociclib plus letrozole or placebo plus letrozole. However, updated OS did not show improvement in survival**

Landmark Trial is **MONARCH-E (2020):**

- RCT of 5k+ patients, intention to treat analysis of ER/PR+ Operable Breast Cancer with high rx feature (LN 4+ OR LN1-3 with 1 of; G3, >-5cm, Ki67 >20%)
- Featured both pre and post menopausal with a rate about 1/2 OFS in pre-menopausal patients
- Abemaciclib (2yrs adjuvant) added to standard Endocrine Therapy or Endocrine alone (majority were letrozole)

- Most patients in the trial received adjuvant or NAC with anthracycline and a taxane based regime
- Abemaciclib significantly improves IDFS in women and men with HR+, HER2-, node-positive EBC at high risk of early recurrence- 5-year IDFS rates of 83.6% versus 76%.
- At 36 months showed treatment with abemaciclib reduced the risk of developing invasive disease by 30.4%
- As of July 2022 NICE approved Abemaciclib for ER+ Her2- LN+ve EBC at high risk of recurrence
- Side note - Ki67i did not help in predicting the response to Abemeciclib which was always better than Endocrine alone but it did predict prognosis.
- Adverse events in abemaciclib vs control arms: VTE 2.3% vs 0.5% (PE 0.9% vs 0.1%), Interstitial lung disease (ILD) 2.7% vs 1.2% and Grade 3 AEs in 45.9% vs 12.9%.

PALLAS (2022 update at ASCO)

- Palpociclib Combined with Endocrine Therapy for the Adjuvant Treatment of HR+, HER2- EBC (Stage II-III) –
- Contrasts to MONARCH-E by failing to show a benefit of adding palbo in EBC.
- Agrees with findings in PENELOPE-B So bottom line is that the evidence is good in MBC but conflicting in EBC.

Guidelines

Currently licenced CDK4/6 inhibitors:

- Abemaciclib (Verzenio)
- Palbociclib (Ibrance)
- Ribociclib (Kisqali)
- As of July 2022 NICE approved Abemaciclib for all ER+ Her2- LN+ve disease (prior only in Metastatic disease based on Monarch 2 and 3 trials).
- Small print - LN2 automatically eligible. LN1 needs either size>5cm or G3. LN1 without these are not eligible. Remember that these patients will also be eligible for oncotype, licenced for chemotherapy RS in LN0 high rx or LN+ve, ER+ disease
- https://www.nice.org.uk/guidance/ta810/evidence/committee-papers-pdf-11137628269
- Latest NICE is based mainly on MonarchE and Ki67 proposed as being included in risk.

BIOMARKERS-and prognostic tools to stratify treatment

There are many of these but the 3 Genomic tests licenced in the UK

1. **ONCOTYPE**

   21 genes with 4 reference genes, gives a RS score of 0-100. Patients grouped into <11, 11-25, 25. Some trials further sub-group 1-15 or 16-24 in the intermediate group.

   NICE licensed for use in LN0, high rx and LN1 ER+ disease

- **TailorX** - 10k patients 3 groups: 1) Score 11-25 oncotype randomised to chemo-endocrine or endocrine alone (4k) 2) low rx <11 chemo omitted 3) high rx>25 given chemo. Justified that in N0 patients could omit chemo if intermediate score and aged >51yrs and some <51yrs if 11-15 score (underpowered) but raised the question of what to do if node positive hence RxPonder.
- **RxPonder** - Can we omit chemo in LN+ve disease? Interim analysis (54% events rate achieved) suggests yes in post-menopausal.
- Note there is a ONCOTYPE DCIS 12 gene panel but only available privately.

2. **ENDOPREDICT**

   12 genes + size and nodal status RS>3.3287 confers >10% rx recurrence (this is the national guidance for LRR at <10%)

3. **Prosigna**

   58 gene again 0-100 but used to estimate after 5 year hormone therapy

Proliferative Index - Ki67

IMPACT trial 2007 M Dowsett (UK) - Higher Ki67 expression after 2/52 endocrine therapy associated with lower recurrence free survival. Whereas higher Ki67 expression at baseline was not. Larger baseline tumour size and lower oestrogen receptor level after 2 weeks of treatment were also statistically significantly associated with poorer recurrence-free survival. So, it is the change rather than the baseline that is important. Combined these to produce overall prognostic indicator.

