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Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered. Biosimilars or alternate formulations (along with the reference products) are considered on pathway unless otherwise specified by health plan formularies, medical policies, or preferred product rules.

Carelon Medical Benefits Management

Cancer Treatment Pathways

Proprietary

Table of Contents

Q2 Pathway Updates Effective 7/22/2024

Melanoma

- In the “Adjuvant Therapy” section, the two sub-sections for staging will be updated:
  - From: “Stages IIB-IIIC” to “Stages IIB-III”
  - From: “Stages IIIA-IIIC” to “Stage III”

NHL: Diffuse Large B-Cell Lymphoma (DLBCL)

- Term the Second Line of Therapy and regimens

Carelon Cancer Treatment Pathways

The goal of the medical oncology programs administered by Carelon Medical Benefits Management on behalf of our clients is to help provide access to quality and affordable cancer care. Carelon Cancer Treatment Pathways are a key component of each program.

Carelon Pathways are developed using a rigorous process of evidence-based medicine. Pathways differ from clinical practice guidelines in that the objective of a Pathway is to identify a subset of regimens supported by clinical evidence and practice guidelines with the goal of further reducing unwarranted variation in care and cost. Pathways are selected based on clinical benefit (efficacy), safety/side effects (especially those leading to hospitalizations & impacting quality of life), strength of national guideline recommendations, and cost of regimens. Dosage and drug schedules (i.e. the interval between doses) may be considered in the selection of Pathway regimens. Carelon Pathways are intended to support the use of quality cancer care.

Pathways are not available for every medical condition but are intended to be applicable for individuals with the most common cancer types. Within each cancer type, separate Pathways are usually available for early stage and advanced cancer, sub-types of cancer (e.g., HER2 positive) and different lines of therapy. When selecting the best cancer treatment for a patient a treating oncologist should consider the type of cancer, the stage, the biomarkers or specific genetic profile of the cancer, and unique aspects the individual's medical condition. Given the complexity of cancer and all the unique individual circumstances, it would not be possible to have a Pathway option available for every specific situation. The treating oncologist will determine if, in his/her medical opinion, an Carelon Pathway treatment regimen is the best option for a patient or whether, given his or her unique circumstances, another treatment regimen will be a better choice.

It is important to note that, for some health plans, we will review requested services in accordance with client medical policies and clinical guidelines. If a request is received from a provider that is not an Carelon Pathway regimen, it may be reviewed and may be authorized if it is determined to be medically necessary pursuant to medical policies and clinical guidelines.

Bladder Cancer (Urothelial) Pathways

Neoadjuvant Therapy

- Clinical Stage II, III, or IV Without Evidence of Metastases (cT2, cT3, cT4a, cT4b, M0)
  - **ddMVAC***: dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with G-CSF[1-8]
  - Gemcitabine (Gemzar) and cisplatin†[1, 2, 9-13]

Adjuvant Therapy

- Stage 0 (Ta, Tis) or Stage I
  - Following Transurethral Resection of Bladder Tumor (TURBT) OR Resection of Recurrent/Persistent Disease, 1-2 sets of treatment
    - **BCG**: bacillus calmette-guerin, intravesical[14-18]
  - For low-grade histology only, Following TURBT OR Resection of Recurrent/Persistent Disease
    - Gemcitabine (Gemzar), intravesical[19]

First Line of Therapy (1st Line)

- Stages IV or Recurrent
  - Enfortumab vedotin plus pembrolizumab[20, 21]

Second Line of Therapy (2nd Line)

- Stages IV or Recurrent
  - Gemcitabine (Gemzar)[22, 23]
  - Paclitaxel[24, 25]
  - Pembrolizumab (Keytruda)[26-29]
- Prior therapy with platinum-based chemotherapy AND PD-1/PD-L1 inhibitor
  - Enfortumab Vedotin[30-32]

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* Administration of ddMVAC is limited to 6 cycles

† Administration of Gemcitabine-cisplatin is limited to 4 cycles

Bladder Cancer (Urothelial) References

NCCN Practice Guidelines: Bladder Cancer Version 3.2023

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These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinical seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care core treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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Breast Cancer* Pathways: Neoadjuvant and Adjuvant (Non-Hormonal)

Neoadjuvant Therapy

- HER2 Positive
  - Stages IA† through IIIC
    - **TCH+P**: docetaxel (Taxotere), carboplatin, trastuzumab, and pertuzumab (Perjeta)[1-6]
- HER2 Negative, Hormone Receptor (ER or PR) Positive
  - Stage I-IIIC‡
    - **ddAC → weekly T**: dose dense doxorubicin (Adriamycin) and cyclophosphamide followed by weekly paclitaxel[7-13]
    - **Weekly T → ddAC**: weekly paclitaxel followed by dose dense doxorubicin (Adriamycin) and cyclophosphamide[7-13]
    - **TC**: docetaxel (Taxotere) and cyclophosphamide[14, 15]
- Triple Negative Breast Cancer (ER and PR, HER2 negative)
  - Stage II-IIIC
    - Pembrolizumab (Keytruda), carboplatin, and paclitaxel[16]
    - Pembrolizumab (Keytruda), doxorubicin, and cyclophosphamide[16]

Adjuvant Therapy

- HER2 Positive
  - Stages IA and IB
    - **TH§**: paclitaxel and trastuzumab [17-19]
  - Residual Disease following Neoadjuvant Therapy
    - Ado-trastuzumab emtansine (Kadcyla)[20]
- HER2 negative, Hormone Receptor (ER or PR) Positive
  - Stage I-IIIC‡
    - **ddAC → weekly T**: dose dense doxorubicin (Adriamycin) and cyclophosphamide followed by weekly paclitaxel[7-13]
    - **Weekly T → ddAC**: weekly paclitaxel followed by dose dense doxorubicin (Adriamycin) and cyclophosphamide[7-13]
    - **TC**: docetaxel (Taxotere) and cyclophosphamide[14, 15]
- Triple Negative Breast Cancer (ER, PR, and HER2 negative)
  - Stage II-IIIC**:** Continuation following Neoadjuvant Therapy
    - Pembrolizumab (Keytruda), following neoadjuvant pembrolizumab-based treatment[16]
  - Residual Disease following Neoadjuvant Therapy
    - Capecitabine (Xeloda)[21]

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* Breast cancer histologies include invasive ductal, invasive filtrating lobular, inflammatory, and invasive NOS.

