NCCN 10th Annual Congress:
Hematologic Malignancies™

Patient Case Studies & Panel Discussion

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CASE 1

Ranjana H. Advani, MD
Stanford Cancer Institute

Case 1: Lymphoma Panel Discussion

- 70 year old man presents to his primary care physician with a 6 week history of a non-tender L neck mass which is increasing in size. He is otherwise asymptomatic.
- On exam, he is noted to have bilateral mid-cervical lymph nodes (1.5 cm), R inguinal lymph node (2 cm), and a palpable spleen (12 cm).
- Labs: WBC 9.9 K/ul (65% lymphocytes), Hgb 14.3 g/dl, plt 303 K/ul. Metabolic panel normal. LDH 121 U/L (reference <340).
- An FNA of L neck lymph node shows scant small cells which are CD10- and CD20+.

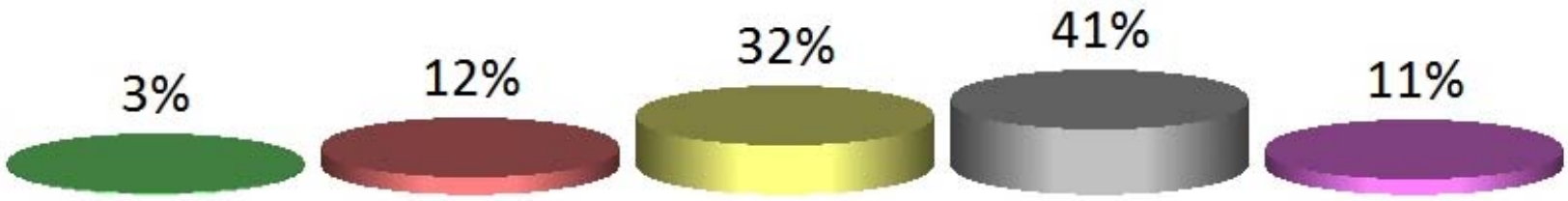
ARS Questions

Case 1

- A core biopsy of neck lymph node shows a proliferation of small to intermediate-sized lymphocytes with mild nuclear irregularities. IHC shows CD20+, CD5 equivocal, CD10-, BCL6-, BCL2-, cyclinD1 equivocal, CD23-.

Q 1.1: You reviewed the pathology at case conference. What additional studies were recommended to clarify the diagnosis?

1. IHC for CD 200
2. IHC for SOX 11
3. IHC for CCND2, CCND3 expression
4. 1, 2, 3
5. 1, 2



1	2	3	4	5
3	12	31	40	11

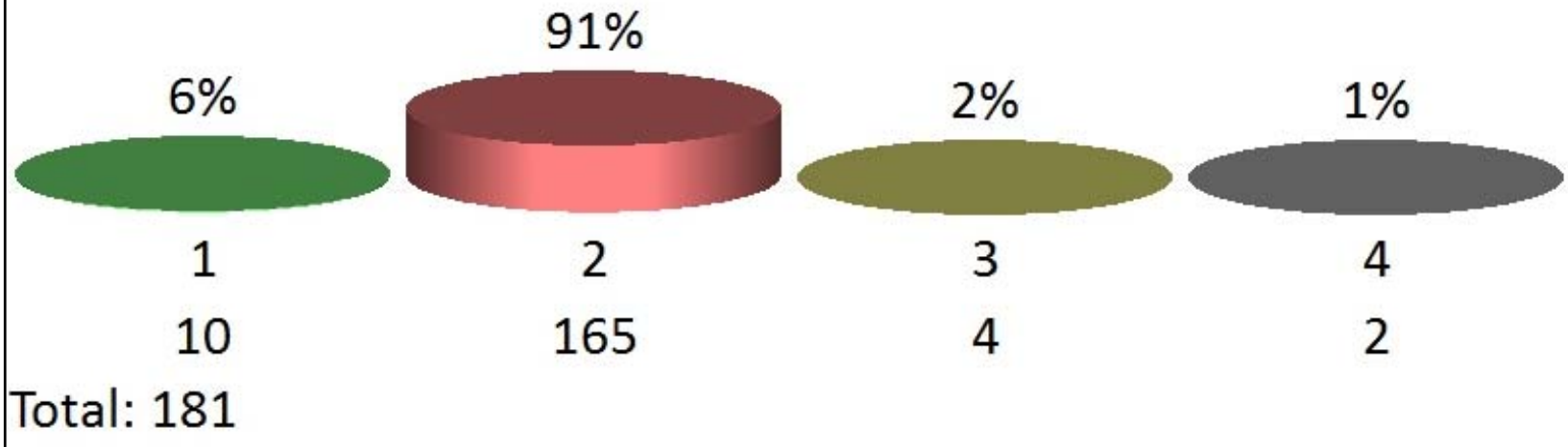
Total: 97

Case 1

- The IHC for SOX11 is positive, and CD200 is negative.

Q 1.2: What is the diagnosis?

