Clinical Updates: Solid Organ Tumor Pharmacotherapy

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Objective

- Briefly review clinical trials pertaining to key updates to the National Comprehensive Cancer Network (NCCN) Guidelines® for the treatment of various solid organ tumors (Bladder, Breast, Non-Small Cell Lung Cancers).

Outline of Key Trials

- Bladder Cancer
  - VESPER
  - JAVELIN Bladder 100
  - EV-302/Keynote-A39
- Breast Cancer
  - MonarchE
  - NATALEE
  - KEYNOTE-522
  - OlympiA
- Non-Small Cell Lung Cancer
  - CheckMate816
  - KEYNOTE 671
  - ADAURA
  - FLAURA2
  - MARIPOSA-2
  - PAPILLON

Bladder Cancer General Overview

Non-muscle Invasive

- TURBT → perioperative vesicular chemo
- BCG or chemo
- Maintenance

Localized Muscle Invasive

- Neoadjuvant cisplatin-based chemo **(VESPER trial)**
- Cystectomy

Metastatic

- Platinum Based Chemo
  - Maintenance Avelumab **(JAVELIN 100 trial)**
- Immunotherapy
  - Pembrolizumab + enfortumab vedotin 1st line **(EV-302 / KEYNOTE-A39)**
- Targeted Therapy

VESPER Trial

- Multicenter, phase III, muscle invasive bladder cancer patients (n=500)
  - Perioperative Chemotherapy With **ddMVAC** (dose-dense methotrexate, vinblastine, doxorubicin, cisplatin) vs **GC** (gemcitabine + cisplatin)
  - 3 year PFS higher for those received neoadjuvant ddMVAC compared to neoadjuvant GC (66% vs. 56%; HR, 0.70; 95% CI, 0.51–0.96; *P* = 0.025)
- NCCN preferred
  - **DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3–6 cycles**
- Other recommended
  - **Gemcitabine and cisplatin for 4 cycles**

Pfister C et al. J Clin Oncol. 2022;40:2013-2022.
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer.

JAVELIN Bladder 100 Trial

- Multicenter, randomized phase III, trial studied 700 metastatic patients who responded to or stable after 4-6 cycles platinum-based first-line chemotherapy
  - After a 4-10–week interval post chemotherapy: avelumab + best supportive care (BSC) vs BSC alone
  - Avelumab arm significantly prolonged OS over BSC (median OS, 21.4 vs. 14.3 months; HR, 0.69; 95% CI, 0.56–0.86; *P* = .001)
  - Grade ≥3 AEs were reported in 47.4% of patients treated with avelumab compared to 25.2% of those with BSC
  - In ≥ 2 years of follow-up, OS remained longer with avelumab + BSC versus BSC alone in all patients
    - HR= 0.76 [95% CI, 0.63 to 0.91]; 2-sided P = .0036)
- NCCN Category 1 Recommendation: **Gemcitabine and cisplatin followed by avelumab maintenance therapy as first-line systemic therapy for locally advanced or metastatic disease (Stage IV)**

Powles T et al. J Clin Oncol. 2023 Jul 1;41(19):3486-3492.
Powles T et al. N Engl J Med. 2020;383:1218-1230.
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer. V.4.2024, 5/09/24, © 2024 National Comprehensive Cancer Network, Inc., All Rights Reserved.

EV-302/KEYNOTE-A39 Trial

- Randomized phase III trial, 886 treatment naive locally advanced / metastatic urothelial carcinoma
  - Enfortumab vedotin (EV) + pembrolizumab or gemcitabine in combination with either cisplatin or carboplatin with median follow-up 17.2 months
  - Median PFS with EV + pembrolizumab significantly longer compared to chemotherapy (12.5 months vs. 6.3 months; HR, 0.45; 95% CI, 0.38–0.54; P < .001)
  - Median OS significantly longer with EV + pembrolizumab (31.5 months vs. 16.1 months
    - HR, 0.47; 95% CI, 0.38– 0.58; < .001
  - ORR was 67.7% and 44.4% for EV + pembrolizumab and chemotherapy, respectively (P < .001).
- NCCN Recommendation: **Enfortumab vedotin + pembrolizumab is the preferred first-line systemic therapy option for advanced / metastatic urothelial carcinoma, regardless of cisplatin eligibility.**

Powles T et al. N Engl J Med 2024;390:875-888
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Breast Cancer Neoadjuvant / Adjuvant Overview

