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Lymphoma Management in North Carolina: Updates for 2023
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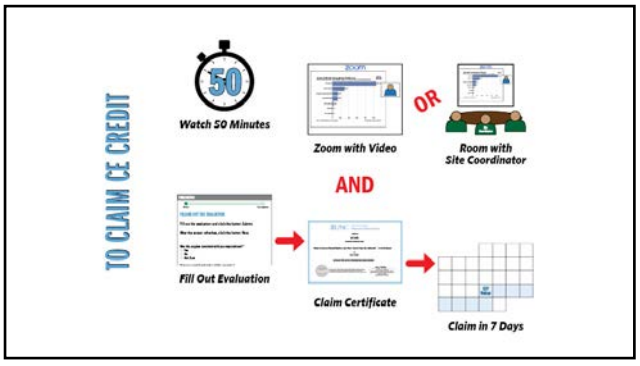
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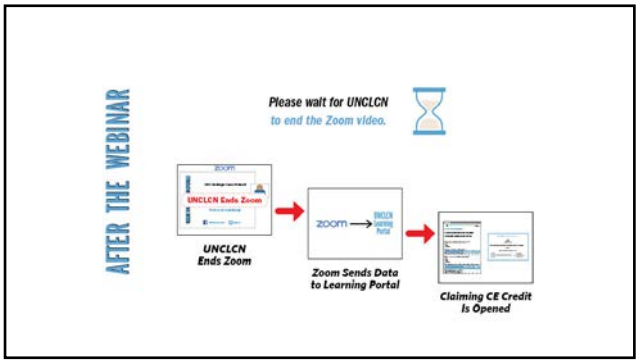
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RESEARCH TO PRACTICE
Natalie Grover, MD
Lymphoma Management in North Carolina: Updates for 2023
June 28

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OUR PRESENTER

Natalie Grover, MD

Natalie Grover, MD, is an assistant professor in the Division of Hematology/Oncology. Her primary clinical interest is management of lymphoma. Her research interests include novel treatment strategies in lymphoma, particularly immunotherapy, and she is currently involved in the clinical trials of chimeric antigen receptor T-cell (CAR-T) therapy for patients with lymphoma.

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OUR PRESENTER

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OUR PRESENTER

4. Natalie Grover, MD, is an assistant professor in the Division of Hematology/Oncology.

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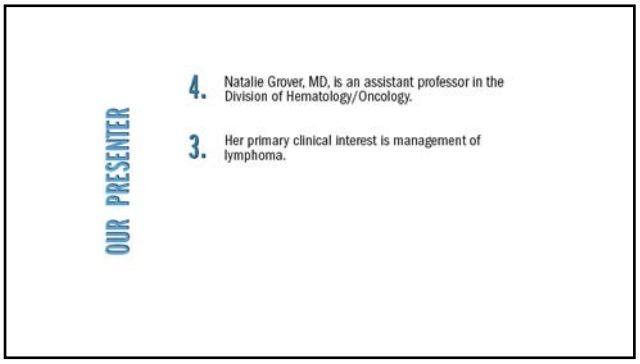
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3. Her primary clinical interest is management of lymphoma.