1. Chronic lymphocytic leukemia
2. Mantle cell lymphoma
3. Atypical chronic lymphocytic leukemia
4. Non-germinal center diffuse large B cell lymphoma



Case 1

- The pathologists confirm the diagnosis of mantle cell lymphoma. Ki67 is 30%.
- PET/CT: bilateral neck level 3 nodes 1.5 x 1.2 cm (SUV 4), R axillary node 3 x 2 cm (SUV 3.5), L axillary node 1.5 x 2.1 cm (SUV 3), gastrohepatic conglomerate 4.9 x 4.4 cm (SUV 3.3), portohepatic conglomerate 3.2 x 4.2 cm (SUV 3.6), R inguinal node 2.1 x 3.1 cm (SUV 2.6), L inguinal node 1.9 x 1.0 cm (SUV 2.4). Spleen is 15 x 20 cm (SUV 3).
- Peripheral blood flow cytometry confirms the presence of circulating lymphoma cells.

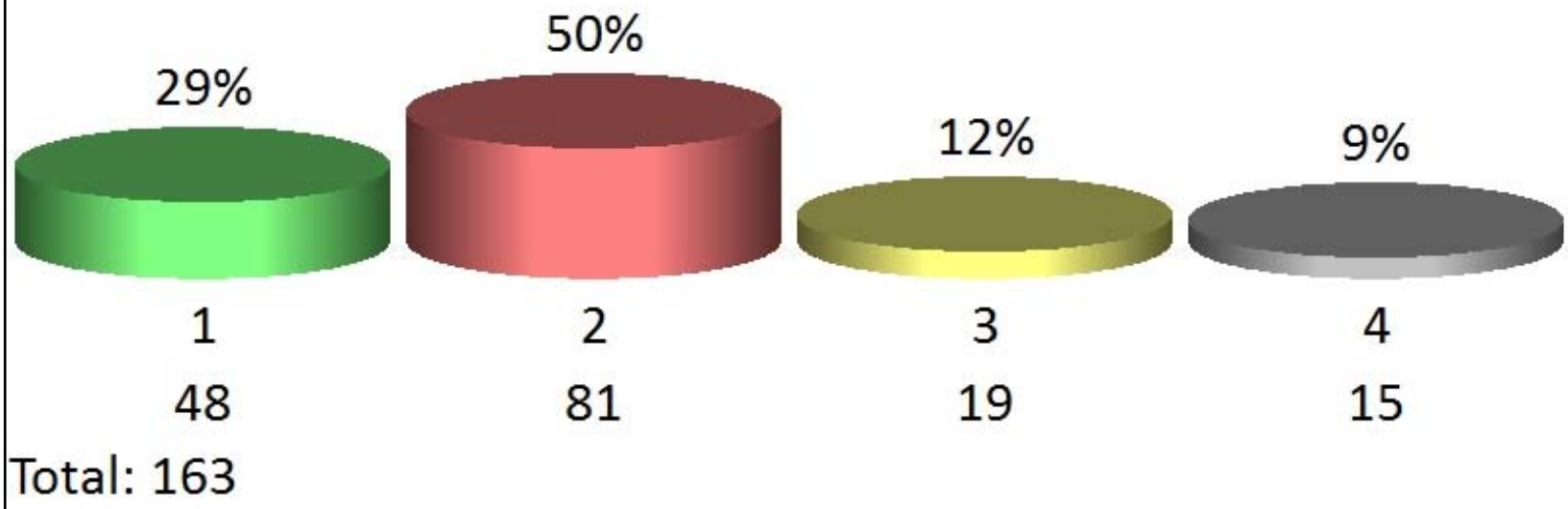
ARS Questions

FINAL DIAGNOSIS:

Stage IVA Mantle Cell Lymphoma

Q 1.3: What treatment would you choose?

