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FRAMEWORK FOR MEASURING CANCER TREATMENT COST AND QUALITY

User Guide

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# Use of Framework files, permissions, and disclaimers

These files are being made openly available for research use.

Any publications using this resource should cite it by DOI: **10.5281/zenodo.15101778**

Please note that only the **first tab** of each spreadsheet contains final analytic variables. Subsequent tabs contain intermediate / “scratch” work, which may be incomplete or obsolete.

In addition, we ask that any users reference and cite the initial research studies developing and applying the Framework:

* Quality of Treatment Selection for Medicare Beneficiaries With Cancer. PMID: 39393041
* The Accuracy and Usefulness of the National Comprehensive Cancer Network Evidence Blocks Affordability Rating. PMID: 32201922 PMCID: PMC8357422
* Association Between Clinical Value and Financial Cost of Cancer Treatments: A Cross-Sectional Analysis. PMID: 33022648 PMCID: PMC8354655

**The Framework data files are highly complex**, reflecting the underlying complexity and continually evolving nature of oncology clinical practice and clinical evidence. The abstraction of clinical practice guidelines into discreet data elements has often involved assumptions and simplifications. Any researchers considering using the Framework are highly encouraged to reach out ahead of time! We anticipate that discussion with the Framework development team will help facilitate ease of use, and avoid errors or misapplications. The goal is effective collaboration. First point of contact is study PI Dr. Aaron Mitchell:

[Mitchea2@mskcc.org](mailto:Mitchea2@mskcc.org)

# Included Documents & Files

* Framework version January 2016
* Framework version January 2017
* Framework version January 2018
* Framework version January 2019
* Framework version January 2020
* Framework version January 2021
* Framework version January 2022
* Framework version July 2016
* Framework version July 2017
* Framework version July 2018
* Framework version July 2019
* Framework version July 2020
* Framework version July 2021
* Data Dictionary
* Individual Drug Prices
* Unique ID Key

# Requesting NCCN Guidelines

Go to <https://www.nccn.org/about/permissions/request_form.aspx>

* Fill in personal information and list Epi/Bio address
* Intended use: Academic, Format: Journal Article
* Journal/Book Name, Authors/Editors, Publisher: Unknown at this time
* Media formats: print and internet
* Project sponsor: Aaron Mitchell
* Will the content being requesting be used with Health Info Tech? No
* If you’ve heard no respond from NCCN after a week, send a follow up message to this email: [PermissionRequest@nccn.org](mailto:PermissionRequest@nccn.org)

# Downloading CMS ASP Files

* Download the version active as of each January 1st and July 1st 
  + January 1 = Q1
  + July 1 = Q3
* ASP file versions are available at (<https://www.cms.gov/medicare/payment/part-b-drugs/asp-pricing-files>)

# NCCN Abstractions

* Use most current version of guidelines available as of each January 1st and July 1st
* List all regimens for which there are "evidence box" ratings
* Manually extract the following columns for each regimen: Guideline edition, Cancer subtype, Indication subset, Unique ID, Regimen name, Evidence Block scores, Category of Evidence, Preferred Status

# Unique ID

* A Unique ID assigned to each regimen to allow the same regimen to be identified across time (eg., across spreadsheet versions)
* The first two numbers in each ID are cancer-type specific (see “Unique ID Key” spreadsheet in the 'Unique ID Key’ folder)
* For each Unique ID, some regimen characteristics (such as whether radiation therapy or stem cell transplant is included, the emetic and neutropenic fever risk, and the component drugs) are static and do not change over time, except in rare circumstances. Some regimen characteristics, such as NCCN Evidence Blocks score, level of evidence, and treatment costs, **do** change over time.

# Radiation Therapy/Stem Cell Transplant

* Regimens which include with radiation therapy (RT)/stem cell transplants (SCT or HSCT) exhibit significant additional costs outside of chemotherapy and supportive drugs. We identify regimens with RT/SCT so that we are only comparing regimens within groups that have the same indication and expected additional costs outside of chemotherapy and supportive drugs (see Emetic Risk/Growth Factor below).
* SCT should occur only in guidelines for multiple myeloma, lymphomas, leukemias, and testicular cancer
  + Keep an eye out for phrases: “stem cell transfer,” “hematopoietic cell transfer,” HSCT/HCT, “induction”

# Categories of Consensus and Evidence

* Assign a consensus category to each regimen
* Search for consensus assignment in this order:

1. Table containing all treatments and consensus category on the slide preceding the evidence blocks
2. Flow charts of regimens towards the beginning of the slide deck
3. If consensus category is not specified in either guideline location, assign level 2A

* In some cases, the NCCN assigns consensus and evidence scores more granularly than evidence block scores (e.g. evidence block indication is for ‘adjuvant and neoadjuvant chemo’ while consensus and evidence score differs whether the setting is adjuvant or neoadjuvant). In these cases, we created to separate unique IDs to describe the treatment, with each assigned a different consensus and evidence score.

# Regimen Types

* ‘Regimen type’ is used to differentiate whether a given treatment is ‘time limited’ (aka, “defined course”) or ‘time unlimited’ (aka, “undefined” course)
* **Time limited** treatments (aka, “defined” course) are those that are intended to be administered for certain duration (typically, a number of cycles or a number of months) and then stopped. This often occurs in patients receiving "adjuvant” or “neoadjuvant” treatment for curable disease.
  + For time limited treatments, we calculate the cost for the full course of treatment.
* **Time unlimited** treatments (aka, “undefined” course) are those that are continued “until disease progression or unacceptable toxicity” – eg., as long as the treatment continues to work. Often just months, but in some cases mean years. These treatments often apply to patients with metastatic, incurable disease.
  + For time unlimited treatments, we calculate the cost per month of treatment.
  + Note: in order to account for instances where the cost of treatment varies across the initial months of therapy (such as cases wherein a drug dose is slowing escalated, or an initial higher “loading dose” is given), our monthly cost is obtained conceptually by calculating the cost over the first full year of therapy, and then dividing by 12.

# Dosing

When drug dose is based on body mass or surface area, we assume 70 kg body mass and 1.7 m2 body surface area

## **Hierarchy of information sources for dosing:**

1. dosing schedules specified within the NCCN guidelines
2. standard dosing levels specified on the drug label (<https://www.uptodate.com/contents/search>)
   1. When both on-label and off-label dosing schedules are specified, prioritize on-label.
3. a dosing schedule from the reference or references cited by the NCCN guidelines for each treatment
4. a dosing schedule listed in the NCCN Drugs & Biologics Compendium (<https://www.nccn.org/professionals/drug_compendium/content/>)
5. a manual literature search in PubMed for a dosing schedule corresponding to the relevant indication
6. If an applicable dosing schedule was not attainable through any of these sources, the treatment was excluded (eg., “exclude” column = 1)

## **Regimens with multiple dosing schedules:**

* In cases where there is a difference in dosing frequency, chose the option with LESS frequent dosing (e.g., 10 units of drug every two weeks, rather than 5 units of drug every week)
* In cases where the dosing schedule is the same but there is a range of doses, choose the LOWER end of the dosing range (e.g., if NCCN says 800-1,200mg of gemcitabine, go with 800)

