

Table S1 Definitions of lines of therapy

Initial lines of therapy

Each line of therapy is defined by the temporal relationship and sequencing of treatment received

First line

- A treatment is considered first-line when the patient receives chemotherapy, radiation therapy, and/or biologic medication during the first 28 days after the initiation of treatment
- The number of cycles per regimen will be determined from the number of IV administrations and oral prescription fills
- The regimen is only considered complete if the number of cycles is >4

Maintenance

- A treatment is considered maintenance therapy when the patient has received ≥ 4 cycles of first-line therapy without disease progression
- The key clinical distinction between maintenance and second-line therapy is the presence of disease progression in the latter.
- Where clinical notes document disease progression, this will be used to indicate a change to second-line treatment. However, in the event of information regarding disease progression not being documented and ≥ 4 cycles of first-line therapy having been completed:
- If subsequent treatment is initiated within 6 weeks, this will be classified as maintenance therapy
- If there is a gap of >6 weeks before subsequent treatment, this will be classified as second-line therapy

Subclassification of maintenance therapy:

- Continuation: defined as the continuation of ≥ 1 agent from the first-line setting after 4 to 6 cycles, within 6 weeks of completion of the initial regimen, without disease progression
- Switching: defined as the continuation of agents different to those received in the first-line setting after 4 to 6 cycles of first-line therapy, within 6 weeks of completion of the initial regimen, without disease progression.

Subsequent lines of therapy

For patients who received first-line therapy, consecutive treatment cycles will be compared to examine any changes in therapy

Second-line

- A treatment is considered second line when a patient receives a new therapy after they have completed ≥ 4 cycles of first-line therapy, with a time gap of >6 weeks without chemotherapy and/or biologic therapy between 2 consecutive cycles; or
- A patient has completed <4 cycles of first-line therapy and there is evidence of subsequent administration of a new treatment regimen not including any agent from the first-line regimen, regardless of the duration of time since the end of the first-line therapy

Note, the discontinuation of a single drug from a combination regimen will not be considered a change in line of therapy

Third-line

- A treatment is considered third-line when a patient receives a new line of therapy after completing ≥ 4 cycles of second-line therapy, with a time gap of >6 weeks without chemotherapy and/or biologic treatment between 2 consecutive cycles, or
- If after <4 cycles of second-line therapy, a new treatment (that was not included in the second-line regimen) was administered regardless of the length of time since the end of the second-line therapy

Note, discontinuation of a single drug from a combination regimen will not be considered a change in line of therapy

Fourth-line and beyond

- A treatment is considered fourth-line when there is a gap of > 6 weeks in third-line therapy, or
- There is evidence of the administration of systemic therapy (excluding any agents used in the third-line regimen), regardless of the length of time since the end of the third-line therapy