1. R-CHOP 21
2. R-Bendamustine
3. R-HyperCVAD
4. R-CHOP 21 alternating with R-DHAP

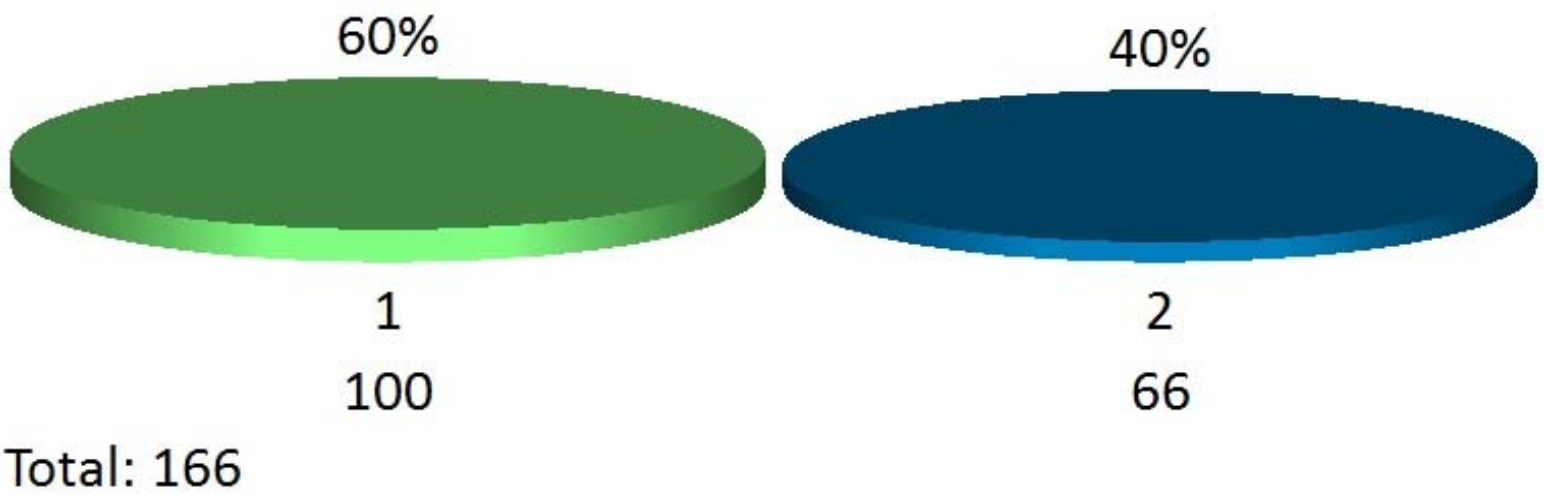


Case 1

- The patient receives R-Bendamustine.
- Interim CT scan after 4 cycles shows resolution of all adenopathy, except porta hepatis mass, which is now 2.5 x 3 cm. Spleen is still enlarged at 18 cm.

Q 1.4: What would you do next?

1. Two additional cycles of R-Bendamustine
2. Change therapy to alternative chemotherapy



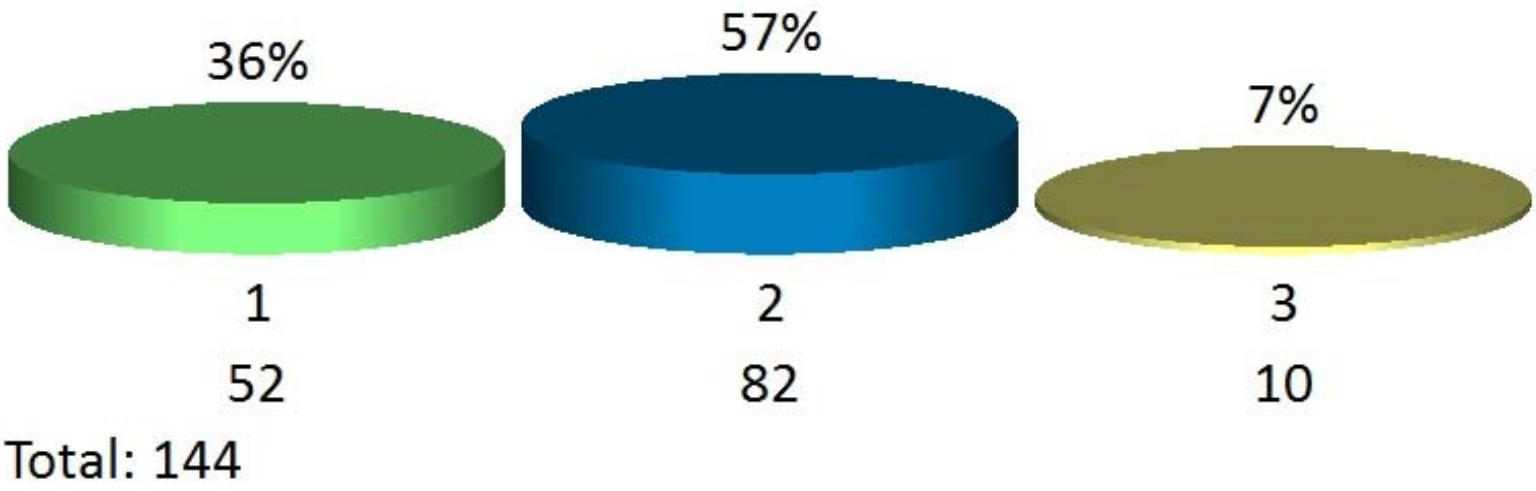
Total: 166

Case 1

- The patient receives 2 additional cycles of R-Bendamustine.
- PET/CT scan at the end of therapy shows a metabolic CR.

Q 1.5: What treatment would you recommend?