† Stage I tumors must be at least >10 mm

‡ Therapy is indicated for T1b or larger tumors for patients under 50 years old with a 21 gene Recurrence Score that is intermediate or high (16+) or any patient with a 21 gene Recurrence Score that is high (26+)

§ Administration of trastuzumab is limited to 1 year

Breast Cancer Adjuvant and Neoadjuvant (Non-Hormonal) References

NCCN Clinical Practice Guidelines: *Breast Cancer*. Version 4.2023

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These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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Breast Cancer* Pathways: Advanced/Metastatic Disease

First Line of Therapy (1st Line)

- Stage IV and Recurrent, HER2 Positive
  - Pertuzumab (Perjeta), trastuzumab, and docetaxel (Taxotere)[1-6]
  - Pertuzumab (Perjeta), trastuzumab, and paclitaxel[7-10]

Second Line of Therapy (2nd Line)

- Stage IV and Recurrent
  - HER2 Positive
    - Fam-trastuzumab deruxtecan-nxki (Enhertu)[11-13]
  - HER2 Low
    - Fam-trastuzumab deruxtecan-nxki (Enhertu)[14]

First Line of Therapy (1st Line)

- Stage IV and Recurrent
  - Triple Negative Breast Cancer (ER, PR, and HER2 negative), CPS ≥ 10
    - Pembrolizumab (Keytruda) and nab-paclitaxel (Abraxane)[15]
    - Pembrolizumab (Keytruda) and paclitaxel[15]
    - Pembrolizumab (Keytruda), gemcitabine (Gemzar), and carboplatin[15]

First, Second, and Third Lines of Therapy (1st, 2nd, and 3rd Line)

- Stage IV and Recurrent
  - Triple Negative Breast Cancer (ER, PR, and HER2 negative)
    - Capecitabine (Xeloda)[16-21]
    - Doxorubicin (Adriamycin)[21-28]
    - Gemcitabine (Gemzar)[29, 30]
    - Paclitaxel[21, 31-35]
    - Vinorelbine (Navelbine)[36-38]
    - Sacituzumab govitecan-hziy (Trodelvy)[39-41] **(third line only)**
  - Hormone Receptor (ER or PR) Positive and HER2 Negative
    - Capecitabine (Xeloda)[16-20, 27]
    - Doxorubicin (Adriamycin)[22-28]
    - Gemcitabine (Gemzar)[29, 30]
    - Paclitaxel[22, 27, 31-35]
    - Vinorelbine (Navelbine)[36-38]
    - Sacituzumab govitecan-hziy (Trodelvy) (third line only)[42, 43]

* Breast cancer histologies include invasive ductal, invasive lobular, inflammatory, and invasive NOS.

Breast Cancer Advanced/Metastatic References

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Breast Cancer* Pathways: Endocrine Therapy for Hormone Receptor Positive Advanced/Metastatic Disease†

First Line of Therapy (1st Line)

- Stages IV and Recurrent
  - HER2 Negative
    - Anastrozole (Arimidex) and ribociclib (Kisqali)[1, 2]
    - Letrozole (Femara) and ribociclib (Kisqali)[1-4]
    - Anastrozole (Arimidex)[5-13]
    - Fulvestrant (Faslodex) high dose[7-10, 12-17]
    - Fulvestrant (Faslodex) and ribociclib (Kisqali)[18, 19]
    - Letrozole (Femara)[20-25]
    - Tamoxifen‡[15, 24, 26, 27]

Second Line of Therapy (2nd Line)

- Stages IV and Recurrent
  - HER2 Negative
    - Anastrozole (Arimidex)[5-13]
    - Fulvestrant (Faslodex) high dose[7-10, 12-17]
    - Fulvestrant (Faslodex) and ribociclib (Kisqali) §[18, 19]
    - Letrozole (Femara)[20-25]
    - Tamoxifen‡[15, 24, 26, 27]
    - Exemestane (Aromasin)[16, 28-30]

Second or Third Line of Therapy (2nd or 3rd Line)

  - PIK3CA/AKT1/PTEN Mutated and HER2 Negative
    - Fulvestrant (Faslodex) and alpelisib (PIQRAY) || ¶[31-33]
    - Fulvestrant (Faslodex) and capivasertib (TRUQAP) ¶[34]

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* Breast cancer histologies include invasive ductal, invasive lobular, inflammatory and invasive NOS

† With ovarian suppression for premenopausal individuals. Ovarian suppression utilizes LHRH agonists given as monthly injections. 3-month depot dosing does not reliably suppress estrogen levels.