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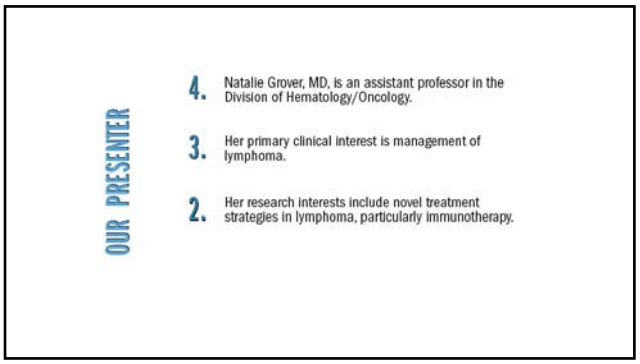
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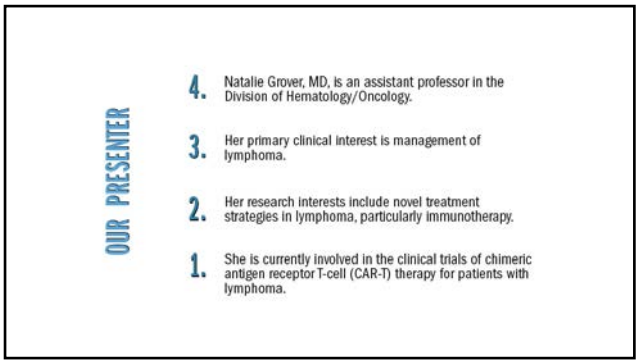
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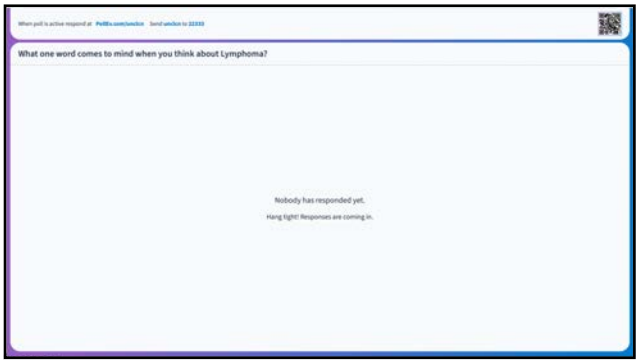
What one word comes to mind when you think about Lymphoma?
Nobody has responded yet.
Hang tight! Responses are coming in.

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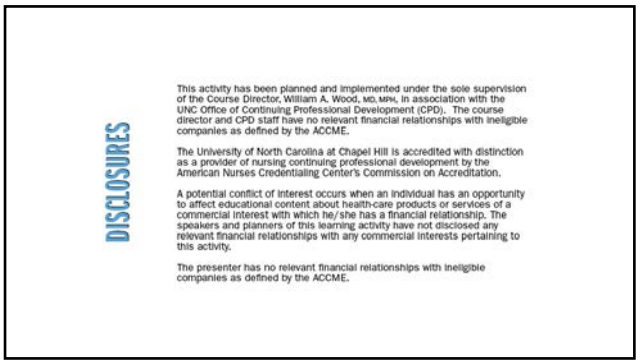
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UNC CANCER CARE

Lymphoma Management in North Carolina: Updates for 2023

Natalie Grover, MD
Assistant Professor of Medicine
Division of Hematology, Lymphoma Program
Clinical Director of Cellular Therapy Program

June 28th, 2023

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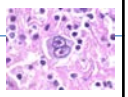
Case Example



- 28 yo F presents with enlarged neck nodes
- Excisional biopsy consistent with classical Hodgkin lymphoma
- PET/CT with multistation hypermetabolic lymphadenopathy along neck, chest, and retroperitoneum with FDG uptake significantly greater than liver as well as pulmonary nodules suspicious for lymphomatous involvement

Webpathology.com UNC LINEBERGER COMPREHENSIVE CANCER CENTER

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How would you treat this patient?

ABVD x 6 cycles 0% 0

ABVD x 2 cycles followed by PET/CT for response adapted therapy 0% 0

escBEACOPP x 6 cycles 0% 0

Brentuximab vedotin + AVD x 6 cycles 0% 0

Nivolumab + AVD x 6 cycles 0% 0

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Standard of Care for Advanced Stage Hodgkin Lymphoma Rapidly Changing!

- Standard of Care had been ABVD x 6
- Had been using PET adapted therapy frequently – start with ABVD x 2
  - If interim PET/CT Deauville 1-3 -> drop bleomycin
  - If interim PET/CT Deauville 4-5 (but responding) -> escalated BEACOPP
- Advantages
  - Most patients respond and really nice to be able to drop bleomycin after 2 cycles
- Drawbacks
  - Rely on expertise/assessment of nuclear medicine
  - Don't love escalating to BEACOPP (adds more toxicity!!)