1. Observation
2. Maintenance rituximab
3. Consolidation with ASCT



Case 1

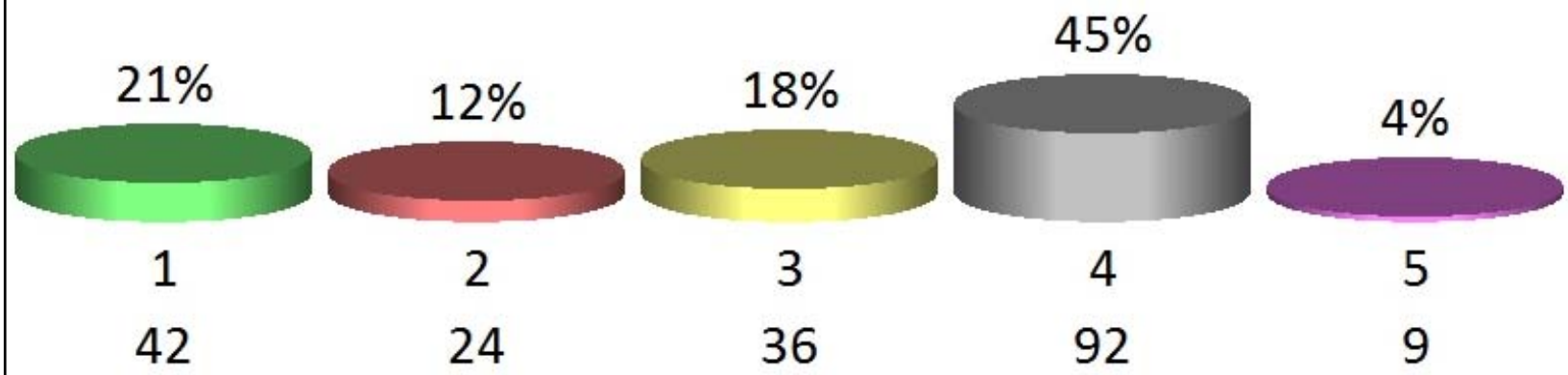
- Patient is taken to ASCT.
- Six months after ASCT, a surveillance CT scan shows retroperitoneal lymph nodes 2-3 cm, as well as a 1.6 cm paratracheal node and a 1.9 cm subcarinal node. He is asymptomatic.
- Core biopsy of sub carinal node confirms recurrent mantle cell lymphoma similar to original diagnosis. Ki67 is 20%.

ARS Question

Case 1

Q 1.6: What treatment would you recommend?

1. Observation
2. Bortezomib
3. Lenalidomide +/- rituximab
4. Ibrutinib +/- rituximab
5. Allogenic transplant



Total: 203

Case 1

- He is started on ibrutinib and tolerates treatment well.
- PET/CT scan after 4 cycles shows a CR, and he is continued on therapy with scans every 3 months. He does well for 15 months.
- One month after his last visit, he presents to your clinic for an unscheduled visit with severe abdominal pain and confusion. You note abdominal distention, massive splenomegaly, and L leg edema.
- Labs: WBC 38K/ul with 92% large atypical cells, Hgb 12.9 g/dl, plt 241 K/ul. LDH is 510 U/L (reference <340). Ca 14.1 mg/dl (reference 8.5-10.5).
- Flow of peripheral blood shows mantle cell lymphoma with blastic morphology.
- Patient is started on DHAP but rapidly declines, and family opts for comfort care.

Case 1: Take Home Points

- Though >95% of cases of MCL are positive for cyclin D1 or the t(11;14) translocation, rare cases are not. In this situation, SOX11 can be used to confirm the diagnosis of MCL.
  - Some cases can be shown to have translocation of CCND2 or CCND3
  - CD200 can also be used to distinguish CLL and variant-MCL
- Treatment of relapsed MCL is highly variable, and takes into account patient age and performance status.
- There is increasing recognition of the heterogeneity of MCL, ranging from the indolent variant to the blastic subtype.

Case 1: Take Home Points

- In younger (transplant-eligible) patients, data suggest that treatment should include an aggressive chemotherapy regimen followed by ASCT.[1,2]
- Emerging data suggests that an Ara-C containing regimen may improve outcome in transplant-eligible patients.
- The optimal front-line treatment of patients over the age of 60 remains unknown. The STIL trial and BRIGHT trial suggest that R-bendamustine has better outcomes than R-CHOP in MCL.[3]
- Role of maintenance rituximab after R-bendamustine is being evaluated in clinical trials.
- Ibrutinib is approved for MCL after failing one line of therapy; the overall response rate was 68% and estimated PFS was 13.9 months in the pivotal trial.[4]

CASE 2

Ranjana H. Advani, MD
Stanford Cancer Institute

Case 2: Lymphoma Panel Discussion

- A 59 year old male presents with diffuse abdominal pain and distension to his PCP. He has no fevers, weight loss, or night sweats.
- Labs: WBC 8.4 K/μL with a normal differential, hemoglobin 12 g/dL, platelet 444 K/μL, normal renal and liver function tests, and LDH 600 U/L (elevated).
- CT abdomen pelvis: enlarged lymph nodes in the central mesentery including a very large low density conglomerate 6.7 x 2.5 cm in size.
- Laparoscopic core biopsy of the mesenteric mass: shows pleomorphic large cell infiltrate with enlarged nuclei, irregular nuclear contours, and variable amounts of cytoplasm.
  - The atypical cells label strongly with CD30.
  - CD45 is weak and variable in much of the infiltrate and cells are ALK-1 negative. CD15, PAX-5, CD20, CD2, CD3, CD4, CD138, mixed keratin, and S100 are negative.
- The final diagnosis is ALK-1 negative anaplastic large cell lymphoma (ALCL).