## **Cycle Calculations (time-unlimited vs. time-limited):**

* For time unlimited regimens:
  + Cycles are calculated on a 52-week year
    - Determined by the number of days/weeks as indicated by administration instructions
    - Ie., If a drug is administered 1x every 28 days until disease progression or unacceptable toxicity (i.e., once every 4 weeks), the calculation would be 52/4= 13. This equates to 13 total cycles over the course of 52 weeks
  + Oral drugs are usually calculated on a daily basis depending on daily specifications from dosing guideline
    - Eg., once a day until disease progression = 365 doses per year
    - Eg., twice a day, each day of a 4-week cycle until disease progression = (2\*28)\*(52/4) = 728 doses per year
* For time limited regimens:
  + The number of drug administrations are determined in accordance with the planned number of cycles
    - Example: a drug is administered on day 1 of a 28 day cycle, for 10 cycles
      * The drug is assumed to be administered for 10 doses total

**Other notes:**

* Mesna is assumed to always be given along with ifosfamide, even in cases where Mesna is not explicitly mentioned in the NCCN Guidelines
* Dosages that are listed as given “for up to” a year or longer will be marked as time limited with a treatment duration of 1 year.
* An exception to this is the immunotherapy drugs (eg., pembrolizumab) which for some indications have a specified treatment duration of “up to two years.” These regimens are coded as time unlimited (and prices are therefore presented as per month), to better reflect the reality that the large majority of patients will have progression and discontinue therapy prior to two years.

# Supportive Care: Emetic Risk/Growth Factor

* For **antiemesis treatment**, Go to NCCN Guidelines for Supportive Care --> Antiemesis
  + Emesis risk ratings (in accordance with NCCN Guidelines)
    - 0 = minimal (no administration associated with this rating) | <10% frequency of emesis
    - 1 = low | 10%-30% frequency of emesis
    - 2 = moderate | 30%-90% frequency of emesis
    - 3 = high | >90% frequency of emesis
  + For each treatment regimen, we first identify the specific agent with the highest emetic risk.
    - Ex) three drugs in regimen, two with low risk and one with moderate -> the moderate-risk drug would be used to determine the antiemesis dosing for that regimen
  + Emetic risk is a function of both the drug and the drug dose
  + In cases where a specific drug’s (or treatment regimen’s) emetic risk was not specified by NCCN Guidelines, we extrapolated from other treatment regimens (extrapolations across cancer type, eg. From breast to lung, were allowed) with the assumption that a drug would always confer an emetic risk at least as high as it did elsewhere, when given at a higher dose or in combination.
    - Eg., If 15mg of drug X had emetic risk that was not specified in NCCN Guidelines, but 10mg of drug X had emetic risk = 2, we assumed 15mg would also have emetic risk of 2.
    - Eg., If drug X monotherapy had emetic risk of 1 and drug Y monotherapy had emetic risk of 2, and a treatment regimen of X + Y had emetic risk that was not specified in NCCN Guidelines, we assumed the regimen of X + Y would have emetic risk of 2.
  + Antiemetic treatment is assumed to be provided at the time of **each administration** of that highest-risk agent.
    - Eg., of the highest risk drug is given 3 times per cycle, then we assume three administrations of antiemetic drugs per cycle.
  + We include antiemetic agents that are given routinely in the 2-3 days surrounding treatment for acute and delayed emesis prevention, but do not include agents recommended to be prescribed for as-needed use (eg., oral ondansetron to be taken at home)
  + Note: Assign growth factor of 1 to paclitaxel regimens if it is administered every 21 days (or more frequently) and at a dose close to or greater than the dose for breast cancer
* For **growth factor support**, refer to NCCN Guidelines for Supportive Care --> Hematopoietic Growth Factors
* Neutropenic fever risk levels
  + 0 = low | <10% febrile neutropenia risk
  + 1 = intermediate | 10%-20% febrile neutropenia risk
  + 2 = high | >20% febrile neutropenia risk
* To determine the risk level of a specific regimen, our source hierarchy is:
  + 1) The NCCN Guidelines themselves, for the specific regimen and for the specific cancer type in question.
  + 2) The NCCN Guidelines, with extrapolation across cancer types. Eg., if treatment regimen with drugs X+Y+Z is specified as being “intermediate risk” as a breast cancer treatment, then that same combination can be assumed to have intermediate risk when given for a different cancer.
  + 3) The published literature, searched via Pubmed. We would identify a clinical study (trial or observational) of the treatment regimen in question, in which GCSF was not given routinely, and which reported the incidence of neutropenic fever. We then assigned the neutropenic risk level in accordance with the NCCN thresholds specified above.
  + Treatments given on a weekly basis are assumed to have low neutropenic fever risk
* Treatments with high (>20%) risk of neutropenic fever are assumed to receive a single dose of peg-filgrastim per cycle.
* Treatments with low (<10%) risk of NF are assumed to receive no growth factor.
* Treatments with intermediate risk of NF are assumed to receive either no growth factor or a single dose of peg-filgrastim per cycle, depending on whether “high margin” or “low margin” prices are being calculated (see below).
* When we encountered cases where the NCCN Guidelines changed the specified risk level (for emesis or NF) for a given treatment, we included this change in our assigned risk level concurrently.
  + For example, atezolizumab was previously specified as low emetic risk, and was then changed to minimal risk during the time period between January and July 2019. Therefore, in the Jan 2019 abstraction atezolizumab retains an emetic risk = low (1), and in the July 2019 abstraction (and thereafter) emetic risk = minimal (0).
* For each treatment regimen, we calculate three cost estimates: 1) chemotherapy price, 2) high-margin treatment price, and 3) low-margin treatment price. The chemotherapy price incorporates the antineoplastic drug and administration costs (eg., supportive care costs are not included). The high-margin and low-margin prices incorporate the cost of supportive care as described below:
  + High-margin: assumes supportive care meds are given more aggressively and with higher-cost options
  + Low-margin: assumes supportive care meds are given less aggressively and with lower-cost options
    - For growth factor support, treatments with intermediate risk for NF (GCSF risk = 1), are assumed to receive no GCSF in the “low margin” price and to receive a single dose of peg-filgrastim per cycle in the “high margin” price.
    - For both antiemesis and growth factor support, the lowest price and highest price guideline-concordant options are determined by calculations in the **special cases supportive care** tab.
      * These calculations are repeated in each spreadsheet version, in order to reflect either changes to recommended supportive care treatments by NCCN, price changes of existing agents, and newly available supportive care agents (eg., generics and biosimilars)
    - For both antiemesis and growth factor support, the lowest price option is assumed to be used in the “low margin” price, and the highest price option is assumed to be used in the “high margin” price.