‡ Tamoxifen is considered pathway for premenopausal individuals with or without ovarian suppression

§ Ribociclib regimens are not considered pathway when continued in the second line setting if the patient has received an available CDK4/6 inhibitor regimen in the first line setting

|| Regimen applies only to the subset of PIK3CA mutations

¶ After progression on prior therapy with a CDK 4/6 inhibitor

Breast Cancer Endocrine Therapy for Advanced/Metastatic Disease References

NCCN Clinical Practice Guidelines: *Breast Cancer*. Version 1.2024

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These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

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Biliary Tract Cancer (intra and extrahepatic cholangiocarcinoma) Pathway

First Line of Therapy (1st Line)

- Stages II-IVB, and Recurrent (unresectable and metastatic disease)
  - Durvalumab (Imfinzi), gemcitabine (Gemzar), and cisplatin[1]
  - Gemcitabine (Gemzar) and cisplatin[2-9]

Biliary Tract Cancer (intra and extrahepatic cholangiocarcinoma) References

NCCN Practice Guidelines: Biliary Tract Cancers Version 2.2024

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These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

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Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL) Pathways

First Line of Therapy (1st Line)

- Initial Therapy
  - Any 17p/TP53 status
    - Acalabrutinib (Calquence)[1-5]
    - Ibrutinib (Imbruvica)[6-12]
    - Zanubrutinib (Brukinsa)[13, 14]
  - Without 17p Deletion AND Without TP53 Mutation
    - Venetoclax (Venclexta) and obinutuzumab (Gazyva)[15, 16]

Second Line of Therapy (2nd Line)

- Recurrent / Relapsed Disease
  - Any 17p/TP53 status
    - Acalabrutinib (Calquence)[1-5]
    - Venetoclax (Venclexta) and rituximab[17-22]
    - Zanubrutinib (Brukinsa)[23-25]

Chronic Lymphocytic Leukemia (CLL) / Small Lymphocytic Lymphoma (SLL) References

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Chronic Myelogenous Leukemia- Chronic Phase Pathways

New Diagnosis of CML

- Low, Intermediate, or High-Risk Disease*
  - Imatinib (Gleevec)[1-13]
- Intermediate or High-Risk Disease*
  - Dasatinib (Sprycel)[8, 9, 12, 14-16]
  - Nilotinib (Tasigna)[10, 11, 13, 17-19]

Second Line of Therapy (2nd Line)

- Resistant disease to primary treatment, Suboptimal Response†, or Intolerance to 1st Line
  - Bosutinib (Bosulif)[6, 20, 21]
  - Dasatinib (Sprycel)[9, 22-26]
  - Nilotinib (Tasigna)[18, 19, 27-30]
- Presence of T315I mutation
  - Ponatinib (Iclusig)[31, 32]

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* For patients with intermediate or high-risk disease based on Sokal or Hasford score:

Sokal: Intermediate Risk=0.8-1.2; High Risk>1.2

Hasford: Intermediate Risk=781-1480; High Risk>1480

† Defined as lack of complete hematologic response or BCR-ABL1 transcripts > 10% (IS) or lack of partial cytogenetic response on bone marrow cytogenetics.

Chronic Myelogenous Leukemia- Chronic Phase References

NCCN Clinical Practice Guidelines: Chronic Myeloid Leukemia. Version 2.2024

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These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

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Colorectal Adenocarcinoma Pathways

Adjuvant Therapy

- Stage III
  - Limited to Colon Cancer
    - Capecitabine (Xeloda)[1]
    - **FULV**: fluorouracil (5FU) and leucovorin[1-9]
    - **CAPOX**: capecitabine (Xeloda) and oxaliplatin (limited to 3 months duration)[3-5, 10-13]
    - **FOLFOX**: fluorouracil (5-FU), leucovorin, and oxaliplatin[2, 4, 12, 14-21]

First or Second Lines of Therapy (1st or 2nd Line)

- Stages IV and Recurrent
  - RAS Wild Type (WT) or Mutant (MT)*
    - Capecitabine (Xeloda)[22, 23]
  - RAS Wild Type (WT) or Mutant (MT)* - Can Be Used With or Without Bevacizumab
    - **FOLFIRI**: fluorouracil (5FU), leucovorin, and irinotecan (Camptosar)[24-36]
    - **FOLFIRINOX**: fluorouracil (5FU), leucovorin, irinotecan (Camptosar), and oxaliplatin†[14, 37]
    - **mFOLFIRINOX**: fluorouracil (5FU), leucovorin, irinotecan (Camptosar), and oxaliplatin‡[14, 37]
    - **FOLFOX**: fluorouracil (5FU), leucovorin, oxaliplatin[17, 18, 24, 29, 33, 34, 38-45]
    - **FULV**: fluorouracil (5FU) and leucovorin[8, 23, 31, 32, 46-49]
  - RAS Wild Type (WT) and BRAF Wild Type (WT)
    - **FOLFIRI + panitumumab**: fluorouracil (5FU), leucovorin, and irinotecan (Camptosar) with panitumumab (Vectibix)§[50-52]
    - **FOLFOX + panitumumab**: fluorouracil (5-FU), leucovorin, and oxaliplatin with panitumumab (Vectibix)§[53-58]
    - Irinotecan (Camptosar) and panitumumab (Vectibix)§[50, 51, 59, 60]
  - MSI-H or dMMR
    - Pembrolizumab (Keytruda)||[61-64]

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* Individuals with metastatic colorectal cancer should have tumor genotyped for RAS (KRAS and NRAS) and BRAF mutations individually or as part of an NGS panel.