Case 2

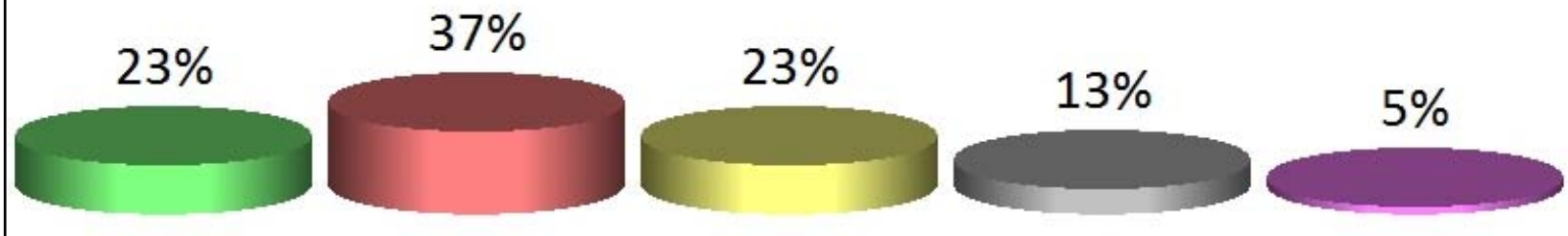
- He is now referred to you for further evaluation. You perform a BM biopsy, which is negative.
- PET/CT shows left axillary node 1 x 1.5 cm (SUV 3.5), periportal node 2.1 x 1.8 cm (SUV 9.9), confluent lower mid abdominal lymph nodes 5 x 8 x 4 cm (SUV 12.1), paraaortic node 3.1 x 1.2 cm (SUV 9.5), left paracolic gutter foci 2 x 1.2 cm (SUV 9.7), and pelvic node 2.1 x 1.8 cm (SUV 11.4). There is a focal splenic lesion 4 x 3 cm (SUV 12).

ARS Questions

Case 2

Q 2.1: What do you recommend for first line chemotherapy for stage IIIAS disease?

1. CHOP-21
2. CHOEP-21 x 6 cycles
3. HyperCVAD
4. Brentuximab vedotin
5. Gemcitabine, cisplatin based regimen



Total: 132

Case 2

- He is started on CHOEP.
- Night sweats resolve within 2 weeks.
- Restaging CT after 4 shows an excellent response and a PET/CT and end of 6 cycles demonstrates CR.

Q 2.2: What is the next step in management?

1. Observation without further therapy
2. Consolidate with autologous stem cell transplant
3. Type siblings for possible allogeneic transplant
4. Start maintenance brentuximab vedotin
5. Check for DUSP22 rearrangement

1	2	3	4	5
40	66	21	11	7

Total: 145

Case 2

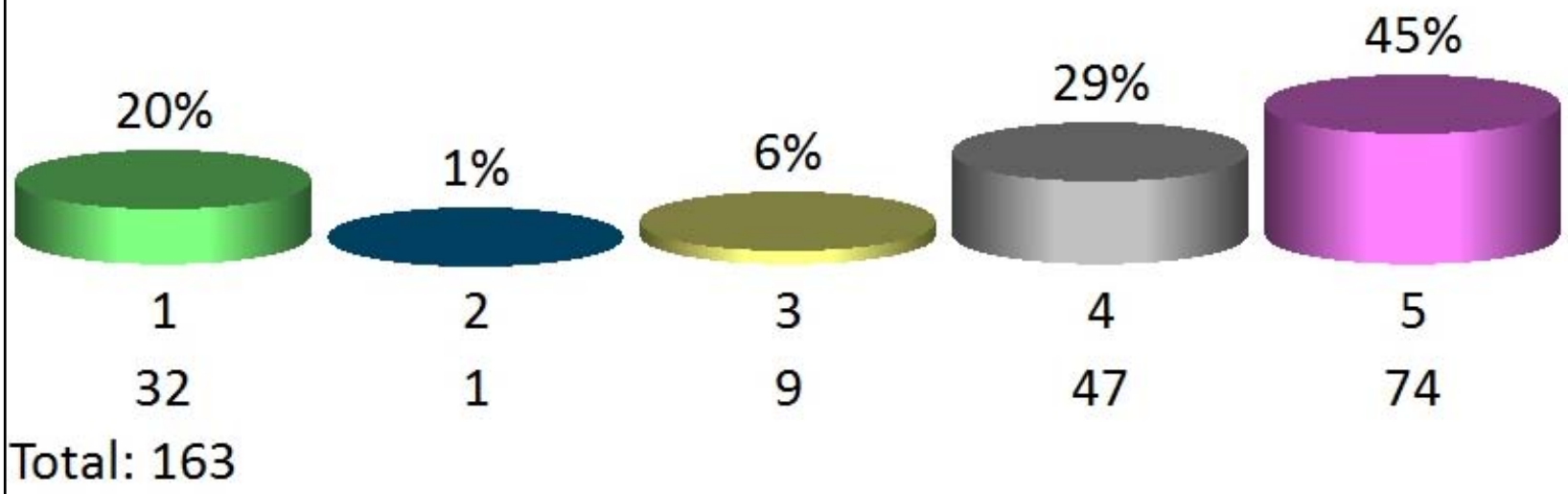
- DUSP22 rearrangement is negative
- He undergoes consolidation with HDT and ASCT. Eight months post transplant he develops abdominal pain, similar to what he had at original diagnosis.
- On exam, he is well appearing and you palpate a mid abdominal mass. CT confirms a 4 x 6 cm mesenteric mass and core biopsy shows recurrent ALCL.
- He has an HLA matched sibling.