# Drug Administration Costs

* Each drug-ROA combination was assigned a CPT/HCPCS code (or codes) for administration costs. We used CPT/HCPCS codes corresponding to drug class as appropriate (eg., separate billing codes for chemotherapeutic vs. hormonal agents, or intravenous vs. subcutaneous administration).
* For intravenous agents, we referred to administration guidelines on the drug label to ascertain length of infusion time. For agents taking up to one hour, we coded CPT 96413. For agents taking more than one hour, we used CPT 96413 and additionally CPT 96415 for each additional half hour as appropriate, rounded to the nearest half hour.
* When looking at dosage schedules for fluorouracil (aka, 5-fluorouracil or 5-FU), when the NCCN describes the administration as “IV bolus” we code this as drug route “IV”, and when NCCN describes as “continuous infusion” we code as drug route “PUMP”
  + In cases where the drug administration route is “PUMP,” we assume that durations of 48hrs or less would occur with a single continuous infusion. If the duration is longer than 48hrs, then the patient will need to go in to have the pump refilled, and hence we account for an additional billed administration code for “pump refill/maintenance.”
* Administration costs were obtained from the CMS [Physician Fee Schedule search tool](https://www.cms.gov/medicare/physician-fee-schedule/search?Y=0&T=0&HT=0&CT=0&H1=96405&M=5). Prices are updated **yearly** and found using the following selections:
  + Type of information: pricing
  + HCPCS criteria: single HCPCS code
  + MAC option: national payment amount
  + Modifiers: all modifiers
  + For each search, we reported the **non-facility price**
* Administration costs for supportive care drugs were not included

# Pricing

* For regimens that have a **defined** treatment course (time limited), calculate costs over the planned duration of therapy
* For regimens that have an undefined treatment (time unlimited), calculate anticipated costs over the first year of therapy and divide to get monthly price
* For regimens with both defined and undefined components (e.g., one drug that is given for a short duration and another drug is given for a longer period, or “dose escalating” regimens where the initial administrations of a drug are given at a lower dose), we typically code these regimens as **undefined** (regimen type = 1). In these cases, we calculate the anticipated costs over first year of therapy, including the time-limited portion, and then divide by 12 to calculate the average monthly cost during the first year of therapy.
* In cases where one or more drugs from the original regimen could be continued as maintenance therapy, we typically code these regimens as defined/time-limited for the specified number of cycles, and code (and price) the maintenance portion as a separate regimen.
* In cases where the NCCN guidelines named a class of drugs (e.g., “aromatase inhibitor”) rather than a specific drug, use the cheapest option within the class in current use in the US
* Price extraction notes:
  + We use prices that were active as of January or July 1st, corresponding to the same date on which the NCCN guidelines are downloaded
  + **Part B** drug prices are obtained from CMS ASP file
    - For Part B drugs without an available ASP at a given time point, our source hierarchy for price data was:
    - 1) Future ASP prices
      * This would typically apply to newly-approved physician administered drugs, as there is a two-quarter lag until CMS can report ASP
    - 2) Contemporary WAC prices, from Redbook.
    - 3) Nearest available (temporally) historic WAC prices
    - 4) Press releases with mention of drug price
    - 5) Peer-reviewed research studies mentioning drug price
    - Drugs with no available pricing data were excluded (‘1’ entered in the Exclude column)
  + **Part D** drug prices are pulled from historic WAC from Redbook
    - For drugs with no generic versions, we extracted the WAC price for the NDC with the highest strength (leading to the lowest per mg price)
      * To pull the historic WAC for brand name drugs, divide the AWP by 1.2
    - For drugs with available generics, we extract price for the most commonly prescribed NDC, defined as having the highest integrated units sold according to Bloomberg Drug Explorer data.
  + For **part B biologic drugs with biosimilars**, we use the ASP price for the most commonly prescribed drug among the parent biologic and all biosimilars, based on integrated units/manufacturer sales from Bloomberg data.
    - An exception to this process is the kidney cancer guidelines, which specify brand name bevacizumab (Avastin) vs biosimilars
  + **CAR-T therapies** have HCPCS codes but no corresponding ASP price. We follow this hierarchy for pricing:
    - If no WAC is available, we look for a press release with a reimbursement price
    - When a WAC price is available, we multiply it by 1.06 to get the reimbursement price and calculate the physician margin

# Provider Billing Margin

* When we extract prices for Part B drugs, we use ASP’s payment limit which incorporates a 6% markup to the average sales price. We refer to this markup as the “physician margin.”
* We use the following formula to calculate the physician margin:
  + (ASP payment limit / 1.06) \* 0.06
  + Dividing the payment limit by 1.06 gives us the true average sales price and multiplying by 6% gives us the markup.
* We assume that there is no provider markup on oral / Part D-covered cancer drugs
* We assume that other services besides the drug itself (eg., administration costs) are effectively revenue-neutral to the provider and hence do not factor into billing/profit margin.

# Regimen Abbreviations (not comprehensive)

* AC (doxorubicin, cyclophosphamide)
* AD (doxorubicin, dacarbazine)
* AIM (doxorubicin, ifosfamide, mesna)
* ATRA (tretinoin)
* BEP (bleomycin, etoposide, cisplatin)
* CapeOx (capecitabine + oxaliplatin)
* CEOP (cyclophosphamide, etoposide, vincristine, prednisone)
* CEPP (cyclophosphamide, etoposide, procarbazine, prednisone)
* CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
* CMF (cyclophosphamide, methotrexate, fluorouracil)
* CMV (cisplatin, methotrexate, vinblastine)
* CODOX-M (cyclophosphamide, vincristine, doxorubicin, methotrexate, leucovorin, cytarabine)
* CVD (cisplatin, vinblastine, dacarbazine)
* CVP (cyclophosphamide, vincristine, prednisone)
* DA-EPOCH/EPOCH (cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide)
* DCF (fluorouracil, cisplatin, docetaxel)
* ddMVAC (methotrexate, vinblastine, doxorubicin, cisplatin)
* DHAP (dexamethasone, cytarabine, cisplatin)
* DHAX (dexamethasone, cytarabine, oxaliplatin)
* EC (epirubicin, cyclophosphamide)
* ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
* FCR (fludarabine, cyclophosphamide, rituximab)
* FLOT (fluorouracil, leucovorin, oxaliplatin, docetaxel)
* FOLFIRI (fluorouracil, leucovorin, irinotecan)
* FOLFOX (fluorouracil, leucovorin, oxaliplatin)
* FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, irinotecan)
* FR (fludarabine, rituximab)
* GemOx (gemcitabine, oxaliplatin)
* GDP (gemcitabine, dexamethasone, cisplatin)
* GTX (gemcitabine, docetaxel, capecitabine)
* HiDAC (cytarabine)
* HyperCVAD (cyclophosphamide, doxorubicin, vincristine, dexamethasone)
* ICE (ifosfamide, mesna, carboplatin, etoposide)
* IROX (irinotecan, oxaliplatin)
* MAID (mesna, doxorubicin, ifosfamide, dacarbazine)
* MINE (mitoxantrone, ifosfamide, mesna, etoposide)
* OFAR (oxaliplatin, fludarabine, cytarabine, rituximab)
* OFF (fluorouracil, leucovorin, oxaliplatin)
* PEPC (prednisone, etoposide, procarbazine, cyclophosphamide)
* PCR (pentostatin + cyclophosphamide + rituximab)
* PCV (procarbazine, lomustine, vincristine)
* RBAC (rituximab, bendamustine, cytarabine)
* RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)
* RCEPP (rituximab, cyclophosphamide, etoposide, procarbazine, prednisone)
* RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
* RCVP (rituximab, cyclophosphamide, vincristine, prednisone)
* RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone)
* RGDP (rituximab, gemcitabine, dexamethasone, cisplatin)
* RICE (rituximab, ifosfamide, carboplatin, etoposide)
* RIVAC (rituximab, ifosfamide, cytarabine, etoposide)
* TAC (doxorubicin, cyclophosphamide, docetaxel)
* TC (docetaxel, cyclophosphamide)
* TCH (docetaxel, carboplatin, trastuzumab)
* TI-CE (paclitaxel, ifosfamide, mesna)
* TIP (paclitaxel, ifosfamide, mesna cisplatin)
* TMZ (temozolomide)
* VAC (vincristine, dactinomycin, cyclophosphamide)
* VeIP (vinblastine, ifosfamide, cisplatin)
* VIP (etoposide, ifosfamide, mesna, cisplatin)VR-CAP (cyclophosphamide, doxorubicin, bortezomib, prednisone, rituximab)