† FOLFIRINOX regimen has replaced FOLFOXIRI, as it is the recommended schedule/dosing of this drug combination for Colorectal Cancer,

‡ Modified FOLFIRINOX: Bolus 5-FU is not administered and Irinotecan dose is 150mg/m2

§ Limit to one line of therapy

|| Administered at a dose of 200 mg every 3 weeks OR 400 mg every 6 weeks per the FDA label OR 2 mg/kg (up to a maximum of 200 mg) every 3 weeks, as clinically appropriate

Colorectal Adenocarcinoma References

NCCN Clinical Practice Guidelines: Colon Cancer. Version 2.2023; Rectal Cancer. Version 4.2023

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These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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Gastric, Esophageal, and Gastroesophageal Junction Adenocarcinoma Pathways

Neoadjuvant Therapy (Pre-Operative, Peri-Operative, Primary Therapy)

- Potentially Resectable Disease
  - Cisplatin and fluorouracil (5FU)[1, 2]
  - Fluorouracil (5FU) and cisplatin with concurrent radiation therapy (RT)[3-5]
  - **FLOT:** Fluorouracil (5FU), leucovorin, oxaliplatin, and docetaxel (Taxotere)[6, 7]
  - Paclitaxel and carboplatin with concurrent RT*[8, 9]

Adjuvant Therapy (Post Operative-Adjuvant)

- Resected Disease
  - Fluorouracil (5FU) and leucovorin with concurrent RT[10-12]
  - Nivolumab (Opdivo)*[13]

First Line of Therapy

- Locally Advanced, Metastatic, or Recurrent Disease
  - Unresectable, HER2 Positive
    - Cisplatin, fluorouracil (5FU), and trastuzumab[14]
  - HER2 Negative
    - Fluorouracil (5FU) and Cisplatin†[14-18]
    - Fluorouracil (5FU) +/- Leucovorin and irinotecan (Camptosar) FOLFIRI[16, 19, 20]
    - **FLO/FOLFOX**: fluorouracil (5FU), leucovorin, and oxaliplatin[21, 22]
    - **FLP**: fluorouracil (5FU), leucovorin, and cisplatin[21]
    - FOLFOX + nivolumab: fluorouracil (5FU), leucovorin, oxaliplatin, and nivolumab (Opdivo) (**CPS ≥ 5**)[23]
    - Pembrolizumab (Keytruda), fluorouracil (5FU) and cisplatin **(CPS ≥10)**[24, 25]
    - Pembrolizumab (Keytruda), capecitabine (Xeloda) and oxaliplatin **(CPS ≥10)**[24, 25]

Second Line of Therapy (2nd Line)

- Unresectable Locally Advanced, Metastatic, or Recurrent Disease
  - Irinotecan (Camptosar)[26-30]
  - Paclitaxel[27, 28, 31]
  - Trastuzumab deruxtecan (Enhertu)‡ – (**HER2 Positive Only**)[32]

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* Limited to esophageal and gastroesophageal junction cancers only. Maximum duration of treatment is one year.

† Limited to gastric tumors only

‡ Use only after prior trastuzumab based therapy

Gastric, Esophageal, and Gastroesophageal Junction Adenocarcinomas References

NCCN Clinical Practice Guidelines: *Gastric Cancer*. Version 1.2024; *Esophageal and Esophagogastric Junction Cancers*. Version 1.2024

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Head and Neck Cancer Pathways

Adjuvant Therapy (Post-Operative Systemic Therapy)

- Stages II-IV (M0) - Candidate for Local Therapy
  - **Non-Nasopharyngeal** (Squamous Cell Carcinoma)
    - High dose cisplatin* with concurrent RT[1-13]

First Line of Therapy (1st Line)

- Stages II- IVB M0 (Primary/definitive) Candidate for Local Therapy
  - **Non-Nasopharyngeal** (Squamous Cell Carcinoma)
    - High dose cisplatin* with concurrent RT[1-13]
- Stages III-IV, Unresectable and Recurrent
  - **Non-Nasopharyngeal** (Squamous Cell Carcinoma)
    - Carboplatin, fluorouracil (5FU), and cetuximab (Erbitux)[14]
    - Cisplatin, fluorouracil (5FU), and cetuximab (Erbitux)[14]
    - Pembrolizumab (Keytruda)†[15, 16] **(CPS ≥ 20)**
    - Pembrolizumab (Keytruda), cisplatin, and fluorouracil (5FU)[15, 16] **(CPS ≥ 1)**
    - Pembrolizumab (Keytruda), carboplatin, and fluorouracil (5FU)[15, 16] **(CPS ≥ 1)**
- Stage II-IVA Candidate for Local Therapy (M0) (Induction, Primary/definitive and sequential therapy)
  - **Nasopharynx**
    - Cisplatin with concurrent RT[9, 12, 13, 17]
    - Cisplatin and gemcitabine (Gemzar) followed by concurrent cisplatin/RT[18]
- Stages IVB and Recurrent (Metastatic and Recurrent Disease)
  - **Nasopharynx**
    - Cisplatin, gemcitabine (Gemzar), and toripalimab (Loqtorzi)[19]

Second Line of Therapy (2nd Line)

- Stages IV and Recurrent
  - **Non-Nasopharyngeal** (Squamous Cell Carcinoma)
    - Nivolumab (Opdivo)[21, 22] **(CPS ≥ 1)**
    - Paclitaxel[20]

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* Cisplatin dosed at 100 mg/m^2 every three to four weeks OR dosed at 40 mg/m^2 weekly over the course of radiotherapy.

