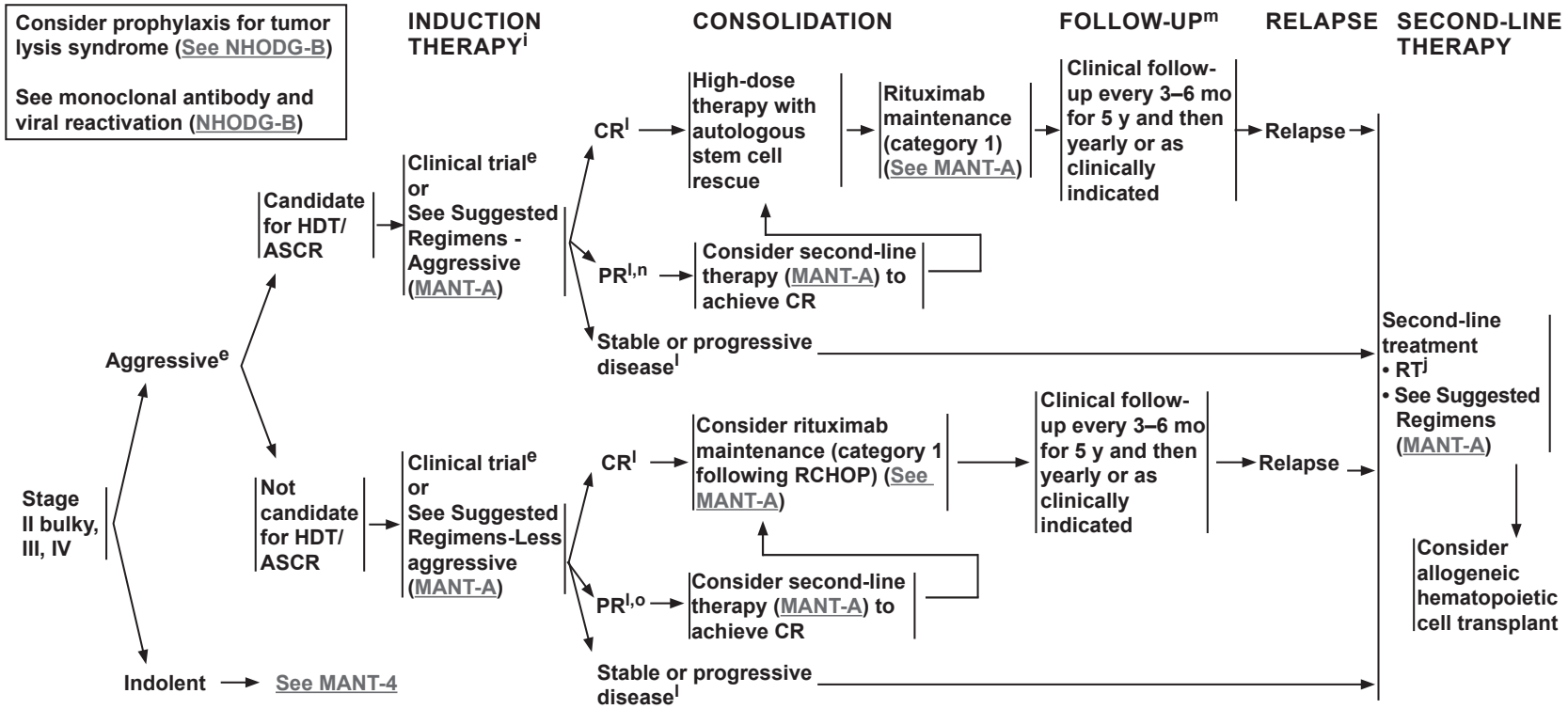

[e] *TP53* mutation has been associated with poor prognosis in patients treated with conventional therapy, including transplant. Clinical trial is strongly suggested for these patients.

[i] Early referral for high-dose therapy with stem cell rescue is advisable for planning purposes.

[j] See Principles of Radiation Therapy (NHODG-D).

[l] See Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C).

[m] Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated.

[n] Patients who have achieved near CR can proceed to HDT/ASCR. Patients who have achieved minimal PR with substantial disease should be treated as having stable, refractory disease. Patients who have achieved a very good PR may be treated with additional therapy to achieve CR with the goal of proceeding to HDT/ASCR.

[o] Patients who have achieved a very good PR or better can be observed or consider rituximab maintenance. Patients who have achieved minimal PR with substantial disease should be treated as having stable, refractory disease.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a,b]

An FDA-approved biosimilar is an appropriate substitute for rituximab.

Second-line Therapy

- **Partial response[f] with intention to proceed to transplant**
  - **Preferred regimens (in alphabetical order)**
    - ◊ **Bendamustine[d] ± rituximab (if not previously given)**
    - ◊ **Bortezomib ± rituximab**
    - ◊ **Lenalidomide ± rituximab**
    - ◊ **RCHOP or VRCAP (if not previously given)**
- **Short response duration to prior chemoimmunotherapy (< expected median PFS)**
  - **Preferred regimens (in alphabetical order)**
    - ◊ **BTK inhibitors[g]**
      - **– Acalabrutinib[h]**
      - **– Ibrutinib ± rituximab**
      - **– Zanubrutinib**
    - ◊ **Lenalidomide ± rituximab**
    - ◊ **Venetoclax[g]**
  - **Other recommended regimens**
    - ◊ **Ibrutinib,[g] lenalidomide, rituximab (category 2B)**
    - ◊ **Venetoclax + ibrutinib[g] (category 2B)**
- **Extended response duration to prior chemoimmunotherapy (> expected median PFS)**
  - **Preferred regimens (in alphabetical order)**
    - ◊ **Bendamustine ± rituximab (if not previously given)**
    - ◊ **Bortezomib ± rituximab**
    - ◊ **BTK inhibitors[g]**
      - **– Acalabrutinib[h]**
      - **– Ibrutinib ± rituximab**
      - **– Zanubrutinib**
    - ◊ **Lenalidomide ± rituximab**
  - **Other recommended regimens (in alphabetical order by category)**
    - ◊ **Venetoclax[g]**
    - ◊ **Bendamustine, bortezomib, and rituximab (category 2B)**
    - ◊ **PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab (category 2B)**
    - ◊ **RCHOP or VRCAP (if not previously given) (category 2B)**
    - ◊ **See Second-line Therapy for DLBCL (BCEL-C 2 of 4) without regard to transplantability**

Second-line Consolidation

- **Allogeneic hematopoietic cell transplant (nonmyeloablative or myeloablative)**

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a] See references for regimens MANT-A 3 of 4 and MANT-A 4 of 4.
[b] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[d] In patients intended to receive HDT/ASCR, bendamustine should be used with caution as there are conflicting data regarding ability to collect peripheral progenitor cell collection.
[f] Patients who have achieved near CR can proceed to HDT/ASCR. Patients who have achieved minimal PR with substantial disease should be treated as having stable, refractory disease. Patients who have achieved a very good PR may be treated with additional therapy to achieve CR with the goal of proceeding to HDT/ASCR.
[g] See Special Considerations for Use of Small-Molecule Inhibitors (NHODG-E).
[h] The phase 2 ACE-LY-004 study excluded patients treated with Bruton's tyrosine kinase (BTK) or BCL-2 inhibitor and concomitant warfarin or equivalent vitamin K antagonists.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.