# Initial NCCN Evidence Blocks appearance and inclusion in Framework files for each cancer type

NCCN first developed and published Evidence Blocks-containing guidelines asynchronously for each cancer type. Our general process was to start including a cancer type in the Framework Files if it was presented in the NCCN Evidence Blocks for any portion of the subsequent 6 month period. For example, if NCCN Evidence blocks were first published for a given cancer type in March 2016, that cancer would be included in the January 2016

|  |  |  |
| --- | --- | --- |
| **Cancer Type** | **NCCN Evidence Blocks** | **Framework File** |
| Breast | March 2016 | January 2016 |
| Chronic Myeloid Leukemia (CML) | October 2015 | January 2016 |
| Colon | March 2016 | January 2016 |
| Hepatobiliary (Gallbladder, Liver, Pancreas1) | May 2016 | January 2016 |
| Kidney | December 2015 | January 2016 |
| Melanoma | March 2016 | January 2016 |
| Myeloma | October 2015 | January 2016 |
| Non-Small Cell Lung (NSCL) | March 2016 | January 2016 |
| Prostate | April 2016 | January 2016 |
| Rectum | March 2016 | January 2016 |
| Brain | September 2016 | July 2016 |
| Chronic Lymphocytic Leukemia (CLL) | December 2016 | July 2016 |
| Head & Neck | August 2016 | July 2016 |
| Ovarian | August 2016 | July 2016 |
| Small-Cell Lung | October 2016 | July 2016 |
| Gastric (Stomach, Esophagus) | September 2016 | July 2016 |
| Cervical | January 2017 | January 2017 |
| Pancreas | April 2017 | January 2017 |
| Uterine | April 2017 | January 2017 |
| Bladder | Jul7 2017 | July 2017 |
| Esophagus2 | August 2017 | July 2017 |
| Hodgkin Lymphoma | July 2017 | January 2018 |
| Sarcoma (Soft Tissue, GIST) | June 2017 | July 2017 |
| Anal | March 2017 | July 2017 |
| Non-Hodgkin’s Lymphoma (NHL, B-cell) | February 2016 | July 2016 |
| Acute Myeloid Leukemia (AML) | May 2019 | July 2019 |
| Testis | August 2016 | January 2017 |

1 Pancreas was originally included within Hepatobiliary guidelines until the NCCN created its own guideline in April 2017  
2 Esophagus was originally included within Gastric guidelines until the NCCN created its own guideline in August 2017

# Peer-reviewed studies using Framework

The Accuracy and Usefulness of the National Comprehensive Cancer Network Evidence Blocks Affordability Rating. Mitchell AP, Dey P, Ohn JA, Tabatabai SM, Curry MA, Bach PB. Pharmacoeconomics. 2020 Jul;38(7):737-745. doi: 10.1007/s40273-020-00901-x.

PMID: 32201922 PMCID: PMC8357422

Association Between Clinical Value and Financial Cost of Cancer Treatments: A Cross-Sectional Analysis. Mitchell AP, Tabatabai SM, Dey P, Ohn JA, Curry MA, Bach PB.

J Natl Compr Canc Netw. 2020 Oct 1;18(10):1349-1353. doi: 10.6004/jnccn.2020.7574.

PMID: 33022648 PMCID: PMC8354655

Quality of Treatment Selection for Medicare Beneficiaries With Cancer.

Mitchell AP, Persaud S, Mishra Meza A, Fuchs HE, De P, Tabatabai S, Chakraborty N, Dey P, Trivedi NU, Mailankody S, Blinder V, Green A, Epstein AS, Daly B, Roeker L, Bach PB, Gönen M. J Clin Oncol. 2025 Feb 10;43(5):524-535. doi: 10.1200/JCO.24.00459.