Subset of Monarch E - High baseline Ki67 patients greatly benefited from addition of Ademeciclib. All benefited from Ademeciclb i.e. cannot use it to decide who will benefit BUT the 3yr event rate was worse if patients had a high versus low baseline Ki67i. Hence incorporated into Lilly application for approval of ademeciclib EBC - >20% Ki67 is a high rx patient.

Currently being used in POETIC -A trial as above and initially Investigated in the UK POETIC trial whereby post-menopausal women were allocated in a 2:1 basis to 2/52 AI pre op versus straight to surgery. Measured the change in Ki67 and then the 5 year Recurrence Rates. Clear differences in patients who start high and remain high Ki67 (19.6% Absolute risk recurrence). Whereas those who are either low at baseline (best) or high then low after 2/52 AI have a good prognosis (4.5 and 8.9% ARR respectively at 5 years)

Combining genetics and biological markers

IHC4+ C score

The IHC4+C score is a prognostic tool that estimates the residual risk of distant recurrence at 10 years in post-menopausal women with ER+ breast cancer who have received 5 years of endocrine therapy. It incorporates clinicopathological parameters used traditionally, IHC for routine receptors and the Ki67 on IHC

1. Clinicopathological parameters: SIze, Grade, Nodal status (ie Nottingham Prognostic Index)
2. immunohistochemical parameters: ER, PR, HER2 AND Ki67
3. Type of endocrine therapy

Currently being used in the PRIMETIME TRIAL whereby a very low IHC4+ C score assigns patients to omission of radiotherapy (pragmatic design so also the option for patient choice)

WSG- ADAPT trial (Germany) combined Ki67 with Oncotype scores. Interestingly - women aged >50yrs with poor initial response (and therefore who received Chemotherapy) did nearly as well as those whom had a good response and required no additional chemotherapy - so Ki67 and Oncotype were successful in stratifying these. Unfortunately, young (<50yrs) woman who had a poor response were not rescued with chemotherapy.

Section 3 CDK4/6 - Current trials looking at use in Early breast cancer:

POETIC-A is a phase III, multicentre trial RCT in post-menopausal, ER+ HER2 -, >1.5cm and G2/3 breast cancer which is, with high 5-year risk of relapse*. Patients are randmised to receive standard therapy (AI) versus addition of abemaciclib (CDK4/6-) for 2 years. Uses Ki67 index to define rx: residual Ki67 ≥8% following treatment with a short course of endocrine therapy (ET) prior to surgery.
(Uk based so 2 weeks to 6 months of endocrine - impact of COVID-19)
AIR CIS

ADAPT cycle - Patients cohorts combination of risk factor (high, intermediate and low features)

1. LN 3, RS <-25 and post AI Ki67i<-10%
2. LN 1-2, RS >25 and post AI Ki67 <-10%
3. LN1-2, RS <-25 but post AI >10%

Stratified to chemotherapy 16-24wks then Endocrine versus Ribiciclib +AI then Endocrine alone.
(Germans give the AI for 2-4weeks then operate)

Use of CDK4/6- Neoadjuvantly

Neo Monarch and Pallet (UK). Overall take home is that unfortunately they do not seem to increase pCR in ER+ patients - Pallet it was just 3% in both arms.

PD1 AND PDL1

PD1 - Programmed Death receptor/ligand is the receptor=/ligand pathway for antigen presenting cell interaction with T cells and acts as a checkpoint for immune regulation. The immune-evasion of the tumour (with assistance of immune cells) often modulates T cell killing via the PD1 receptor/ligand. Therefore, drugs can target the receptor or the ligand and promote T cell killing of the tumour.

PD1 targets - Pembroluzimab.