ARS Questions

Case 2

Q 2.3: What is the next step?

1. Radiotherapy for localized disease
2. Single agent vinblastine
3. Gemcitabine and oxaliplatin
4. Treatment with brentuximab vedotin
5. Refer to allogenic transplant



Case 2

- He is started on brentuximab vedotin (BV) and achieves CR after 4 doses.

Q 2.4: What will you do next?

1. Continue BV for 1 year (maximum 16 doses)
2. Refer now for allo transplant
3. Consider a trial with crizotinib

Total: 167

ALCL: Take Home Points

- ALCL is a rare subtype of peripheral T cell lymphoma (PTCL) and consists of two subtypes, ALK-positive and ALK-negative disease.
- For patients <60 years old, CHOEP improves EFS when compared with CHOP. Other etoposide containing regimens have also shown improved outcomes especially for patients with ALK-negative disease.[5,6]
- The role of consolidative ASCT in patients with a CR is controversial.
- Brentuximab vedotin (BV) at 1.8mg/kg administered q 3 weeks is very active in the relapsed or refractory setting with an ORR of 86%.[7, 8]
- The duration of response after BV can be very durable. Thus, the utility of transplant for patients in remission post BV is debatable.

ALCL: Take Home Points

- Front line BV + CHP has shown excellent data in a phase 2 study. These promising results have led to an ongoing phase 3 study comparing CHOP to BV + CHP as frontline therapy for patients with mature CD30+ T-cell lymphomas.
- Crizotinib (ALK inhibitor) is being evaluated in recurrent ALK-positive ALCL. It is currently FDA approved for ALK-positive NSCL cancer.[9]
- DUSP22 positive ALK-negative ALCL has an excellent prognosis and can likely be rx with CHOP and observation if in a CR.

CASE 3

Andrew D. Zelenetz, MD, PhD
Memorial Sloan Kettering Cancer Center

Case 3: Lymphoma Panel Discussion

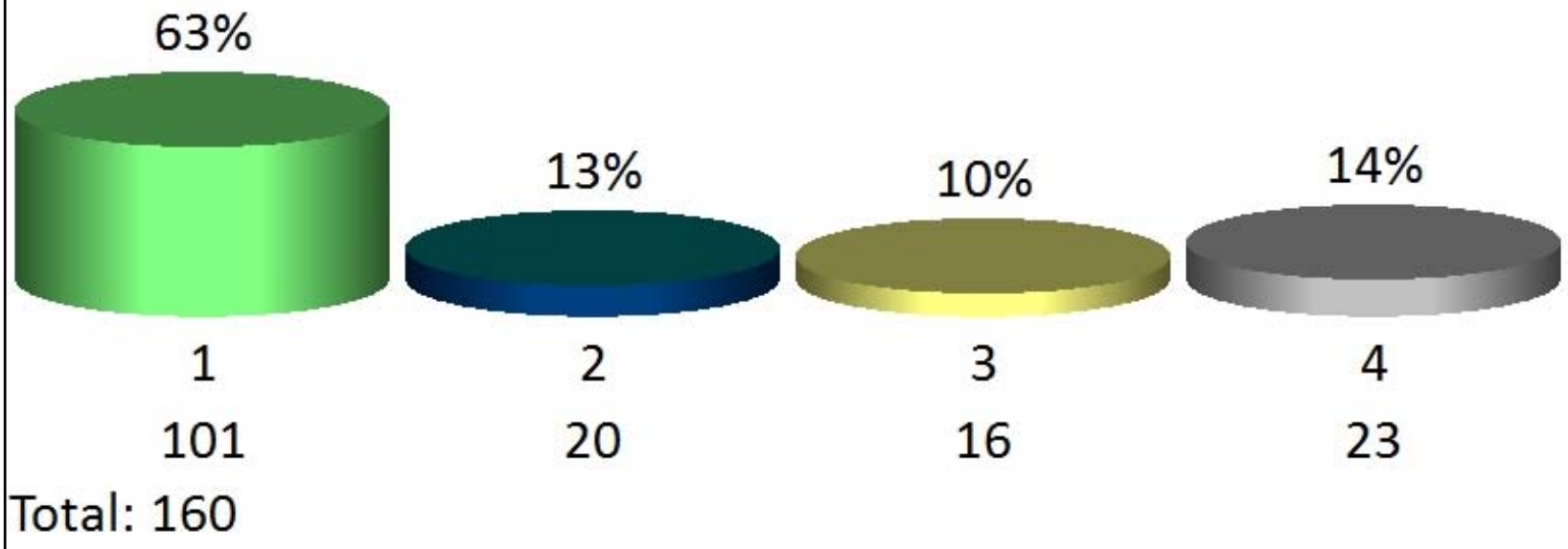
- 47-year-old Caucasian man presents to his internist with a painless cervical mass and on exam has a firm cervical lymph node.
- CT of the neck demonstrates bilateral cervical adenopathy up to 3.4 cm in the posterior chain. The upper portion of the the chest included on the CT of the neck demonstrated an anterior mediastinal mass.
- The patient was referred to a surgeon and an excisional cervical node biopsy demonstrated diffuse large B cell lymphoma, not otherwise specified.
- Immunohistochemistry shows: the cells EXPRESS CD20, CD79A, CD10, BCL2, BCL6, MYC in 40% of the cells and DO NOT EXPRESS MUM1/IRF4A, TP53. The proliferation index is 90%.