- Endocrine Therapy
  - Tamoxifen
  - Aromatase Inhibitors
  - Ovarian Function Suppression (with tamoxifen and/or AI sequential)
- Endocrine Therapy (ET) + CDK 4/6 inhibitors
    - **Abemaciclib (MonarchE trial)**
    - **Ribociclib (NATALEE trial)**
- Chemotherapy
  - Anthracycline based regimens
  - Taxane based regimens
- Chemotherapy + Immunotherapy
    - **Pembrolizumab (KEYNOTE-522)**
- Targeted Therapy
  - HER2: trastuzumab, pertuzumab, ado-trastuzumab emtansine
  - **PARP: Olaparib (OlympiA)**
- Bisphosphonates
  - Zoledronic acid

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. V.3.2024, 6/17/24,

MonarchE

- Open-label randomized phase 3 trial, 5637, HR+ / HER2-, high risk early stage breast cancer
  - Endocrine Therapy (ET) + abemaciclib 150 mg PO BID x 2 years vs ET
  - Addition of 2 years found ARR decrease of 6.4% (HR 0.664, 95% CI 0.578-0.762, P < .0001) in HR+ / HER2-negative, high-risk breast cancer
    - High Risk: 4+ lymph nodes and/or 1–3 lymph nodes with additional high risk features (tumor ≥ 5 cm or grade 3 histology)
  - Invasive DFS in abemaciclib + ET (83.6%) vs ET (76%); (HR 0.680; 95% CI 0.599 – 0.772; P < 0.001)
- NCCN recommendation: **offer two years of abemaciclib concurrently with endocrine therapy to patients with high-risk features**
- ASCO recommend to use according to FDA indication or as outlined by NCCN
  - FDA approval: Adjuvant treatment of HR+ / HER2- ; node + early stage, with high-risk of recurrence

Johnston SR et al. J Clin Oncol. 2020;38:3987-98.
Harbeck N et al. Ann Oncol. 2023;.34:S1256.
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer.

NATALEE

- Multicenter, randomized, open-label, Phase III trial in 5101 patients with HR+/HER2− breast cancer
  - Endocrine Therapy (ET) + ribociclib 400mg/day (3w-on/1w-off) x 3 years vs ET
    - Reduced dose compared to advanced breast cancer
  - Statistically significant improvement (3.3%) in invasive DFS with ribociclib +ET vs ET
    - HR-0.75, 95% CI 0.62-0.91, *P* = .003
  - The 3-year invasive disease–free survival rate was 90.7% with ribociclib + ET vs 87.6% ET
  - DFS observed across all patient subgroups: node-negative, stage II, and stage III disease.
    - Node-negative disease, the 3-year invasive disease–free survival rate was 93.2% vs 90.6.
    - Stage II disease, DFS of 94.2% vs 92.6% (30% risk reduction)
    - Stage III disease, DFS 88.1% vs 83.8% (24.5% risk reduction)
- NCCN recommends **additional follow up to characterize long term efficacy**

Slamon D et al. N Engl J Med 2024;390:1080-1091
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. V.3.2024, 6/17/24, © 2024 National Comprehensive Cancer Network, Inc., All Rights Reserved.

KEYNOTE-522

- Multicenter, Phase III, randomized, double-blind trial of 1174 treatment naive stage II or III triple negative breast cancer patients.
  - Neoadjuvant pembrolizumab + chemo → adjuvant pembrolizumab x 9 cycles

    vs neoadjuvant chemo + placebo → adjuvant placebo
    - Neoadjuvant chemo: paclitaxel weekly + carboplatin weekly or q3w x12 followed by

      AC (doxorubicin + cyclophosphamide) or EC (Epirubicin + cyclophosphamide) q3w x 4 cycles
  - 3-year event-free survival (EFS) rates were 84.5% (pembrolizumab) vs 76.8% (placebo)
    - HR = 0.63, 95% CI = 0.48–0.82; P < .001
  - 5-year EFS rate in pembrolizumab addition vs with the placebo arm (81.3% vs. 72.3%), with risk reduction in recurrence, progression, complications, or death of 37%
    - HR = 0.63; 95% CI, 0.49-0.81
- NCCN and ASCO Recommendation: **Pembrolizumab to be considered for stage II and III triple negative patients**

Schmid P et al. Ann Oncol 2023;34:S1256 - 7.
Schmid P et al. N Engl J Med 2020;382:810-21.
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer.