PDL1 targets- Atezolizumab, Darvalumab (GEPAR-Neuvo 2)

Pembrolizumab is a humanized monoclonal IgG4-k antibody with a high affinity and selectivity against PD-1, which is currently approved by FDA and/or EMA in a large number of malignancies. As of 2022, UK approved for NAC in TN - so NAC young patient TN would now want Taxane + platinum + pembroluzimab.

**Common AEs include transfusion reactions and endocrinopathies - especially hypothyroidism, and any itis-pneumonitis and hepatitis. In the longer term there is concern with regards to initiating auto-immune disease and haematological malignancy. Older trials are based in melanoma and lung cancer but long-term survival awful so tricky!

Keynote series have published extensively on Pembroluzimab;

- Phase 1b = Keynote-012
- Phase 2 = Keynote-086
- Phase 3 RCT = Keynote -119 “Pembro monotherapy did not significantly improve OS as 2/3L treatment for mTNBC vs chemo, although the pembro treatment effect increased as PD-L1 enrichment increased. Pembro was generally well tolerated and had less high-grade toxicity than chemo”
- Keynote 355 in metastatic setting- OS benefit shown in pembrolizumab combined with paclitaxel chemotherapy. Pembrolizumab plus chemotherapy is recommended for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer
- **Keynote 522 interim report in NEJM 2022 - 4 cycles of pembrolizumab or placebo every 3 weeks plus paclitaxel and carboplatin, followed by four cycles of pembrolizumab or placebo plus doxorubicin–cyclophosphamide or epirubicin–cyclophosphamide. Showed significant benefit (EFS 36 months was 84.5% vs 76.8% in placebo). Adjuvant therapy was continued after surgery - raising the question of whether this is necessary?**
- **So, in TN II/III give this regimen in NAC if funded then if not pCR then capecitabine can be offered adjuvantly.**

Atezolizumab with nab paclitaxel is recommended for triple-negative, unresectable, PD L1 positive, locally advanced or metastatic breast cancer in adults who have not had chemotherapy for metastatic disease. The approval was based on the clinical data presented from IMpassion130 trial

The flow currently should be upfront pembroluzimab NAC with taxane + platinum and prompt gene testing in all triple negative patients under 60. Post NAC will depend on response:- good response - complete adjuvant pembroluzimab- poor response - PARP/capecitabine depending on gBRCA

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NATALEE Trial (2024)

Phase III, RCT >5K with stage II or III HR-positive, HER 2 negative EBC patients were randomized to receive adjuvant ribociclib (400 mg daily for 3 years) +NSAI vs NSAI

Eligible patient: Stage IIB or III disease eligible regardless of nodal status; stage IIA eligible with specific nodal or tumour characteristics (e.g., involved lymph nodes, high Ki-67 index>20% , or high genomic risk); N0 patients can be included if they present with high-risk features.

At 3 years IDFS was significantly higher with the addition of ribociclib to an NSAI than with the NSAI; 90.4% vs 87.1 respectively

Overall survival data are currently immature.

A key feature of the NATALEE trial design was the use of a reduced dose of ribociclib (400 mg per day) to improve safety and adherence over a 3-year period while maintaining efficacy.

The NATALEE trial showed that ribociclib treatment benefits a broad population of patients with early breast cancer who are at increased risk for recurrence, unlike MONARCH-E trial.

PARP

PARP is a partner with BRCA genes which usually repair DNA so can target this in BRCA mutated cancers only.

Olaparib is recommended, within its marketing authorisation, as an option for the adjuvant treatment of HER2 negative high-risk early breast cancer that has been treated with neoadjuvant or adjuvant chemotherapy in adults with germline BRCA1 or 2 mutations

The criteria for defining high risk in OlympiA were:

i• for people with triple-negative breast cancer who had neoadjuvant chemotherapy: residual invasive cancer in the breast, the resected lymph nodes (non-pathological complete response) or both at the time of surgery
• for people with hormone receptor-positive HER2 negative breast cancer who had neoadjuvant chemotherapy: residual invasive cancer in the breast, the resected lymph nodes (non-pathologic complete response) or both at the time of surgery, and a score of 3 or more based on pretreatment clinical and post-treatment pathological stage, receptor status and histological grade
• for people with triple-negative breast cancer who had adjuvant chemotherapy: node-positive or node-negative cancer with a primary tumour of 2 cm or more
• for people with hormone receptor-positive HER2 negative breast cancer who had adjuvant chemotherapy: 4 or more pathologically confirmed positive lymph nodes.