† Administered at a dose of 200 mg every 3 weeks OR 400 mg every 6 weeks per the FDA label

Head and Neck Cancer References

NCCN Clinical Practice Guidelines: Head and Neck Cancers V2.2024

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Hepatocellular Carcinoma Pathways

First Line of Therapy (1st Line)

- Stages II-IVB, and Recurrent - Unresectable and Metastatic Disease
  - Atezolizumab (Tecentriq) and bevacizumab[1, 2]
  - Sorafenib (Nexavar)[3-5]

Second Line of Therapy (2nd Line)

- Stages II-IVB, and Recurrent - Unresectable and Metastatic Disease
  - Cabozantinib (Cabometyx)[6]
  - Regorafenib (Stivarga)[7]

Hepatocellular Carcinoma References

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Hodgkin Lymphoma Pathways

First Line of Therapy (1st Line)

- Stages IA-IIB* (Early Stage)
  - Classical Hodgkin's Lymphoma, Favorable and Unfavorable Risk
    - **ABVD**: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (DTIC) ± ISRT†[1-9]
- Stages IIIA-IVB* (Advanced Stage)
  - Classical Hodgkin's Lymphoma
    - **ABVD**: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (DTIC) ± ISRT†[10-14]
    - **A-AVD:** brentuximab vedotin (Adcetris), doxorubicin (Adriamycin), vinblastine, and dacarbazine[15]

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* With or without extranodal disease

† ISRT – Involved site radiation therapy

Hodgkin Lymphoma References

NCCN Clinical Practice Guidelines: Hodgkin Lymphoma V1.2024

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Kidney Cancer (Clear Cell Carcinoma) Pathway

First Line of Therapy (1st Line)

- Stages IV and Recurrent
  - Nivolumab (Opdivo) and cabozantinib (Cabometyx)[1, 2]
  - Nivolumab (Opdivo) and ipilimumab (Yervoy)*[3-5]
  - Pembrolizumab (Keytruda) and axitinib (Inlyta)[6]

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* Excludes favorable risk tumors

Kidney Cancer (Clear Cell Carcinoma) References

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Lung Cancer: Non-Small Cell Lung Cancer (NSCLC) Pathways

Chemoradiation for Localized Disease

- Stages IA-IIIC - Definitive Concurrent Chemoradiation
  - Cisplatin and etoposide[1, 2]
  - Paclitaxel and carboplatin[3]

Adjuvant Therapy

- Stages IB-IIIB
  - Carboplatin and paclitaxel[4]
  - Cisplatin and gemcitabine (Gemzar)[5]
  - Cisplatin and pemetrexed (Alimta)[6, 7]
  - Cisplatin and vinorelbine (Navelbine)[8-11]

First Line of Therapy (1st Line) – Stages IIIB-IV, and Recurrent

- Squamous and Non-Squamous Cell Carcinoma
  - PD-L1 Expression (TPS) greater or equal to 50%, **without known actionable oncogenic targets***
    - Cemiplimab-rwlc (Libtayo)[12]
    - Pembrolizumab (Keytruda)†[13-16]
  - Ineligible for Immunotherapy
    - Carboplatin or cisplatin and paclitaxel[17-23]
    - Carboplatin or cisplatin and gemcitabine (Gemzar)[21, 24-29]
  - ALK Rearrangement Positive
    - Alectinib (Alecensa)[30, 31]
    - Lorlatinib (Lobrena)[32]
  - EGFR exon 19 deletion or exon 21 L858R mutation positive
    - Osimertinib (Tagrisso)[33-36]
    - Carboplatin or cisplatin, pemetrexed, and osimertinib (Tagrisso) **(Non-Squamous Only)** [37, 38]
- Non-Squamous Cell Carcinoma Only
  - PD-L1 Expression (TPS) less than 50%, without known actionable oncogenic targets*
    - Carboplatin or cisplatin, pemetrexed (Alimta), and pembrolizumab (Keytruda)†[39-42]
    - Carboplatin or cisplatin, pemetrexed (Alimta), and cemiplimab-rwlc (Libtayo)[43, 44]
  - PD-L1 Expression (TPS) greater or equal to 50%, **without known actionable oncogenic targets***
    - Atezolizumab (Tecentriq)[45, 46]
  - Ineligible for Immunotherapy
    - Carboplatin, paclitaxel, and bevacizumab [47-49]
    - Carboplatin or cisplatin and pemetrexed (Alimta)[28, 50]
- Squamous Cell Carcinoma Only
  - PD-L1 Expression (TPS) less than 50%, without known actionable oncogenic targets*
    - Pembrolizumab (Keytruda)†, carboplatin, and paclitaxel[51]
    - Carboplatin or cisplatin, paclitaxel, and cemiplimab-rwlc (Libtayo)[43, 44]

Second Line of Therapy (2nd Line) – Stages IIIB-IV, and Recurrent

- Squamous and Non-Squamous Cell Carcinoma
  - Carboplatin or cisplatin and paclitaxel‡[18]
  - Carboplatin or cisplatin and gemcitabine (Gemzar)‡[52]
  - Carboplatin or cisplatin and pemetrexed (Alimta)‡[24, 53, 54]
  - No prior immunotherapy has been given
    - Atezolizumab (Tecentriq)[55]
    - Nivolumab (Opdivo)[56-62]
  - With known **actionable oncogenic target*** and prior targeted therapy
    - Carboplatin or cisplatin and paclitaxel[18, 53]
    - Carboplatin or cisplatin and gemcitabine (Gemzar)[52, 53]
    - Carboplatin or cisplatin and pemetrexed (Alimta)[24, 53, 54]

Maintenance Therapy – Stages IIIB-IV, and Recurrent

- Non-Squamous Cell Carcinoma Only
  - Continuation bevacizumab[63, 64]
  - Continuation pemetrexed (Alimta)[65-67]
  - Switch pemetrexed (Alimta)[65, 68]
  - If previously treated with carboplatin‡, pemetrexed, and pembrolizumab
    - Pembrolizumab (Keytruda)† and pemetrexed (Alimta)[69]

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* Actionable oncogenic targets refer to the driver aberrations in EGFR, ALK, and ROS1

† Administered at a dose of 200 mg every 3 weeks OR 400 mg every 6 weeks per the FDA label OR 2 mg/kg (up to a maximum of 200 mg) every 3 weeks, as clinically appropriate

‡ Eligible only if immunotherapy alone was administered as first line treatment. Ineligible if chemotherapy was used in the first line setting.

