The different lines of therapy used for each patient will be identified with the help of the following general business rules established for this purpose. This exercise will help determine the start and end dates of each line of treatment, and the associated drug or combination of drugs in the line of treatment. For the purpose of these rules, 2 sets of melanoma drugs are relevant – core melanoma drugs (“core drugs” in Table 3.3-1) and non-core melanoma drugs (“non-core drugs” in Table 3.3-1).

* The first use of any of the core or non-core drugs during the study period will be identified for each patient and will signal the commencement of the first line of treatment. This drug, and any other core or non-core drug during the next 21 days will be collectively considered as the first line of treatment regimen (LOT1 regimen) for the patient.
* LOT1 will be considered to have ended:
  1. if there is a gap of more than 60 days between successive uses of all of the core LOT1 drugs; the LOT1 regimen will be considered to have ended after the effective period of the last use of the relevant core drug with the gap of more than 60 days. The second line of treatment (LOT2) will be considered to start upon the occurrence of any of the core or non-core drugs any time after the end of LOT1 period.
  2. If, after the initial 21-day period, there is an occurrence of use of any of the core drugs other than the core drugs contained in LOT1 regimen. This occurrence will signal the commencement of the second line of treatment (LOT2).
* The drug that signals the commencement of LOT2 and any other core or non-core drugs within 21 days of start of LOT2 will collectively be considered as the LOT2 regimen.

Other considerations:

* In addition to NDC codes and HCPCS codes, healthcare providers will also often use ICD-9-CM diagnosis codes V58.1 (encounter for antineoplastic chemotherapy and immunotherapy) and 99.25 (injection or infusion of cancer chemotherapeutic substance) when billing for chemotherapy-related services. When defining a 60-day treatment gap between regimens, a claim with an ICD-9-CM diagnosis code of V58.1 (ICD 10 code Z51.1) or an ICD-9-CM procedure code of 99.25 is considered a continuation of the existing regimen.
* The effective period for any drug will be the last date of administration of an infused therapy (no clinical benefit added) or the last date the oral therapy is available (defined as the prescription fill date plus the days supply).

Table 3.3-1: List of relevant melanoma drugs for LOT determination

| Type of drugs | Drugs |
| --- | --- |
| Core drugs | * Ipilimumab (Yervoy) * Nivolumab (Opdivo) * Pembrolizumab (Keytruda) * Vemurafenib (Zelboraf) * Dabrafenib (Tafinlar) * Trametinib (Mekinist) * Cobimetinib (Cotellic) * T-VEC (Imlygic) * Imatinib (Gleevec) * Temozolomide (Temodar) * Interleukin-2 (Proleukin) |
| Non-core drugs | * Dacarbazine (DTIC-Dome) * Interferon alpha/peginterferon alpha * Fluorouracil (5-FU) (Adrucil, Carac, Efudex, Fluoroplex) * Cisplatin (Platinol-AQ) * Vinblastine (Velban) * Paclitaxel (Taxol, Onxol, Nov-Onxol, Paclitaxel Novaplus) * Melphalan (Alkeran) * Carboplatin (Paraplatin, Paraplatin NovaPlus) * Rituximab (Rituxan) * Vincristine (Vincasar Pfs, Vincristine Sulfate, Vincristine Sulfate Novaplus) * Bleomycin (Bleo 15K, Bleomycin, Bleomycin Sulfate) * Cyclophosphamide (Amerinet Choice Cyclophosphamide, Cyclophosphamide, Cyclophosphamide Monohydrate, Cyclophosphamide Novaplus, Premierpro Rx Cyclophosphamide) * Lomustine (Gleostine) * Fludarabine (Fludarabine Phosphate, Fludarabine Phosphate Novaplus) * Pazopanib (Votrient) * Gemcitabine (Gemcitabine, Gemcitabine Hcl, Gemcitabine Novaplus, Gemzar, Premierpro Rx Gemcitabine) * Capecitabine (Capecitabine, Xeloda) * Lapatinib (Tykerb) * Bevacizumab (Avastin) * Carmustine (Bicnu, Gliadel) * Dasatinib (Sprycel) * Palbociclib (Ibrance) * Crizotinib (Xalkori) |