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What about novel agents?

- Brentuximab vedotin (anti-CD30 antibody drug conjugate) and PD-1 inhibitors (nivolumab, pembrolizumab) very effective in relapsed/refractory HL
- Can these agents be incorporated in frontline therapy to improve patient outcomes?

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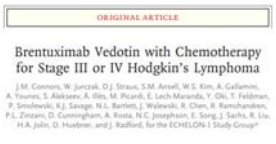
Brentuximab Vedotin as Frontline Therapy



ORIGINAL ARTICLE

Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma

- Phase 3 randomized control trial
- N= 1334 patients
- Advanced stage HL
- Median age 36 (up to age 83)
- BV-AVD vs ABVD for 6 cycles

Connors et al, NEJM 2017

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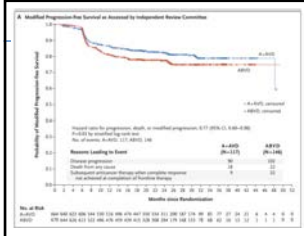

2-Year PFS:
BV-AVD: 82.1%
ABVD: 77.2%

Connors et al, NEJM, 2017

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BV-AVD Has Higher Rates of Toxicity

- **Higher rates of febrile neutropenia – need to use GCSF**
  - **24% in BV-AVD arm compared to 9% in ABVD**
- **More neuropathy**
  - **BV-AVD 67% vs ABVD 43%**

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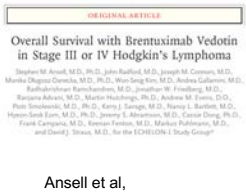
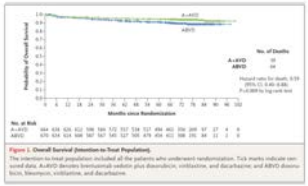
2022 Update: BV-AVD has Overall Survival Benefit over ABVD

6 year OS for BV-AVD – 93.9%
6 year OS for ABVD – 89.4%



Overall Survival with Brentuximab Vedotin in Stage III or IV Hodgkin's Lymphoma



Ansell et al, NEJM, 2022

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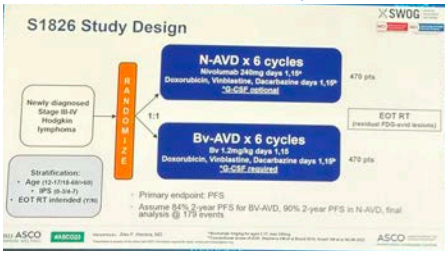
But wait, there's more – update for 2023!



Herrera et al, ASCO 2023

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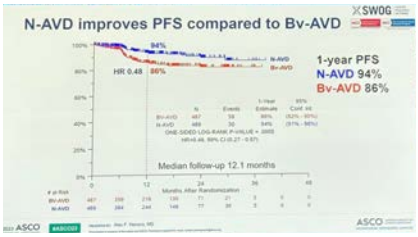
Nivo-AVD had Improved PFS Compared to Bv-AVD



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Toxicity Comparison

- **Nivo-AVD had less peripheral neuropathy (29% vs 55%) compared to BV-AVD**
- **Similar rates of febrile neutropenia (5% nivo vs 7% BV) despite only 54% N-AVD arm got GCSF compared to 95% BV-AVD arm**
- **Most common immune-related adverse event – thyroid dysfunction – 10% in nivo-AVD arm (compared to 1% for BV-AVD)**
- **No increased infectious toxicity in Nivo-AVD arm**

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How do we treat advanced stage Hodgkin lymphoma in 2023?

- Caveat: Follow up is still short!!
- If trends continue, I expect my preference may soon nivo-AVD for most patients -> improved PFS and favorable toxicity compared to Bv-AVD
- Also included pediatric patients! A more standardized approach for adults and peds?
- In the interim (until NCCN guidelines/FDA approval catch up for insurance authorization), treating most patients with Bv-AVD given overall survival benefit over ABVD

What's Next?