Lung Cancer: Non-Small Cell Lung Cancer (NSCLC) References

NCCN Clinical Practice Guidelines: Non-Small Cell Lung Cancer V2.2024

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These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

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Lung Cancer: Small Cell Lung Cancer Pathways

Adjuvant Therapy

- Limited Stage
  - With or without concurrent radiation therapy
    - Carboplatin and etoposide[1]
    - Cisplatin and etoposide[2-4]

Neoadjuvant Therapy, Primary Therapy, First Line Therapy

- Limited Stage
  - With or without concurrent radiation therapy
    - Carboplatin and etoposide[1]
    - Cisplatin and etoposide[2-4]
- Extensive Stage
    - Atezolizumab (Tecentriq), carboplatin,and etoposide[5]
    - Carboplatin and etoposide[2-4]

Lung Cancer: Small Cell Lung Cancer References

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These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

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Melanoma (Cutaneous Melanoma) Pathways

Neoadjuvant Therapy

- Stages IIIB-IV (resectable)
  - Pembrolizumab (Keytruda)[1]

Adjuvant Therapy

- ~~Stages IIB-IIIC~~ – **Termed Effective 7/22/2024**
- Stages IIB-III – **Added Effective 7/22/2024**
  - Resected
    - Pembrolizumab (Keytruda)[1-3]
- ~~Stages IIIA-IIIC~~ – **Termed Effective 7/22/2024**
- Stage III – **Added Effective 7/22/2024**
  - Resected
    - Nivolumab (Opdivo)[4, 5]

First Line of Therapy (1st Line)

- Stages IV and Recurrent
  - Any BRAF Status
    - Nivolumab (Opdivo)[6-9]
    - Nivolumab (Opdivo) and ipilimumab (Yervoy)[10-18]
    - Pembrolizumab (Keytruda)*[19-24]
  - BRAF Mutated†
    - Encorafenib (Braftovi) and binimetinib (Mektovi)‡[25]

Second and Subsequent Lines of Therapy (2nd Line+)

- Stages IV and Recurrent
  - BRAF Mutated† (and no prior BRAF targeted therapy)
    - Encorafenib (Braftovi) and binimetinib (Mektovi)[25]

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* Administered at a dose of 200 mg every 3 weeks OR 400 mg every 6 weeks per the FDA label OR 2 mg/kg (up to a maximum of 200 mg) every 3 weeks, as clinically appropriate

† BRAF V600E or V600K mutations

‡ First line only if the patient is not considered a suitable candidate for immunotherapy.

Melanoma: Cutaneous Melanoma References

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Multiple Myeloma Pathways

First Line of Therapy (1st Line)

- New Diagnosis
  - Transplant Candidates
    - **VRD/VDR**: bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone[1-4]
    - **D-VTd:** daratumumab (Darzalex), bortezomib (Velcade), thalidomide (Thalomid), and dexamethasone[5]
    - **D-VRd:** daratumumab (Darzalex), bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone[6, 7]
  - Non-Transplant Candidates
    - **CyBorD or VDC:** bortezomib (Velcade), cyclophosphamide, and dexamethasone[2, 4, 8, 9]
    - **DRd:** daratumumab (Darzalex), lenalidomide (Revlimid), and dexamethasone[10, 11]
    - **Rd**: lenalidomide (Revlimid) and low-dose dexamethasone[12-14]
    - **VRd**: bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone[1-4, 15]
    - **Vd**: bortezomib (Velcade) and dexamethasone[16]

Second or Third Lines of Therapy (2nd or 3rd Line)

- Early Relapsed Disease
    - **CRd or KRd**: carfilzomib (Kyprolis), lenalidomide (Revlimid), and dexamethasone[17, 18]
    - **DRd:** daratumumab (Darzalex), lenalidomide (Revlimid), and dexamethasone[19]
    - **DVd:** daratumumab (Darzalex), bortezomib (Velcade), and dexamethasone[20]
    - **PVd:** pomalidomide (Pomalyst), bortezomib (Velcade), and dexamethasone*[21]

Maintenance Therapy

- Post-Transplant
    - Lenalidomide (Revlimid)[22-27]

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* Eligible only if patient has received prior therapy with lenalidomide and proteasome inhibitor

Multiple Myeloma References

NCCN Clinical Practice Guidelines: *Multiple Myeloma*. Version 2.2024

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These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

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NHL: Diffuse Large B-Cell Lymphoma Pathways

First Line of Therapy (1st Line)

- Stages I-IV
  - **R-CHOP (21)**: cyclophosphamide, doxorubicin (Adriamycin), vincristine (Vincasar), prednisone, and rituximab[1-3]
  - When there is a contraindication to anthracycline
    - **R-CEOP**: cyclophosphamide, etoposide, vincristine (Vincasar), prednisone, and rituximab[4-6]

Second Line of Therapy (2nd Line) – Termed effective 7/22/2024

- Stages I-IV and Recurrent
  - Transplant Candidates
    - **R-ICE**: ifosfamide (Ifex), carboplatin, etoposide, and rituximab **– Termed Effective 7/22/2024**
  - Non-Transplant Candidates
    - **R-GemOx**: gemcitabine (Gemzar), oxaliplatin, and rituximab **– Termed Effective 7/22/2024**
  - Transplant and Non-Transplant Candidates
    - **R-GDP**: gemcitabine (Gemzar), dexamethasone, cisplatin, and rituximab **– Termed Effective 7/22/2024**
    - **R-GDP**: gemcitabine (Gemzar), dexamethasone, carboplatin, and rituximab **– Termed Effective 7/22/2024**