PMID: 39393041

|  |  |  |  |
| --- | --- | --- | --- |
| Case-Specific Notes & Decisions | | | |
| Cancer Type | **Regimen** | **Notes** | **Unique ID(s)** |
| Acute Myeloid Leukemia (AML) | Induction: ATRA/gemtuzumab ozogamicin; consolidation: ATRA/gemtuzumab ozogamicin | Assumed length of induction was 28 days based on this source from the Jan 2021 guideline: https://ashpublications.org/blood/article/99/11/4222/106797/Experience-with-gemtuzumab-ozogamycin-mylotarg-and | 10052 |
| Acute Myeloid Leukemia (AML) | Dual-drug liposomal encapsulation of daunorubicin and cytarabine | The dose of Vyxeos (combination daunorubicin + cytarabine) was calculated based on the daunorubicin component | 10033, 1049 |
| Anal | 5-FU, cisplatin, and RT | For the treatment regimen 5-FU + cisplatin + RT for metastatic disease, we assumed the same dosing as for the non-metastatic setting | 11018 |
| Bladder | Ifosfamide, doxorubicin, and gemcitabine | We based dosing of Ifosfamide + doxorubicin + gemcitabine on the study cited by NCCN, although we noted that the patient population appeared to include patients who were cisplatin-eligible | 13014, 13028, 13040, 13051 |
| Bladder | - | For metastatic disease treatment regimens, we assumed the NCCN-recommended maximum of 6 cycles | - |
| Bladder | - | For bladder-sparing regimens with dosing that depends on individual response to treatment, we assumed that patients achieved complete response | - |
| Bladder | - | For low-dose gemcitabine bladder sparing, we assumed a dose of 27 mg/m2 in accordance with institutional standards | - |
| Brain (CNS) | RT + concurrent and adjuvant Temozolomide  Fractionated RT + concurrent and adjuvant TMZ  Standard RT + concurrent and adjuvant lomustine + TMZ | For regimens including RT plus "concurrent and adjuvant temozolomide," we assumed that temozolomide was dosed in accordance with the Stupp et al protocol: https://www.ncbi.nlm.nih.gov/pubmed/15758009 | 15002, 15016, 15019, 15022, 15024, 15211 |
| Brain (CNS) | Fractionated RT + adjuvant PCV  Fractionated RT + neoadjuvant PCV  Fractionated RT + concurrent and adjuvant TMZ  Fractionated RT + adjuvant TMZ | For anaplastic glioma regimens with hypofractionated RT plus "concurrent and adjuvant temozolomide", we based dosing on the Ven den Bent protocol: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5806535/ | 15020 – 15027 |
| Brain (CNS) | Hypofractionated brain RT, concurrent temozolomide, and adjuvant temozolomide | For regimens for glioblastoma with hypofractionated RT plus "concurrent and adjuvant temozolomide", we assumed 2 weeks of RT based on the Malmstrom et al protocol: https://www.ncbi.nlm.nih.gov/pubmed/22877848 | 15073, 15077, 15081 |
| Brain (CNS) | Bevacizumab and carmustine  Bevacizumab and lomustine  Bevacizumab and temozolomide | Because no dosing schedules were available for these combination regimens, we assumed that dosing for each drug was equivalent to monotherapy indications | 15089, 15090, 15091, 15101,  15102, 15103,  15113, 15114, 15115 |
| Brain (CNS) | Somatostatin analogue | We assumed octreotide was used. | 15158 |
| Breast | Doxorubicin | In some cases, the neutropenic fever risk level for doxorubicin-based regimens was inferred from regimens for soft tissue sarcoma with equivalent doxorubicin dosing | 14076 |
| Breast | Fulvestrant monotherapy | Dosed per: https://pubmed.ncbi.nlm.nih.gov/24317176/ | 14073, 14128 |
| Breast | - | For cases where the aromatase inhibitor is not specified, we used the lowest-cost AI drug | - |
| Breast | Tamoxifen and trastuzumab  Aromatase inhibitor, lapatinib, and trastuzumab | For tamoxifen + trastuzumab regimen, we used trastuzumab dosing from when given WITHOUT concurrent chemotherapy. Same with AI+trastuzumab and lapatinib+trastuzumab | 14045, 14071, 14074 |
| Cervical | Carboplatin monotherapy | Dosing was specified in terms of mg/m2. We converted this dose into an AUC-based dose under assumptions of normal renal function. | 16012 |
| Chronic Lymphocytic Leukemia (CLL) | Obinutuzumab monotherapy | Dosing reflects first line dosing per: https://ashpublications.org/blood/article/127/1/79/34915/Randomized-phase-2-study-of-obinutuzumab | 17011, 17048, 17070, 17083 |
| Chronic Lymphocytic Leukemia (CLL) | Nivolumab and rituximab  Pembrolizumab and rituximab | Richter's transformation to DLBCL; we noted that some editions of the NCCN Guidelines appear to erroneously refer to the regimens of [nivolumab or pembrolizumab] + rituximab as [nivolumab or pembrolizumab] + ibrutinib. | 17105, 17107 |
| Chronic Lymphocytic Leukemia (CLL) | Chlorambucil monotherapy  Rituximab monotherapy | We inferred the dosing schedule from chlorambucil + rituximab combination therapy. | 17012, 17013, 17021, 17022 |
| Chronic Lymphocytic Leukemia (CLL) | - | For DLBCL transformation, we followed dosing levels and number of cycles for advanced DLBCL contained in the NCCN Guidelines for lymphoma | - |
| Chronic Lymphocytic Leukemia (CLL) | Nivolumab and rituximab  Pembrolizumab and rituximab | Dosing for each drug was inferred based on standard dosing schedules because no specific guidance for these combination regimens was available. | 17105, 17107 |
| Chronic Lymphocytic Leukemia (CLL) | Venetoclax and rituximab | For venetoclax-based regimens, we assumed a treatment course of 1 year | 17036, 17057, 17086 |
| Chronic Myeloid Leukemia (CML) | Bosutinib and steroids  Dasatinib and steroids  Imatinib and steroids  Nilotinib and steroids  Ponatinib and steroids | For the steroid dose, we used 60 mg/m2 prednisone PO recommendations for Philadelphia chromosome positive ALL according to these sources: [*ponatinib*](https://pmc.ncbi.nlm.nih.gov/articles/PMC8941470/), [*dasatinib*](https://ashpublications.org/blood/article/118/25/6521/29236/Dasatinib-as-first-line-treatment-for-adult), and [*imatinib*](https://ashpublications.org/blood/article/109/9/3676/23616/Imatinib-plus-steroids-induces-complete-remissions) | 18020, 18022, 18024, 18026, 18028 |
| Chronic Myeloid Leukemia (CML) | - | For accelerated phase and blast phase, we assumed the highest dose TKI drugs would be used for drugs with a range of recommended doses. | - |
| Colon | - | Use 6 months of therapy as the standard duration for adjuvant therapy | - |
| Colon | - | For neoadjuvant/adjuvant therapy for resectable metastatic disease, will use 6 cycles = 12 treatment days = 24 weeks = 6 months based on studies cited in UpToDate. While the neoadjuvant period is usually "limited to 2-3 months" per NCCN, we assume that the remainder of the 6-month treatment period is administered adjuvant/post-surgical. | - |
| Colon | CapeOx  CapeOx 3 months  CapeOx 6 months | We used a set number of cycles for defined regimens and number of days-per-year for unlimited regimens. For CapeOx regimens specified as having a three-month treatment duration, this was assumed to comprise exactly four cycles | 19002, 19013, 19014, 19020, 19021, 19027, 19030, 19043, 19047, 19054, 19111, 19114, 19137, 19158, 19212 |
| Colon | FOLFOX  FOLFOX and bevacizumab  FOLFOX and cetuximab  FOLFOX and panitumumab | There are several commonly used variations of the regimen known as “FOLFOX.” We followed dosing for mFOLFOX6 specifically, as detailed in NCCN guidelines. This FOLFOX schedule includes a 400 mg/m2 IV bolus infusion | 19050– 19053 |
| Colon/Rectal | FOLFOX  FOLFOX and cetuximab  FOLFOX and panitumumab  CapeOx and bevacizumab  FOLFIRI  FOLFOXIRI  FOLFOXIRI and bevacizumab  FOLFOXIRI and panitumumab  FOLFOXIRI and cetuximab | For the indication of "Unresectable synchronous liver and/or lung metastases,” we assumed a 6-month treatment period, based on input from clinical experts | 19033– 19041, 32050– 32058 |
| Gallbladder | 5-Fluorouracil | For dosing of 5-FU monotherapy, we based dosing on the following regimen with omission of the other drugs: https://www.ncbi.nlm.nih.gov/pubmed?term=15558814 | 24016, 24029, 24044, 24056 |
| Gallbladder |  | For dosing of oxaliplatin and CAPEOX, we inferred from biliary adenocarcinoma | - |
| Gallbladder | - | For unresectable disease, we inferred dosing of 5-FU + RT from the post-surgery indication | - |
| Gastric | - | For perioperative chemotherapy, we assumed 3 cycles before and 3 cycles after surgery, unless otherwise specified for particular treatment regimens | - |