ARS Questions

Case 3

Q 3.1: The findings are compatible with:

1. Double hit DLBCL (DH DLBCL)
2. Germinal center DLBCL (GC DLBCL)
3. Activated B cell DLBCL (ABC DLBCL)
4. Primary mediastinal B cell lymphoma (PMBL)



Case 3

- The double expression of BCL2 and MYC makes you suspicious of a double hit lymphoma.

Q 3.2: To confirm this, what tests can you request that the pathologist do on the paraffin block?

1. Karyotype
2. FISH
3. Full genomic profile testing (eg FoundationOne Heme)
4. All
5. 2 and 3

1	2	3	4	5
4	91	4	25	56

Total: 180

Case 3

- Labs: WBC 8.3 K/ul with normal differential, Hgb 11.2 g/dl, plt 243. LDH is 393 U/L (reference <340). Cr is 0.8 and LFTs are normal.
- PET/CT scan: L supraclavicular node 1.8 x 2 cm (SUV 7), subcarinal node 1.2 x 1.5 cm (SUV 8.1), and a 10.1 x 8.2 cm mediastinal mass (SUV 17); A 8 cm x 6 cm retroperitonal mass noted (SUV 15) which encases the L kidney with moderate hydroureter. Two areas of distal small bowel thickening are noted as well as a R pleural-based nodule 2 x 1.5 cm (SUV 4).

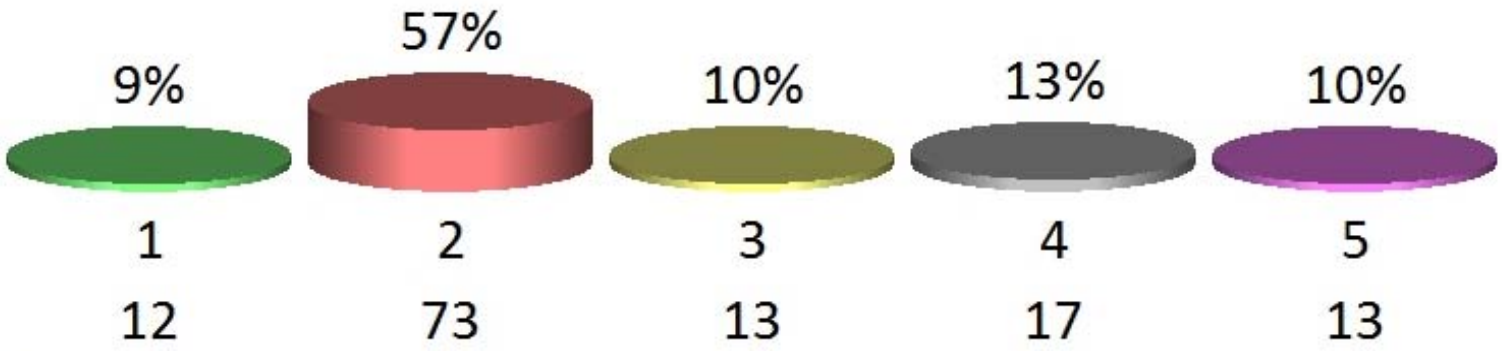
ARS Questions

Case 3

- FISH is diagnostic of a double hit lymphoma with translocation of BCL2 and MYC, there was no translocation of BCL6.