NHL: Diffuse Large B Cell Lymphoma References

NCCN Clinical Practice Guidelines for B-Cell Lymphomas. Version 2.2024

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These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

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NHL: Follicular and Marginal Zone Lymphoma Pathways

First Line of Therapy

- Stages* I-II
  - Gastric MALT† Lymphoma when *H. pylori* positive
    - Antibiotic therapy for *H. pylori* eradication‡[1, 2]
- Stages* I-IV
  - Gastric MALT or Splenic Marginal Zone§
    - Rituximab[3-8]
  - Follicular (Grade 1-3a) and Other Marginal Zone Lymphomas
    - **BR**: Bendamustine (Bendeka, Treanda) and rituximab[9-12]
    - **R-CHOP(21)**: Cyclophosphamide, doxorubicin (Adriamycin), vincristine (Vincasar), prednisone, and rituximab[11, 13-16]
    - **R-CVP**: Cyclophosphamide, vincristine (Vincasar), prednisone, and rituximab[14, 17]
    - Rituximab[3-8, 18-20]
  - Follicular Lymphoma (Grade 3b)
    - **R-CHOP(21)**: Cyclophosphamide, doxorubicin (Adriamycin), vincristine (Vincasar), prednisone, and rituximab[11, 13-16]
    - **R-CEOP**: Cyclophosphamide, etoposide, vincristine (Vincasar), prednisone, and rituximab[21-24]

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* Lugano Staging System for GI lymphomas

† Gastric MALT with translocation 11;18 (t11;18) (q21;q21) predicts a lower response rate to anti-H.pylori treatment. Radiation therapy or other local intervention may be indicated.

‡ Only generic antibiotics are considered pathway options for H. pylori eradication. Clarithromycin and either amoxicillin OR metronidazole are sample regimens that may be selected to maintain pathway adherence. The actual regimen prescribed should be based on current guidelines, local antibiotic resistance patterns, and the most affordable choices.

§ Splenectomy is also a recommended option for splenic marginal zone lymphoma

NHL: Follicular and Marginal Zone Lymphoma References

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These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

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NHL: Mantle Cell Lymphoma Pathways

First Line of Therapy (1st Line)

- Stages I-IV
  - Candidates for Autologous Stem Cell Transplant (ASCT)
    - **Alternating R-CHOP/R-DHAP:** cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine (Vincasar), prednisone, rituximab alternating with dexamethasone, cisplatin, cytarabine (Ara-C), and rituximab[1-8]
    - **Nordic Regimen**: dose intense rituximab, cyclophosphamide, vincristine (Vincasar), doxorubicin (Adriamycin), prednisone alternating with rituximab and high dose cytarabine (Ara-C)[9, 10]
  - Non-Candidates for Autologous Stem Cell Transplant (ASCT)
    - **BR:** bendamustine (Bendeka, Treanda) and rituximab[11-16]

Second Line of Therapy (2nd Line)

- Stages I-IV, and Recurrent
  - Acalabrutinib (Calquence)[17]
  - **BR:** bendamustine (Bendeka, Treanda) and rituximab[18, 19]
  - Bortezomib (Velcade)[7, 20, 21]
  - Ibrutinib (Imbruvica)[6, 7, 22, 23]
  - Lenalidomide (Revlimid)[24-29]

NHL: Mantle Cell Lymphoma References

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These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

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Ovarian Cancer (Epithelial) Pathways

Adjuvant Therapy

- Stages IA/IB (Grade 2 or 3), and IC (Grade 1-3)
  - Carboplatin and paclitaxel[1-5]

Adjuvant, Neoadjuvant, or Primary Therapy

- Stage III
  - Intravenous (IV) paclitaxel and Intraperitoneal (IP) cisplatin and IP paclitaxel[6-9]
- Stages II-IV
  - Carboplatin and paclitaxel **(Administered weekly or every 3 weeks)**[1-6, 10-12]

Initial Treatment for Metastatic or Recurrent Disease

- Platinum Sensitive*
  - Carboplatin[13-15]
  - Carboplatin and gemcitabine (Gemzar)[15-17]
  - Carboplatin and paclitaxel[13, 14, 18]
  - Carboplatin and weekly paclitaxel[19]
- Platinum Resistant
  - Bevacizumab monotherapy[20, 21]
  - Docetaxel (Taxotere)[22]
  - Gemcitabine (Gemzar)[23, 24]
  - Liposomal doxorubicin (Doxil)[23-25]
  - Paclitaxel (weekly)[26-28]
  - Paclitaxel and bevacizumab[29-32]

Maintenance Therapy

- After response to initial treatment for platinum-sensitive disease
  - Sensitive* to platinum-based therapies
    - Niraparib (Zejula)[33-37]
    - Olaparib (Lynparza)[38-45]
    - Rucaparib (Rubraca)[46-51]

* Platinum sensitive disease is defined as recurrence of greater than 6 months after prior platinum-based therapy

Ovarian Cancer (Epithelial) References

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Pancreatic Adenocarcinoma Pathways

Adjuvant Therapy

- Stages I, IA, IB, II, IIA, IIB, and III
  - Capecitabine (Xeloda) and gemcitabine (Gemzar)[1-3]
  - **FULV**: fluorouracil (5FU) and leucovorin[4-6]
  - Gemcitabine (Gemzar)[4, 6-8]
  - **mFOLFIRINOX***: fluorouracil (5FU), leucovorin, irinotecan (Camptosar), and oxaliplatin[9, 10]

First Line of Therapy (1st Line)