- Can we incorporate both BV and nivolumab and potentially use imaging techniques and/or biomarkers to de-escalate treatment in advanced stage Hodgkin lymphoma?
- Incorporating novel agents into early stage Hodgkin lymphoma
  - Cooperative group adult and peds clinical trial randomizing patients to BV/Nivo vs standard of care after interim PET scan

Case Example

- 28 yo F presents with enlarged neck nodes
- Excisional biopsy consistent with classical Hodgkin lymphoma
- PET/CT with multistation hypermetabolic lymphadenopathy along neck, chest, and retroperitoneum with FDG uptake significantly greater than liver as well as pulmonary nodules suspicious for lymphomatous involvement

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Case Example

- **65 year old female presented with right upper quadrant pain and weight loss and found to have diffuse mesenteric, retroperitoneal, mediastinal, and hilar lymphadenopathy. Biopsy consistent with diffuse large B cell lymphoma and FISH negative for MYC rearrangement. Labs significant for elevated LDH above upper limit of normal.**

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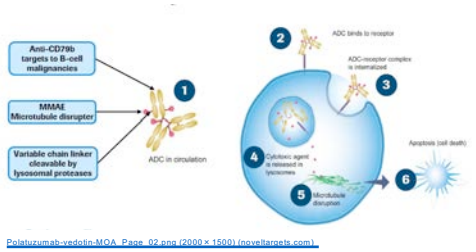
Polatuzumab Vedotin – FDA Approved in 2019 for relapsed/refractory DLBCL



Polatuzumab-vedotin-MOA_Page_02.png (2000 × 1500) (noveltargets.com)

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Polatuzumab with R-CHP vs R-CHOP

- Phase 3 double blind placebo controlled trial
- Inclusion criteria: intermediate and high risk DLBCL by IPI (IPI 2 or higher)
- 879 patients randomized
- 2 year PFS 76.7% vs 70.2%
- No difference in overall survival at 2 years
- Similar toxicity profile
- FDA approved for 1st line April, 2023

Tilly et al, NEJM 2022

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So should we use it?

- Improved PFS (although small)
- Similar toxicity profile
- Higher cost
- Requires growth factor support
- Some subgroups may benefit more?
- I have incorporated this into my standard of care for frontline advanced stage DLBCL

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Case Example

- 65 year old female presented with right upper quadrant pain and weight loss and found to have diffuse mesenteric, retroperitoneal, mediastinal, and hilar lymphadenopathy. Biopsy consistent with diffuse large B cell lymphoma and FISH negative for MYC rearrangement. Labs significant for elevated LDH above upper limit of normal.

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Case Example

- Our patient is treated with Pola-RCHP x 6 cycles. She initially gets into a complete remission but 4 months after completing therapy, she presents with worsening abdominal pain and nausea and is found to have diffuse FDG avid lymphadenopathy consistent with relapsed disease?

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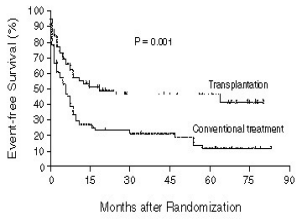
Prior Standard of Care for R/R DLBCL

- High dose chemotherapy followed by ASCT in responding patients (Parma trial)
- All patients got 2 cycles of DHAP and if PR or CR randomized to ASCT or 4 more cycles of DHAP
- 5 year EFS 46% for transplant arm vs 12% for DHAP arm



Philip T et al. N Engl J Med 1995;333:1540-1545.

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Limitations of Autologous Stem Cell Transplant

- Many patients not transplant eligible due to comorbidities or age
- Many patients not transplant eligible because don't respond to salvage therapy (about half)
- In patients who are initially chemorefractory, is more chemotherapy really the right option?