OlympiA

- Multi center, randomized, phase III trial, compared olaparib vs placebo in 1836 patients with germline BRCA 1/2 mutations
  - Post local or adjuvant therapy received Olaparib vs placebo
  - 4-year OS adjuvant olaparib group was 89.8% vs 86.4% in the placebo group (95% CI -0.1% -6.8%)
  - The 4-year invasive DFS for the olaparib group was 82.7% versus 75.4% in the placebo group (95% CI 3.0% - 11.5%)
  - 4-year distant DFS was 86.5% in olaparib versus 79.1% in placebo group (95% CI 3.6% -11.3%)
- NCCN Recommends **consideration of adding of adjuvant olaparib for 1 year after completion of local therapy or chemotherapy in select patients.**
  - Give post neoadjuvant therapy in:
    - Triple negative BC with residual disease
    - HR+,HER2-neg tumors with >4 positive lymph nodes after or residual disease after preoperative therapy and tumor grade (CPS+EG) score >3
  - May be used concurrently with endocrine therapy
    - Optimal sequence unknown in In patients eligible for both adjuvant olaparib and abemaciclib

Geyer C et al. Ann Oncol. 2022 Dec;33(12):1250-1268.
Tutt A et al. N Engl J Med. 2021;384:2394-405.
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer.

Non-Small Cell Lung Cancer – Neoadjuvant Immunotherapy Options

- Recommended Molecular Target Testing in Non-Small Cell Lung Cancer (NSCLC) – **NCCN Category 1 in bold**
  - Nonsquamous histology
    - **PD-L1, EGFR, ALK**, ROS1, BRAF, KRAS, NTRK1/2/3, MET exon, 14 skipping, RET, HER2
  - Squamous cell carcinoma
    - **PD-L1**
    - May consider: EGFR, ALK, ROS1, BRAF, KRAS, NTRK1/2/3, MET exon 14 skipping, RET, HER2
- Targeted therapy towards oncogenic mutation should be prioritized over immune checkpoint inhibitor treatment even with elevated PD-L1 expression

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CheckMate 816

- Randomized, open-label, phase 3 trial on 358 stage IB to IIIA, treatment naïve NSCLC
  - Nivolumab 360 mg IV and platinum-doublet every 3 weeks for 3 cycles
  - Median EFS was 31.6 months with nivolumab+chemo (95% CI, 30.2 – NR) vs 20.8 months with chemotherapy alone (95% CI, 14 – 26.7)
  - HR for disease progression, recurrence, or death (0.63; 97.38% CI, 0.43 to 0.91; P=0.005)
  - pCR was 24% for Nivolumab+Chemo (95% CI, 18.0-31.0) vs 2.2% for chemo alone (95% CI, 0.6-5.6)
- NCCN Recommendation: **Patients with resectable NSCLC (tumors ≥ 4 cm or node + disease) can be considered for nivolumab plus platinum-doublet chemotherapy as neoadjuvant therapy**

Forde PM et al. N Engl J Med. 2022; 386:1973-1985.
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KEYNOTE 671

- Randomized, double-blind, phase 3 trial on 1364 newly diagnosed, stage II, IIIA, or IIIB, NSCLC patients
  - Pembrolizumab + platinum doublet → surgery → pembrolizumab q3w x 13 cycles vs placebo – platinum double → surgery → placebo q3w x 13 cycles
  - EFS at 24 months 62.4% (pembrolizumab group) vs 40.6% (placebo group); (HR, 0.58; 95%CI, 0.46-0.72; P<0.001)
  - Estimated 2 year OS 80.9% (pembrolizumab group) vs 77.6% in the placebo group (P=0.02)
  - mPR = 30.2% (pembrolizumab group) vs. 11% (placebo group); (Δ19.2%, 95%CI, 13.9 to 24.7; P<0.0001)
  - pCR = 18.1% (pembrolizumab group) vs. 4% (placebo group); (Δ14.2%; 95% CI, 10.1 to 18.7; P<0.0001)
- NCCN Category 1: **Patients with resectable (tumors ≥ 4 cm or node positive disease) NSCLC can be considered for pembrolizumab plus cisplatin-doublet chemotherapy as neoadjuvant/adjuvant treatment**

Wakelee H et al. N Engl J Med. 2023; 389:491-503.
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Non-Small Cell Lung Cancer – Adjuvant Targeted Therapy Options