- Stages III, IV, and Recurrent
  - **FOLFIRINOX:** fluorouracil (5FU), leucovorin, irinotecan (Camptosar), and oxaliplatin[11-13]
  - **mFOLFIRINOX**: fluorouracil (5FU), leucovorin, irinotecan (Camptosar), and oxaliplatin[35]
  - Gemcitabine (Gemzar)[11, 14-17]
  - Gemcitabine (Gemzar) and albumin-bound-paclitaxel (Abraxane)[17-19]

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* Modified FOLFIRINOX: Bolus 5-FU not administered and dose of Irinotecan 150mg/m2

Pancreatic Adenocarcinoma References

NCCN Clinical Practice Guidelines: Pancreatic Adenocarcinoma V1.2024

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Prostate Adenocarcinoma Pathways

Adjuvant Therapy

- Stage IVA: Regional disease (lymph node involvement)
  - Post-Prostatectomy
    - Goserelin (Zoladex)[1-3]
    - Leuprolide (Eligard/Lupron)[1-3]
    - Triptorelin (Trelstar)[1-3]

First Line of Therapy (1st Line), Stages I-IV

- Localized favorable intermediate and Localized unfavorable intermediate
  - Primary Treatment with Radiotherapy (RT)
    - Goserelin (Zoladex)*[1-3]
    - Leuprolide (Eligard/Lupron)*[1-3]
    - Triptorelin (Trelstar)*[1-3]
- Localized high risk, Localized very high risk and Regional Disease
  - Primary Treatment with Radiotherapy (RT)
    - Goserelin (Zoladex)[1-3]
    - Goserelin (Zoladex) with abiraterone (Zytiga)[4-7]
    - Leuprolide (Eligard/Lupron)[1-3]
    - Leuprolide (Eligard/Lupron) with abiraterone (Zytiga)[4-7]
    - Triptorelin (Trelstar)[1-3]
    - Triptorelin (Trelstar) with abiraterone (Zytiga)[4-7]

First Line of Therapy (1st line)

- Metastatic/Recurrent, Castration Sensitive Disease
  - Abiraterone (Zytiga) and prednisone with Androgen Deprivation Therapy (ADT)†§ [4, 6-10]
  - Abiraterone (Zytiga), docetaxel (Taxotere), and prednisone with ADT†[11]
  - Apalutamide (Erleada) with ADT†[12-15]
  - Darolutamide (Nubeqa) and docetaxel (Taxotere) with ADT†[16]
  - Enzalutamide (Xtandi) with ADT†§[17-21]
- Metastatic/Recurrent, Castration Resistant Disease
  - Abiraterone (Zytiga) and prednisone with ADT†§[7, 22-29]
  - Docetaxel (Taxotere) (every 3 weeks) with ADT†‡[30-32]
  - Enzalutamide (Xtandi)¶ with ADT†§[33-39]

Bilateral orchiectomy (surgical castration) is an equally effective alternative to medical castration

* May be coadministered with bicalutamide (Casodex) or flutamide (Eulexin) for up to 30-60 days in patients who are at risk of developing symptoms associated with testosterone flare

† ADT pathway options, when given as listed above: goserelin (Zoladex), leuprolide (Eligard/Lupron), triptorelin (Trelstar) or history of bilateral orchiectomy

‡ If not previously used in the first line (1st Line) setting

§ The use of androgen-signaling–targeted inhibitor (e.g., abiraterone or enzalutamide) should be limited to one line of therapy and should be used in combination with ADT unless not indicated due to bilateral orchiectomy.

Prostate Adenocarcinoma References

NCCN Clinical Practice Guidelines: Prostate Cancer. Version 3.2023

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These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

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Testicular Cancer (Germ Cell Tumors) Pathways

Adjuvant Therapy

- Stages II-IIIC and IS
  - Seminoma
    - **BEP:** bleomycin, etoposide, and cisplatin[1]
    - **EP:** etoposide and cisplatin[2]
  - **Non-Seminoma** after Retroperitoneal Lymph Node Dissection (RPLND)
    - **EP:** etoposide and cisplatin[3, 4]

First Line of Therapy (1st Line)

- Stages II-IIIA and IS
  - Seminoma and Non-Seminoma
    - **BEP:** bleomycin, etoposide, and cisplatin[1,3-6]
    - **EP:** etoposide and cisplatin[2]
- Stages IIIB and IIIC
  - **Seminoma** with Good and Intermediate Risk*
    - **BEP:** bleomycin, etoposide, and cisplatin[5]
  - **Seminoma** with Good Risk
    - **EP:** etoposide and cisplatin[2]
  - Non-Seminoma
    - **BEP:** bleomycin, etoposide, and cisplatin[5-9]

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* BEP is typically given for 3 cycles in good risk seminoma, and 4 cycles in intermediate risk.

† EP given for 4 cycles

Testicular Cancer (Germ Cell Tumors) References

NCCN Practice Guidelines: Testicular Cancer 1.2023

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Uterine Cancer (Epithelial Carcinoma) Pathways

Adjuvant or Primary Therapy

- Stages III-IVA
  - Carboplatin, paclitaxel, and dostarlimab-gxly (Jemperli)[1]
  - Carboplatin, paclitaxel, and pembrolizumab[2]

First Line of Therapy (1st Line)

- Stages IVB and Recurrent
  - Cisplatin and doxorubicin (Adriamycin)[3-5]
  - Carboplatin, paclitaxel, and dostarlimab-gxly (Jemperli)[1]
  - Carboplatin, paclitaxel, and pembrolizumab[2]

Uterine Cancer (Epithelial Carcinoma) References

NCCN Practice Guidelines: Uterine Neoplasms Version 2.2024.

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These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

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