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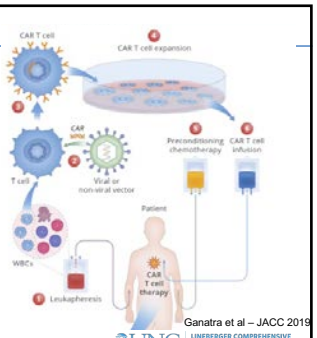
Chimeric Antigen Receptor T Cells

1) Leukapheresis
2) T cells isolated, activated, and transduced with CAR encoding viral vector
3) CAR-T cells can recognize specific antigen on cancer cells
4) CAR-T cells expanded with growth factors -> QC process
5) Lymphodepletion chemotherapy
6) CAR-T cell infusion



Ganatra et al – JACC 2019

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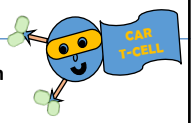
Chimeric Antigen Receptor T Cells



- 3 CAR-T cell products approved for patients with relapsed/refractory DLBCL
  - Axi-cel
  - Liso-cel
  - Tisa-cel
- Complete response rates 40-60% with durable remissions seen in patients in complete response
- Can these therapies be moved to earlier lines of therapy and potentially replace transplant?

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Second Line CAR-T Cell Trials

- Randomized trials comparing 2nd line CAR-T to ASCT
- DLBCL or high grade B cell lymphoma
- Primary refractory or relapse within 12 months of finishing 1L therapy
- Candidates for ASCT

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Zuma-7 (Axi-cel)

- Randomized trial comparing CD19 CAR-T to standard of care salvage to transplant
- DLBCL refractory or relapsed within 12 months of initial therapy
- Reported improved PFS in 2021 and led to FDA approval of axi-cel in 2nd line for DLBCL

Locke et al, NEJM 2021

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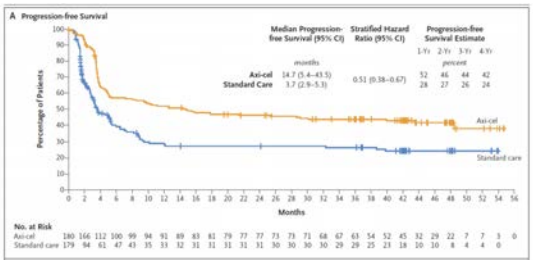
Axi-cel showed PFS benefit over standard of care



Westin et al NEJM 2023

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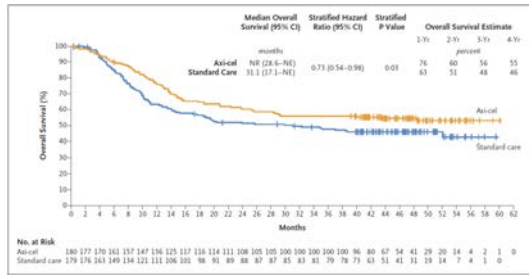
Axi-cel showed overall survival benefit over standard of care!



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Other 2nd Line CAR-T Cell Products

- Liso-cel (Transform trial) – similar results – also improvement over salvage/transplant although data hasn't matured enough so overall survival difference not reported – also FDA approved in 2022 for 2nd line CAR-T
- Tisa-cel (Belinda) – negative study – no difference between CAR-T and standard of care

Should we change management based on results?

- Yes, for primary refractory or early relapsed patients
- Benefit seen even with high cross-over/standard of care CAR-T cell use, suggesting benefit of treating earlier with CAR-T
- Low number of patients received ASCT (even in SOC arm – more received CAR-T than ASCT)

Patient Case

- 82 year old male with a history of high grade B cell lymphoma with MYC and BCL2 rearrangement (double hit lymphoma) treated with R-mini-CHOP 18 months ago presents to clinic.
- Initially in a complete response post chemotherapy but presented with new axillary and inguinal lymphadenopathy with biopsy concerning for relapsed disease.
- Tolerated chemotherapy fairly well
- Lives with his wife and can generally do his daily activities on his own although has had more fatigue with recent diagnosis and daughter has been coming daily to check on him and help.
- Generally walks at home but uses wheelchair to get to clinic due to longer distance to travel.