- Stage IIB
  - Negative Margins
    - Chemotherapy (Category 1) followed by atezolizumab (IMpower010) OR pembrolizumab (PEARLS/KEYNOTE-091) OR osimertinib (**ADAURA**)—EGFR exon 19 deletion or L858R
  - Positive Margins
    - Resection + Chemotherapy or Chemo Radiation (sequential or concurrent)
- Stage IIIA
  - Negative Margins
    - Chemotherapy (Category 1) followed by atezolizumab (IMpower010) OR pembrolizumab (PEARLS/KEYNOTE-091) OR osimertinib (**ADAURA**)— EGFR exon 19 deletion or L858R) OR Sequential chemotherapy and consider RT
  - Positive Margins
    - Chemoradiation (sequential or concurrent) vs Concurrent chemoradiation

ADAURA

- Randomized, phase 3, double-blind trial on 682 patients, post resection of early stage (IB – IIIA) EGFR mutated NSCLC
  - Osimertinib 80 mg po daily vs placebo x3 years or until recurrence, or discontinuation criterion met
  - mDFS: Osimertinib arm not reached at interim analysis vs. placebo was 20.4 months ($p < 0.0001$)
    - Maturity: 33% (osimertinib 11%, placebo 55%)
  - mDFS: Osimertinib arm was not reached at time of interim analysis vs. 28.1 months ($p < 0.0001$)
    - Maturity: 29% (osimertinib 12%, placebo 46%)

  Updated 5 year OS data
  - 5-year OS (Stage II/IIIA) (85%) osimertinib vs (73%) placebo arm (HR 0.49; 0.33-0.73, $p < 0.001$)
  - 5 year OS (Overall population (IB – IIIA)) was 88% in osimertinib arm vs 78% in the placebo arm ($p < 0.001$)
- NCCN 2a Recommendation: **Osimertinib may be considered for patients with completely resected early stage disease (Stage IB – IIIA, or IIIB [T3,N2]) who received previous adjuvant chemotherapy or are ineligible for platinum-based chemotherapy**

Tsuboi M et al. N Engl J Med. 2023; 389:137-147.
Wu YL et al. N Engl J Med. 2020; 383:1711-1723.
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Targetable Molecular Markers

Molecular Marker	Medication	Clinical Trial
EGFR exon 19 deletion*	Osimertinib Amivantanab	**FLAURA2** **MARIPOSA-2**
EGFR exon 20 insertion*	Amivantamab	**PAPILLON**, CHRYSALIS
ALK*	Alectinib Brigatinib Lorlatinib Ceritinib Crizotinib	ALEX ALTA-1L CROWN
ROS1	Entrectinib	ALKA, STARTRK-1, STARTRK-2
MET exon 14 skipping mutation	Capmatinib Tepotinib	GEOMETRY VISION
RET rearrangement	Selpercatinib Pralsetinib	Libretto-001 ARROW
BRAF V600E	Binimetinib+ Encorafenib	PHAROS

*** NCCN Category 1** Recommended Molecular testing in NSCLC

FLAURA2

- Randomized, phase 3, open-label trial, on 557 treatment naive patients with EGFR-mutated (exon 19 del or L858R mutated) advanced NSCLC
  - Osimertinib 80mg po daily vs Chemotherapy (CARBOplatin or CISplatin + Pemetrexed + Osimertinib) x 4 cycles → followed by Pemetrexed + Osimertinib
  - PFS: 25.5 months Osimertinib + Chemotherapy vs 16.7 months osimertinib alone
    - HR 0.62 (95% CI, 0.49-0.79); $p < 0.001$
  - ORR: 83% Osimertinib + Chemotherapy vs 76% osimertinib alone
  - DoR: 24 months Osimertinib + Chemotherapy vs. 15.3 months Osimertinib alone
  - Grade 3 or higher AE incidence from any cause was higher with the combination than monotherapy
- NCCN recommends **single-agent osimertinib as a preferred treatment option in first line setting for patients with advanced or metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R mutations**

Planchard D et al. N Engl J Med. 2023; 389:1935-1948.
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. V.7.2024, 6/26/24, © 2024 National Comprehensive Cancer Network, Inc., All Rights Reserved.