| Head & Neck | Induction cisplatin, epirubicin, and paclitaxel followed by weekly cisplatin with concurrent RT  Induction cisplatin, epirubicin, and paclitaxel followed by weekly carboplatin with concurrent RT | For induction portion, used dosing from this trial (https://www.ncbi.nlm.nih.gov/pubmed/15827691) and extracted weekly dosing + RT based on similar regimens | 23058, 23059 |
| Head & Neck | - | For treatment regimens with induction chemotherapy, we assumed the dosing for weekly cisplatin+RT would be the same as for regimens without induction chemo | - |
| Head & Neck | Carboplatin monotherapy | We excluded carboplatin monotherapy because we were unable to access the text of the citation supporting this regimen and could not identify any other supportive studies. | - |
| Head & Neck | Carboplatin, paclitaxel, and cetuximab  Cisplatin, paclitaxel, and cetuximab | For the treatment regimens carboplatin/paclitaxel/cetuximab and cisplatin/paclitaxel/cetuximab, direct citations were not available, so we inferred drug dosing from similar regimens. | 23073, 23079 |
| Head & Neck | Cisplatin and paclitaxel | For the treatment regimen cisplatin/paclitaxel, we inferred dosing by applying the same paclitaxel dosing schedule as specified for carboplatin/paclitaxel, and inputting a common cisplatin dosing schedule | 23078 |
| Head & Neck | Induction docetaxel + cisplatin + 5-FU followed by weekly carboplatin with concurrent RT  Induction docetaxel + cisplatin followed by weekly carboplatin with concurrent RT  Induction cisplatin + epirubicin + paclitaxel followed by weekly carboplatin with concurrent RT | For the weekly carboplatin dosing, we converted the carboplatin dose of 100mg/m2 to AUC using the Calvert formula. We assumed standard body sizes and an average eGFR of 70 in the Medicare-aged adult population on the basis of studies such as: https://www.kidney-international.org/article/S0085-2538%2815%2952697-5/fulltext | 23051, 23053, 23055, 23059 |
| Head & Neck | Carboplatin + infusional 5-FU + RT | For the carboplatin dosing, we used the Calvert formula to convert the 70 mg/m2 dose to AUC. We assumed standard body sizes and an eGFR of 72.25. | 23002, 23020, 23038 |
| Head & Neck | Induction docetaxel + cisplatin + 5-FU followed by carboplatin + RT  Induction paclitaxel + cisplatin + infusional 5-FU followed by carboplatin + RT  Carboplatin + paclitaxel + RT | For the carboplatin dosing, we used the Calver formula to convert the 100 mg/m2 dose to AUC. We assumed standard body sizes and an eGFR of 72.25. | 23003, 23011, 23016, 23021, 23039 |
| Hodgkin Lymphoma | ABVD x4 and RT  ABVD x2, AVD x4  ABVD x2, AVD x4 and RT  ABVD x4 and RT  ABVD x2, BEACOPP x2 and RT  ABVD x2, BEACOPP x4  ABVD x2, escalated BEACOPP x2, and ISRT | Stage I-II unfavorable BULKY classical (planned combined modality therapy) In response to a NCCN Guidelines, reorganization, we assumed that the regimen “ABVD X2 + BEACOPP X2 + ISRT (Deauville 3-4 and 5, biopsy negative; preferred Deauville 4)” present in the Jan 2019 version was equivalent to same regimen described as “Deauville 4-5, biopsy negative” in July 2019. We maintained the same unique ID for these, and created a new ID for “Deauville 5” | 25016– 25022 |
| Hodgkin Lymphoma | - | Stage I-II unfavorable BULKY classical (planned combined modality therapy) We judged that the consensus category of 1 corresponded to the ABVD and BEACOPP regimens, while AVD was category 2A | - |
| Hodgkin Lymphoma | - | For nodular lymphocyte-predominant, stage IA/IIA, we assumed 2 cycles of chemotherapy in combination with RT (per cited references), except for the CVP regimen in which case we assumed 3 cycles. We made the same assumptions for more advanced/higher-stage disease, because we could not identify references that specified a different number of cycles. | - |
| Hodgkin Lymphoma | Stanford V x12 weeks + ISRT | For Evidence Blocks after July 2019, pricing for Mechlorethamine pulled from July 2019 (most recently available price before becoming commercially unavailable in the U.S.) |  |
| Kidney | Erlotinib | For erlotinib, we assumed the same dosing as for non-small cell lung cancer | 26042 |
| Melanoma | Biochemotherapy | For the “biochemotherapy” regimen, we assumed IV dosing of IFN-a-2b | 20009, 20038 |
| Melanoma | Intra-lesional injections | For intra-lesional injections, we based dosing calculations on the clinical trial of Talimogene Laherparepvec (T-VEC; NCT01740297, https://www.ncbi.nlm.nih.gov/pubmed/28981385) to approximate average lesion size. Based on the median sum of the products of the two longest perpendicular diameters (SPD) of 930mm^2 in the T-VEC arm, this would equate to average lesion measurements 30.5mm x 30.5mm assuming a square lesion, or 3.05cm. This would translate to a dose of “up to two mL” per lesion per dose by standard T-VEC dosing ranges. (We note that assuming a circular lesion would equate to a radius of 1.7cm and a diameter of 3.4cm, which would also receive the same dose of up to 2mL per lesion) | 20031, 20032, 20066, 20082 |
| Melanoma | Isolated limb perfusion (ILP) with melphalan | For limb perfusion therapies, we assumed treatment was give to the arm (rather than leg), and assumed an average arm volume of 3L based on estimates of an average volume of 2.5L when including muscle only (Holzbaur et al, J Biomech 2007: https://pubmed.ncbi.nlm.nih.gov/17241636/ | 20019 |
| Melanoma | Isolated limb infusion (ILI) with melphalan  Isolated limb perfusion (ILP) with melphalan | For ILP/ILI procedures, we assumed minimal emetic risk | 20018, 20019 |
| Myeloma | Bortezomib monotherapy | Dosed per: https://pubmed.ncbi.nlm.nih.gov/23616624/ | 27021, 27100 |
| Myeloma | Ixazomib, cyclophosphamide, and dexamethasone | We were unable to find a reference study for the regimen Ixazomib + cyclophosphamide + dexamethasone for the indication of induction therapy pre-stem cell transplant. We therefore inferred a treatment duration of 8 cycles based on similar induction regimens such as bortezomib+lenalidomide+dexamethasone | 27057 |
| Myeloma | - | For all multiple myeloma cases that included autologous stem-cell transplantation, we assumed the full stem-cell transplantation process would take 8 weeks | - |
| Myeloma | (VTD-PACE) Dexamethasone, Thalidomide, Cisplatin, Doxorubicin, Cyclophosphamide, Etoposide, and Bortezomib | For entire regimen (https://www.nejm.org/doi/10.1056/NEJMoa053583), for the purposes of thalidomide dosing we assumed 4 week intervals between the 4 initial induction cycles | 27010, 27032 |
| Myeloma | Carfilzomib, lenalidomide, and dexamethasone | In cases where the combination carfilzomib+lenalidomide+dexamethasone was given for a defined course that exceeded one year, we based pricing on the first year of therapy. | - |
| Myeloma | Carfilzomib, lenalidomide, and dexamethasone | For the combination carfilzomib + lenalidomide + dexamethasone being given prior to stem cell transplant, we assumed 9 cycles prior to transplant based on findings by Bringhen et al, Blood 2024: https://www.ncbi.nlm.nih.gov/pubmed/24855212 | - |
| Myeloma | Ixazomib, lenalidomide, and dexamethasone | Since there was no publication, for induction therapy pre-stem cell transplant, we inferred 8 cycles from similar induction regimens such as bortezomib+lenalidomide+dexamethasone | - |
| Non-Hodgkin’s Lymphoma (NHL, B-cell) | Bendamustine and rituximab | We assumed 4 cycles for mantle cell lymphoma, and for 6 cycles for follicular lymphoma | 12072, 12074 |
| Non-Hodgkin’s Lymphoma (NHL, B-cell) | Lenalidomide and rituximab | NCCN citation recommends dosing lenalidomide based on maximum tolerable dose; we assumed a daily dose of 25 mg | 12085 |
| Non-Hodgkin’s Lymphoma (NHL, B-cell) | Chlorambucil and rituximab | Dosed per: https://www.ncbi.nlm.nih.gov/pubmed/25047267 | 12027, 12037, 12060 |
| Non-Hodgkin’s Lymphoma (NHL, B-cell) | Ibritumomab tiuxetan | We assumed that patients had normal platelet levels and so could receive full dose. | - |
| Non-Hodgkin’s Lymphoma (NHL, B-cell) | Cyclophosphamide and rituximab | For dosing of cyclophosphamide + rituximab, we based dosing on the FCR regimen, sans fludarabine | - |