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PILOT Study

- Phase 2 study of 2nd line CAR-T (liso-cel) for patients with first relapse DLBCL who were not candidates for transplant based on the following criteria:
- Age >= 70
- ECOG PS 2
- DLCO <=60%
- LVEF < 50%
- Cr Cl < 60 mL/min
- AST/ALT > 2 ULN
- Could have relapsed > 1 year post initial therapy

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PILOT Study

- 61 patients treated
- Median age 74 years old
- 26% had ECOG PS 2
- Overall response rate 80%, complete response – 54%
- Patients in CR -> median duration of response – 21.7 months
- Cytokine release syndrome – 38% (grade 3 in 1 patient)
- Neurologic events – 31% (grade 3 in 3 patients)
- Led to FDA approval of liso-cel in 2nd line for patients who are not transplant candidates (even for later relapses)

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Case Example

- Our 65 yo patient is treated with Pola-RCHP x 6 cycles. She initially gets into a complete remission but 4 months after completing therapy, she presents with worsening abdominal pain and nausea and is found to have diffuse FDG avid lymphadenopathy consistent with relapsed disease?

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- Generally walks at home but uses wheelchair to get to clinic due to longer distance to travel.


How would you treat this patient?
Salvage chemotherapy followed by autologous stem cell transplant
0%
0
Salvage chemotherapy followed by allogeneic stem cell transplant
0%
0
CD19 CAR-T cell therapy
0%
0
Chemotherapy alone
0%
0
Hospice
0%
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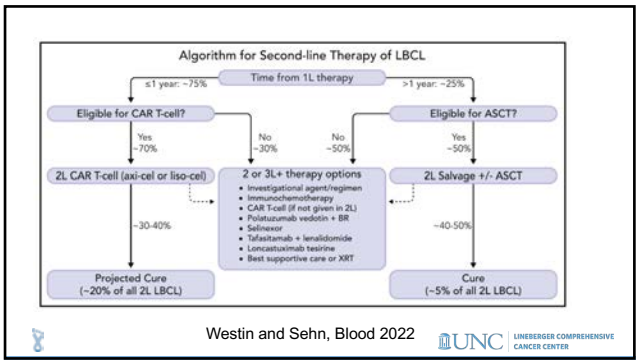
Algorithm for Second-line Therapy of LBCL
Time from 1L therapy
≤1 year: ~75%
>1 year: ~25%
Eligible for CAR T-cell?
Eligible for ASCT?
Yes ~70%
No ~30%
No ~50%
Yes ~50%
2L CAR T-cell (axi-cel or liso-cel)
2 or 3L+ therapy options
• Investigational agent/regimen
• Immunochemotherapy
• CAR T-cell (if not given in 2L)
• Polatuzumab vedotin + BR
• Selinexor
• Tafasitamab + lenalidomide
• Loncastuximab tesirine
• Best supportive care or XRT
2L Salvage +/- ASCT
~30-40%
~40-50%
Projected Cure (~20% of all 2L LBCL)
Cure (~5% of all 2L LBCL)
Westin and Sehn, Blood 2022
UNC LINEBERGER COMPREHENSIVE CANCER CENTER

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What new drugs have been approved in lymphoma in 2022 and 2023?
Mosunetuzumab for follicular lymphoma
0%
0
Mosunetuzumab for DLBCL
0%
0
Epcoritamab for DLBCL
0%
0
Glofitamab for DLBCL
0%
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All of the above
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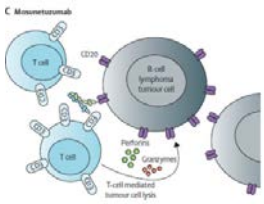
Mosunetuzumab – Bispecific Antibody