MARIPOSA-2

- Randomized, phase 3, on 657 patients with EGFR-mutated (exon 19 deletions or L858R) NSCLC, locally advanced or metastatic, progressed after Osimertinib
  - Amivantamab+Lazertinib+Chemo vs Amivantamab+Chemo vs Chemo only
  - Median PFS: (8.3 months) Amivantamab+Lazertinib+Chemotherapy vs (6.3 months) Amivantamab+Chemotherapy vs (4.2 months) in chemotherapy only arm
  - Amivantamab / Lazertinib / Chemotherapy vs. Chemotherapy:
    - HR for disease progression or death 0.44 (95% CI, 0.35-0.56); $p < 0.001$
  - Amivantamab+Chemotherapy vs. Chemotherapy:
    - HR for disease progression or death 0.48 (95% CI, 0.36-0.64); $p < 0.001$
  - ORR was significantly higher for amivantamab + chemotherapy (64%) and amivantamab + Lazertinib + chemotherapy (63%) vs chemotherapy (36%); $P < 0.001$ for both)
- NCCN recommends: **Amivantamab + CARBOplatin + pemetrexed as subsequent therapy for advanced or metastatic (nonsquamous) NSCLC patients with EGFR exon 19 deletion or exon 21 L858R mutations**

Passaro A et al. Ann Oncol. 2023; S0923-7534:04281-04283.
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PAPILLON

- Randomized, phase 3 trial on 308 treatment naive locally advanced or metastatic NSCLC patients with EGFR exon 20 insertion mutation.
  - Amivantamab + Chemo (CARBOplatin + Pemetrexed) vs Chemo only
  - mPFS of 1.4 months in Amivantamab + Chemo vs 6.7 months in Chemo alone
    - HR 0.4 (95% CI, 0.3 - 0.53); p < 0.001
  - ORR of 73% in Amivantamab + Chemo vs 47% in Chemo alone (p <0.001)
  - mPFS of 1.4 months in Amivantamab + Chemo vs 6.7 months in Chemo alone
  - HR 0.4 (95% CI, 0.3 - 0.53); p < 0.001
  - ORR of 73% in Amivantamab + Chemo vs 47% in Chemo alone (p <0.001)
- NCCN Guideline Recommendations: **Preferred, Category 1: Amivantamab + Chemotherapy as first line therapy for (nonsquamous) patients with EGFR exon 20 insertion mutation**

Zhou C et al. N Engl J Med. 2023; 389:2039-2051.
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. V.7.2024, 6/26/24, © 2024 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Summary

Bladder Cancer

- DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3–6 cycles as NCCN preferred regimen as preoperative chemotherapy for muscle invasive bladder cancer (VESPER trial)
- Gemcitabine and cisplatin followed by avelumab maintenance therapy as first-line systemic therapy for locally advanced or stage IV metastatic disease (JAVELIN Bladder 100 trial)
- Enfortumab vedotin + pembrolizumab is the preferred first-line systemic therapy option for advanced / metastatic urothelial carcinoma, regardless of cisplatin eligibility (EV-302/KEYNOTE-A39 trial)

Summary

Breast Cancer

- Patients with high risk features on endocrine therapy to be offered two years of abemaciclib concurrently (MonarchE trial)
- Neoadjuvant/adjuvant pembrolizumab to be considered for stage II and III triple negative patients (KEYNOTE-522 trial)
- Consideration of adding of adjuvant olaparib for 1 year after completion of local therapy or chemotherapy in select patients with germline BRCA 1/2 mutations (OlympiA trial)

Summary

Non-Small Cell Lung Cancer – Neoadjuvant / Adjuvant Setting

- Patients with resectable NSCLC (tumors ≥ 4 cm or node + disease) can be considered for nivolumab plus platinum-doublet chemotherapy as neoadjuvant therapy (CheckMate 816)
- Patients with resectable NSCLC (tumors ≥ 4 cm or node + disease) can be considered for pembrolizumab plus cisplatin-doublet chemotherapy as neoadjuvant/adjuvant treatment (NCCN Category 1)—(KEYNOTE 671)
- Osimertinib may be considered for EGFR mutation + patients with completely resected early stage disease (Stage IB – IIIA, or IIIB [T3,N2]) who received previous adjuvant chemotherapy or are ineligible for platinum-based therapy (ADAURA)

Summary

Non-Small Cell Lung Cancer – Targeted Therapy

- Single-agent osimertinib as a preferred treatment option in first line setting for patients with advanced or metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R mutations (FLAURA2)
- Amivantamab in combination with chemotherapy (CARBOplatin + pemetrexed) as subsequent therapy for advanced or metastatic NSCLC patients with EGFR exon 19 deletion or exon 21 L858R mutations (MARIPOSA-2)
- Amivantamab with Chemotherapy as first line therapy for patients with locally advanced or metastatic disease and EGFR exon 20 insertion mutation positive (NCCN Category 1)—(PAPILLON trial)

Clinical Updates: Solid Organ Tumor Pharmacotherapy

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