| Non-Hodgkin’s Lymphoma (NHL, B-cell) | R-hyper-CVAD | For r-hyper-CVAD, we assumed the maximum number of doses for Leucovorin, and did not include the intrathecal chemotherapy component | 12071, 12078 |
| Non-Hodgkin’s Lymphoma (NHL, B-cell) | - | Follicular lymphoma, grade I-II, elderly or infirm, stage I-II We assigned consensus category of 2B to regimens of chemotherapy + ISRT, because the NCCN-specified 2B designation seems to be in reference to the addition of ISRT, rather than the systemic therapy agents selected (reference: slide 8, B-cell 4.2019) | - |
| Non-Small Cell Lung (NSCL) | - | For initial cytotoxic therapy for advanced disease, given 4-6 cycles, we assumed 6 cycles. | - |
| Non-Small Cell Lung (NSCL) | - | For initial cytotoxic therapy for advanced disease, we limited to 4 cycles where specified on the drug label (eg., carboplatin+pembrolizumab+bevacizumab) | - |
| Non-Small Cell Lung (NSCL) | Paclitaxel, carboplatin, and thoracic RT | This regimen has two versions. One as written in the previous column and one with additional cycles of paclitaxel and carboplatin. For regimens without additional cycles, anti-emetic risk is low with 6 anti-emetic doses. GCSF risk is low with no doses. For regimens with additional cycles, anti-emetic risk is intermediate with 8 doses. GCSF is intermediate risk with 2 doses. |  |
| Ovarian | Bevacizumab maintenance therapy | As an exception to our standard procedures for maintenance therapies, we included maintenance bevacizumab as part of the first-line regimen, because the maintenance bevacizumab period is included in both the GOG and ICON-7 regimens | 29049 |
| Ovarian | - | Progressive, stable, or persistent high-grade serous disease on primary systemic therapy. In some cases, the evidence & consensus categories were ambiguous; we assigned the consensus categories for platinum-resistant disease indication (reference: slide 47, edition 1.2019) | - |
| Ovarian | Ifosfamide | Frequency of mesna administration for regimens with ifosfamide was inferred from similar regimens in uterine and cervical cancer | 29081, 29116, 29152, 29183 |
| Pancreas | - | For adjuvant therapy, we inferred dosing of single agent capecitabine from gemcitabine+capecitabine, sans gemcitabine. | - |
| Pancreas | Gemcitabine and cisplatin | For gemcitabine+cisplatin, a dosing schedule from UpToDate was used since there were no cited schedules for this regimen in NCCN. | 30071, 30072 |
| Pancreas | - | For dosing of CapeOx, we assumed ECOG status of 0-1 | - |
| Pancreas | Gemcitabine monotherapy | We inferred gemcitabine monotherapy dosing from combination regimens, and the duration (6 months) from other adjuvant recommendations | 30003, 30013, 30019, 30020, 30028, 30033, 30034, 30046 |
| Pancreas | Continuous infusion 5-FU | We inferred dosing from colon cancer dosing, including the treatment duration of 6 months | 30005, 30015, 30022, 30036, 30045 |
| Prostate | Continuous ADT and docetaxel 75 mg/m2  LHRH antagonist and docetaxel | Prior to Jan 2019, this regimen was called “Continuous ADT + docetaxel 75 mg/m2” and the lowest costing drug of leuprolide, goserelin, or triptorelin was used. Now, it is called “LHRH antagonist + docetaxel” and degarelix is used. | 31136 |
| Prostate | LHRH Agonist | For cases where the LHRH agonist is not specified, we will use the lowest-cost drug among leuprolide, goserelin, triptorelin | - |
| Prostate | - | For adjuvant treatment along with ADT, we assumed the duration for high-risk as well as N1 disease was 2 years | - |
| Prostate | - | For first-generation antiandrogens, we assumed bicalutamide | - |
| Prostate | - | For LHRH antagonists, we assumed degarelix | - |
| Prostate | Corticosteroids | For corticosteroids, we used whatever is the lowest-cost among prednisone 40mg/day, hydrocortisone 40mg/day, or dexamethasone 1.5mg/day  We used the following review article: https://www.ncbi.nlm.nih.gov/pubmed/14747046 | 31002, 31010, 31021, 31034, 31047, 31060, 31071, 31083, 31098 |
| Prostate | DES or other estrogen | We referred to the following trial to support dosing at 1mg/kg per day: https://www.ncbi.nlm.nih.gov/pubmed/16215308 | 31007, 31018, 31028, 31028, 31043, 31057, 31067, 31079, 31094, 31107 |
| Prostate | - | In cases where abiraterone or fine-particle abiraterone is specified, we assumed co-administration of prednisone (for abiraterone) or methylprednisone (for fine-particle abiraterone, e.g., Yonsa). | - |
| Prostate | - | For metastatic small cell cancer of the prostate, we presumed that systemic therapy would be administered for 6 cycles following conventions for small cell cancer of the lung | - |
| Rectal | - | Similar to colon cancer, we assumed a total of 6 months of therapy as the standard duration for adjuvant therapy as well as for neoadjuvant/adjuvant/perioperative therapy for resectable metastatic disease | - |
| Rectal | FOLFOX | For all neo/adjuvant FOLFOX regimens, we assumed that 6 months of therapy would equate to 26 weeks / 2 weeks per cycle = 13 cycles | 32006, 32011, 32019, 32026, 32040, 32042, 32072, 32076 |
| Rectal | CapeOx | For all neo/adjuvant CapeOx regimens, we assumed that 6 months of therapy would equate to 26 weeks / 3 weeks per cycle = 8.67 cycles | 32007, 32012, 32020, 32027, 32041, 32043, 32073, 32077 |
| Sarcoma (Soft Tissue) | - | For adjuvant/neoadjuvant therapy, for the treatment regimens AD and AIM, we assumed a number of cycles necessary to get to the specified >400mg of doxorubicin | - |
| Sarcoma (Soft Tissue) | Ifosfamide, epirubicin, and mesna  Epirubicin monotherapy | For advanced disease, we assumed treatment would continue until progression or toxicity (eg., coded as “time unlimited”). | 34004, 34007, 34011, 34014, 34022, 34026 |
| Sarcoma (Soft Tissue) | Single-agent Dacarbazine  Single-agent Gemcitabine  Single-agent Ifosfamide | For adjuvant/neoadjuvant therapy we assumed the same dosing schedule for the individual drugs as in multi-drug combination treatments (eg., MAID) specified in the same guideline. | 34008, 34015, 34024, 34028, 34029, 34123, 34124, 34132 |
| Sarcoma (Soft Tissue) | Sunitinib | For GIST, the duration was assumed to be 3 years, to reflect the treatment duration specified for adjuvant imatinib. For neoadjuvant therapy duration we referred to UpToDate as NCCN did not specify duration. | 34038, 34040, 34043, 34107 |
| Sarcoma (Soft Tissue) | Carboplatin and etoposide | For rhabdomyosarcoma, we inferred dosing from other cancers | 34062 |
| Sarcoma (Soft Tissue) | Ifosfamide and etoposide | For rhabdomyosarcoma, we inferred dosing from other similar regimens | 34067 |
| Sarcoma (Soft Tissue) | (VCD/IE) Vincristine, cyclophosphamide, dactinomycin/ifosfamide and etoposide | For rhabdomyosarcoma, we assumed that the alternating regimen would rotate back to VCD on week 36 of treatment | 34074 |
| Sarcoma (Soft Tissue) | Sunitinib monotherapy | Sunitinib in the neoadjuvant setting are cycled over 8 weeks; for the adjuvant setting cycled over 2 years: https://hemonc.org/wiki/Gastrointestinal\_stromal\_tumor#Sunitinib\_monotherapy | 34038, 34040, 34043 |
| Sarcoma (Soft Tissue) | Everolimus and regorafenib | Dosing schedules for everolimus and regorafenib were inferred from common dosing schedules for other cancers. | 34049 |
| Sarcoma (Soft Tissue) | Everolimus and sunitinib | Dosing schedules for everolimus was inferred from common dosing schedules for other cancers. Dosing for sunitinib was inferred from the following trial: https://www.ncbi.nlm.nih.gov/pubmed?term=19451429 | 34050 |
| Uterine | Progestational agents | For these treatments we presumed progesterone would be used | 36027, 36120, 36124 |
| Uterine | - | We assumed adjuvant therapy would last for 3 cycles for intermediate risk, and 6 cycles for high risk. | - |
| Uterine | - | For adjuvant therapy, drug dosing was inferred from advanced/metastatic regimens. | - |
| Uterine | - | For advanced/metastatic disease we assumed that systemic therapy would continue for a maximum of 7 cycles, based on the results of two pivotal trials, GOG 209 (https://www.gynecologiconcology-online.net/article/S0090-8258(12)00228-4/abstract) and GOG 177 (https://www.ncbi.nlm.nih.gov/pubmed?term=15169803) | - |