- Approved for relapsed/refractory follicular lymphoma after 2 or more lines of therapy
- 90 patients treated - ORR 80%, CR rate 60%
- 18 month EFS 70.2% in complete responders
- CRS in 44% - mostly grade ½ and during dose 1 or 3 (step up dose)
- Fixed duration therapy

Van de Donk and Zweegman, Lancet 2023

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Epcoritamab

- **Another CD3xCD20 T-cell engaging bi-specific antibody**
- **FDA approved for DLBCL – 3rd line - 2023**
- **Subcutaneous administration**
- **157 patients - ORR 63%, CR rate 39%**
- **Median DOR – 12 months; not reached for CR patients**
- **CRS – 49.7% - mostly grade 1 or 2; 2.5% grade 3**
- **Neurotoxicity (ICANS) – 6.4%**
- **Continuous therapy**

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Thieblemont et al, JCO 2023

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Glofitamab

- **Another CD3xCD20 T-cell engaging bi-specific antibody**
- **FDA approved for DLBCL – 3rd line - 2023**
- **IV administration**
- **Pre-treated with obinutuzumab 1 week prior (mitigate CRS)**
- **155 patients treated - CR rate 39% (CR rate 35% for prior CAR-T)**
- **78% of complete responses ongoing at 12 months**
- **CRS – 63% - mostly grade 1 or 2; 4% grade 3**
- **Neurotoxicity (ICANS) – 8%; grade 3 or higher – 3%**
- **Fixed duration – 12 cycles total**

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Dickinson et al, NEJM 2022

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Bispecific Antibodies vs CAR-T?

- Need longer follow up to determine duration of response with bispecifics
- CAR-T – 1 time treatment vs multiple infusions/injections with bispecifics
- Less CRS and neurotoxicity with bispecifics but still can see significant infections (like with CAR-T)
- Can bispecific antibodies be given in community? Education around toxicities or subsequent doses where low risk
- No lymphodepletion with bispecifics
- My approach: Currently mostly going to CAR-T first and saving bispecifics for post CAR-T relapse

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Summary – Biggest Practice Changes for Lymphoma Care This Year

- Incorporation of novel agents in frontline treatment of Hodgkin lymphoma (BV-AVD and now Nivo-AVD coming soon!)
- Incorporation of polatuzumab in frontline therapy for DLBCL
- Overall survival benefit with 2nd line CAR-T -> early referrals to CAR-T treatment center key! More patients may be CAR-T cell candidates than you expect!
- Bispecifics finally FDA approved for lymphoma

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Thank you!
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Questions/Comments?
Nobody has responded yet.
Hang tight! Responses are coming in.

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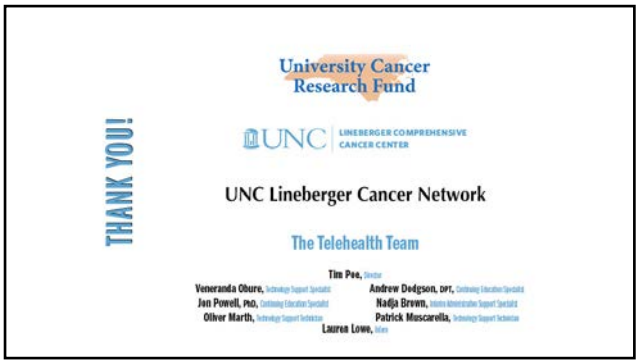
THANK YOU!
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July 12
12:00 PM
ePROs Monitoring in Thoracic Surgery and Oncology Patients
Gita Mody, MD
ADVANCED PRACTICE PROVIDER
July 19
4:00 PM
Overview of Clinical Trials for the APP
Clarissa Urban, PA-C
RESEARCH TO PRACTICE
July 26
12:00 PM
Therapeutic Approaches for Soft Tissue Sarcomas: 2023 Update
Mark Woodcock, MD
Complete details on upcoming Live Webinars:
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