Q 3.3: What do you recommend as induction therapy?

1. R-CHOP 21 x 6 cycles
2. DA-EPOCH-R
3. R-HyperCVAD/R-MA
4. R-CHOP/ICE
5. R-CHOP 14 x 6 cycles followed by maintenance rituximab



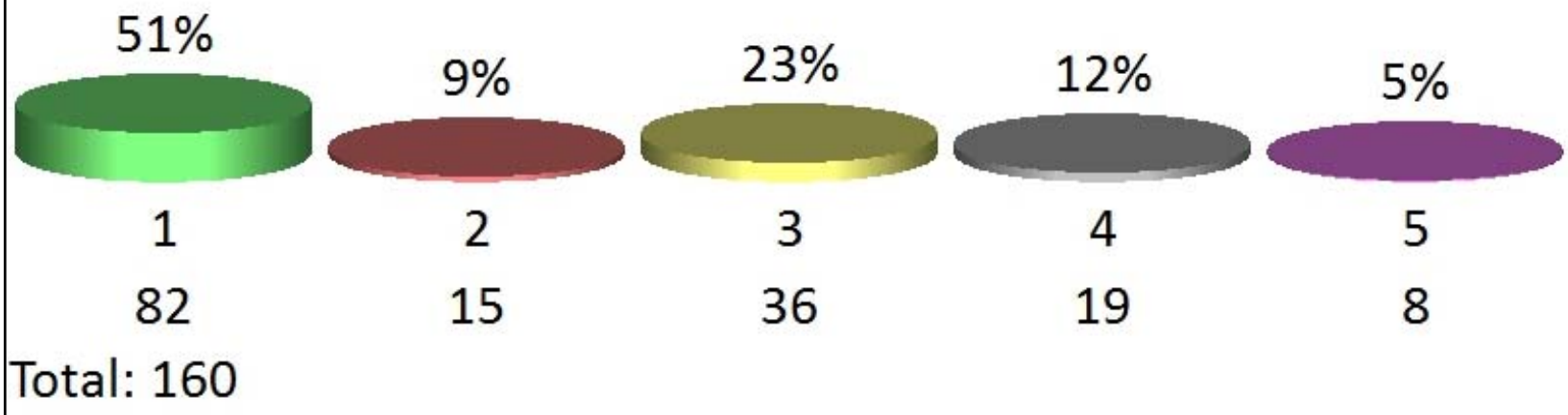
Total: 128

Case 3

- He starts on R-CHOP 21. PET/CT scan after 4 cycles shows near complete resolution of neck and subcarinal lymphadenopathy. Mediastinal mass has not changed in size but is less FDG avid (SUV 6). Retroperitoneal mass is now 2 x 3 cm without avidity
- LDH is 253 (reference <246).

Q 3.4: You recommend:

1. Continue R-CHOP 21 x 2 more cycles
2. Change treatment to RICE
3. Change treatment to DA-EPOCH-R
4. Biopsy residual mass
5. RT to residual mass



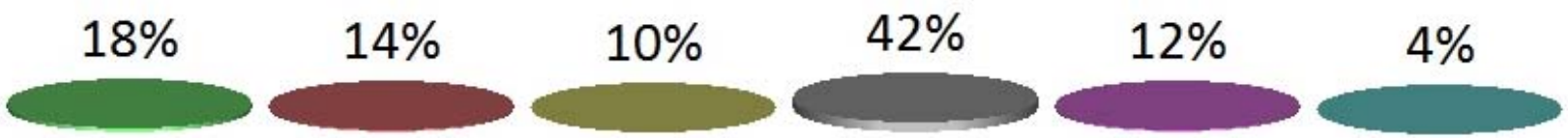
Total: 160

Case 3

- He receives R-CHOP 21 for two additional cycles.
- PET/CT scan shows that the mediastinal mass is slightly smaller (7.1 x 8.1 cm) with unchanged SUV (6).

Q 3.5: What do you recommend?

1. Change treatment to RICE and if response ASCT
2. Change treatment to DA-EPOCH-R
3. Change treatment to R-bendamustine
4. Biopsy mediastinal mass
5. Radiate mediastinal mass
6. Allogenic transplant



1	2	3	4	5	6
28	22	15	65	19	6

Total: 155

Double-hit DLBCL: Take Home Points

- Double expressing (IHC for MYC and BCL2) and double-hit lymphoma are not the same
  - Outcomes of patients with double-hit (translocation of BCL2/BCL6 and MYC) DLBCL with R-CHOP are very poor.
- Some data exists to support better outcomes with a more aggressive front-line approach, such as DA-EPOCH-R or R-CODOX-M/R-IVAC, depending on age of the patient.[10, 11]
  - In retrospective data outcomes are improved with HDT/ASCT.
  - Note: prospective DA-EPOCH-R was censored for SCT consolidation.

References

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