# Supportive Care

The following citations were used to ascertain neutropenic fever risk levels

|  |  |  |  |
| --- | --- | --- | --- |
| Cancer Type | Regimen | NF risk | Citation |
| Bladder | Enfortumab vedotin | Low | <https://pubmed.ncbi.nlm.nih.gov/31356140/> |
| Hodgkin Lymphoma | Stanford V | Inter | <https://pubmed.ncbi.nlm.nih.gov/11821442/> |
| Lymphoma | RCEPP | Low | <https://pubmed.ncbi.nlm.nih.gov/2207307/> |
| Lymphoma | R-CEOP | Inter | <https://pubmed.ncbi.nlm.nih.gov/26397936/> |
| Lymphoma | R-CDOP | High | <https://pubmed.ncbi.nlm.nih.gov/25445468/> |
| Myeloma | VAD (botezomib, doxorubicin, dexamethasone) | Low | <https://pubmed.ncbi.nlm.nih.gov/20823423/> |
| Ovarian | Paclitaxel, ifosfamide | High | <https://pubmed.ncbi.nlm.nih.gov/17290061/> |
| Pancreas | GTX (fixed-dose rate gemcitabine, docetaxel, capecitabine) | Low | <https://pubmed.ncbi.nlm.nih.gov/17440727/> |

# Excluded Treatment Regimens

|  |  |  |  |
| --- | --- | --- | --- |
| Cancer Type | Regimen | Unique ID(s) | Citation |
| Bladder | Docetaxel + RT | 13059 | Dosing information could not be found |
| Brain (CNS) | High-dose cyclophosphamide | 15128, 15132, 15137, 15141 | Dosing information could not be found |
| Brain (CNS) | Cisplatin monotherapy  Carboplatin monotherapy | 15177, 15221 | We excluded the cisplatin and carboplatin monotherapy regimens for ependymoma, because the cited NCCN reference (https//www.ncbi.nlm.nih.gov/pubmed/15912507) did not actually support single-agent platinum and no dosing references for this indication were available. |
| Brain (CNS) | High-dose cyclophosphamide  High-dose cyclophosphamide and etoposide  Carboplatin, etoposide, and cyclophosphamide  Cisplatin, etoposide, and cyclophosphamide | 15128 – 15133, 15137 – 15142 | For medulloblastoma, we excluded the "high dose cyclophosphamide” and platinum/etoposide/cyclophosphamide regimens because no references or external dosing schedules were available |
| Brain (CNS) | - | - | Excluded regimens for brain metastases |
| Chronic Lymphocytic Leukemia (CLL) | Alemtuzumab | - | All alemtuzumab regimens are excluded. Alemtuzumab, brand name Campath, was approved for use in CLL until 2012 when it was pulled from the market. Lemtrada was then introduced as a branded version of alemtuzumab indicated for multiple sclerosis at a much lower dose (and higher price) than the original CLL approval. The pharmaceutical company offers Campath for free to patients with CLL under the US Campath Distribution Program. Sources: [MDedge: MD Use Leads to Free Campath for Leukemia Patients](https://www.mdedge.com/clinicalneurologynews/article/55802/leukemia-myelodysplasia-transplantation/ms-use-leads-free) / [AAPC forum](https://www.aapc.com/discuss/threads/campath-alemtuzumab-hcpcs-change.131972/) |
| Chronic Lymphocytic Leukemia (CLL) | Nivolumab+rituximab and pembrolizumab+rituximab | 17105, 17107 | We were unable to find any supporting evidence for these regimens, and suspected they may have been included erroneously |
| Gallbladder | Fluoropyrimidine-based or gemcitabine-based chemo followed by 5-fluorouracil and RT  Fluoropyrimidine-based or gemcitabine-based chemo followed by capecitabine and RT  5-fluorouracil and RT followed by fluoropyramidine-based or gemcitabine based chemotherapy  Capecitabine and RT followed by fluoropyramidine-based or gemcitabine based chemotherapy  Fluoropyrimidine-based or gemcitabine-based chemo followed by 5-fluoroucil and RT  Fluoropyrimidine-based or gemcitabine-based chemo followed by capecitabine and RT | 24042, 24043, 24068 – 24071 | The regimens "Fluoropyrimidine-based or gemcitabine-based chemo" were excluded due to insufficient specificity regarding the components of these regimens |
| Melanoma | BCG intralesional injection | 20020, 20027 | Excluded BCG injection because the units of drug varied between dosing and pricing sources (vials vs. number of organisms) |
| Melanoma | Topical imiquimod | 20023, 20030 | Difficult to dose and price, and RedBook has different units (% or mg) per quarter |
| Ovarian | Altretamine | 29069, 29103, 29146, 29177 | Not available in the US |
| Ovarian | - | - | We excluded intraperitoneal regimens because sources for standard dosing parameters were not available |
| Ovarian | Maintenance bevacizumab | - | Excluded maintenance bevacizumab because the maintenance period is included in the GOG and ICON-7 regimens (unique ID 29130) |
| Sarcoma (Soft Tissue) | Low-dose interferon | - | For desmoid sarcoma, lack of available dose |
| Sarcoma (Soft Tissue) | (VCD) Vincristine, cyclophosphamide, dactinomycin | - | For rhabdomyosarcoma, no citation for dosing of NON-alternating VCD regimen, and not a regimen specified on label, so excluded |