NOTE: PARP- interact with radiotherapy as they act by preventing DNA repair, so cannot give until 2/52 after

completion.

Criteria for BRCA testing

- Breast cancer (age < 40 years)2
- Diagnosed with breast cancer in both breasts under the age of <50
- Triple negative breast cancer under the age of <60 years
- Have been diagnosed with both breast and ovarian cancer at any age.
- Breast cancer <45 years and a first-degree relative with breast cancer <45 years
- Ashkenazi Jewish ancestry and breast cancer at any age
- Non-mucinous ovarian cancer (including fallopian tube or peritoneal cancer) at any age
- Male breast cancer any age
- Pathology-adjusted Manchester score ≥15 or BOADICEA/CanRisk score above ≥ 10%

As of 2024, Talazoparib is recommended for treating HER2-negative, locally advanced or metastatic breast cancer with germline BRCA1 or BRCA2 mutations in adults who have had chemotherapy or endocrine therapy. The approval was based on the clinical data presented from EMBRACA trial, phase 3 randomised controlled trial showed significant improve in PFS compared to physician's choice of treatment in the overall population.

Other therapies for metastatic breast cancer

- **"SERDS" - Selective Estrogen Receptor Degrader**
    - Reduces rather than blocks receptor
    - **Fulvestrant:** clinically approved for the treatment of postmenopausal patients with ER+ MBC after progression on tamoxifen or AIs.
    - **Elecestrant:** newer and great as **first oral SERD** and being trialled in the **EMERALD trial**. Initial results presented at ASCO looks promising: 500pts randomised to Elecestrant vs Fulvestrant/AI, 22.3% vs 9,4% PFS and got up to around **50% if prove ESR1 mutation**. **higher SE/adverse outcomes 6.3% vs 4.4%.
    - Note - in case you were not aware Tamoxifen is actually a SERM ie modulator.
- **Alpelisib**
    - an alpha-specific class 1 protein kinase inhibitor.
    - Used in combination with Fulvestrant in PIK3CA mutated MBC, usually 2nd line after CD4/6- and no BRCA mutation. Can test for PIK3CA1 mutation.
    - If BRCA mutation then PARP- e.g. Olaparib.
    - **SOLAR-1 phase III** randomised, placebo-controlled trial fulvestrant + placebo OR alpelisib: Postmenopausal women and men previously treated with an AI. In PIK3CA-mutation: Alpelisib PFS benefit of 11.0 versus 5.7 months (HR for progression/ death 0.65, P < 0.001 Median OS was 39.3 months 31.4 months for (HR 0.86).
    - Horrid drug! Toxicity was increased substantially in the alpelisib arm, especially hyperglycaemia, rash, gastrointestinal (GI) toxicity (nausea, vomiting, loss of appetite, mucositis, diarrhoea) and fatigue, which led to dose reductions/ **interruptions in 70% and discontinuations in 25%**. All need to be assessed for DM and started prophylactically on Antihistamine.
    - Most oncology colleagues spoken within the UK do not use it in UK practice but features in European guidance.

- **mTOR Inhibitors EVEROLIMUS**
    - **BOLERO-2 trial**: In the phase III trial, Everolimus addition to exemestane significantly improved median PFS versus placebo exemestane (7.8 versus 3.2 months, HR 0.45) in patients who had progressed on a nonsteroidal AI. BUT no significant OS or quality-of-life (QoL) benefit!
    - Give dexamethasone mouthwash prophylactically as all get stomatitis.

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Summary; In general in the metastatic setting you are looking at progression free survival - most therapies do not cure, they slow. We are not oncologists so just be aware of the options available and the ways you can target the cell. Always consider entry into clinical trials for all eligible patients

(IMAGE currently in development summarising the different targets available)