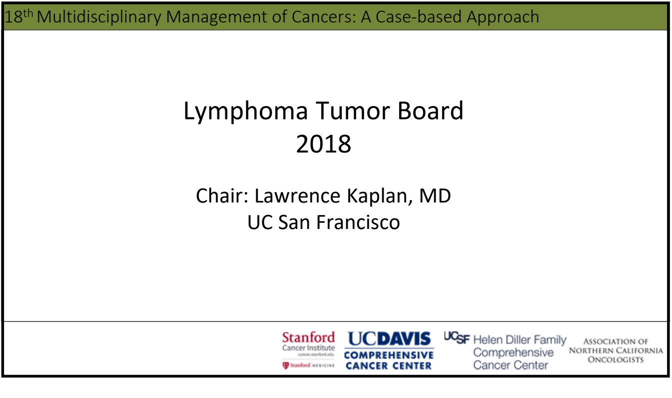
18th Multidisciplinary Management of Cancers: A Case-based Approach
Lymphoma Tumor Board
2018
Chair: Lawrence Kaplan, MD
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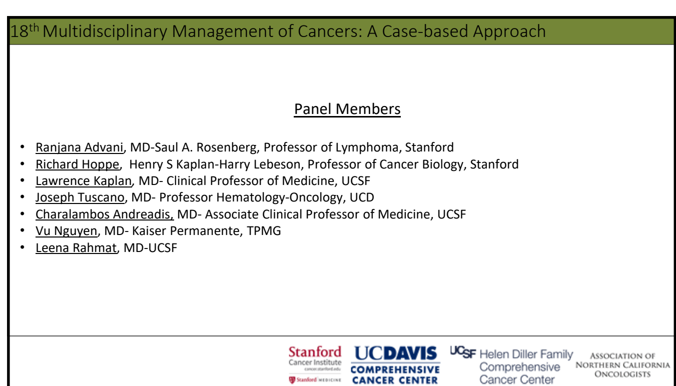
18th Multidisciplinary Management of Cancers: A Case-based Approach
Panel Members
• Ranjana Advani, MD-Saul A. Rosenberg, Professor of Lymphoma, Stanford
• Richard Hoppe, Henry S Kaplan-Harry Lebeson, Professor of Cancer Biology, Stanford
• Lawrence Kaplan, MD- Clinical Professor of Medicine, UCSF
• Joseph Tuscano, MD- Professor Hematology-Oncology, UCD
• Charalambos Andreadis, MD- Associate Clinical Professor of Medicine, UCSF
• Vu Nguyen, MD- Kaiser Permanente, TPMG
• Leena Rahmat, MD-UCSF
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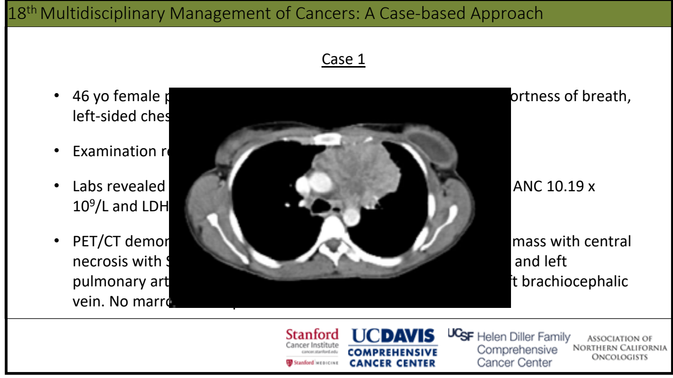
18th Multidisciplinary Management of Cancers: A Case-based Approach
Case 1
• 46 yo female p ortness of breath,
left-sided ches
• Examination r
• Labs revealed ANC 10.19 x
10⁹/L and LDH
• PET/CT demor mass with central
necrosis with and left
pulmonary art t brachiocephalic
vein. No marr
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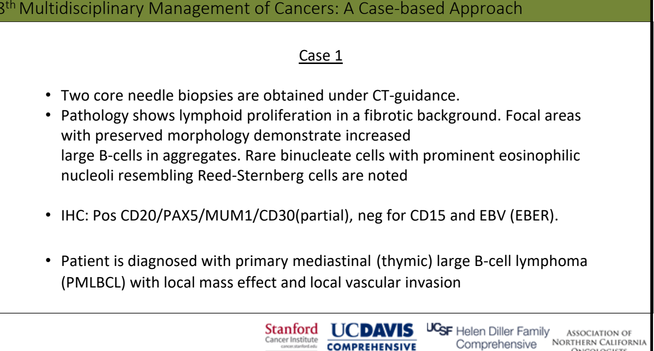
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Case 1
• Two core needle biopsies are obtained under CT-guidance.
• Pathology shows lymphoid proliferation in a fibrotic background. Focal areas with preserved morphology demonstrate increased large B-cells in aggregates. Rare binucleate cells with prominent eosinophilic nucleoli resembling Reed-Sternberg cells are noted
• IHC: Pos CD20/PAX5/MUM1/CD30(partial), neg for CD15 and EBV (EBER).
• Patient is diagnosed with primary mediastinal (thymic) large B-cell lymphoma (PMLBCL) with local mass effect and local vascular invasion
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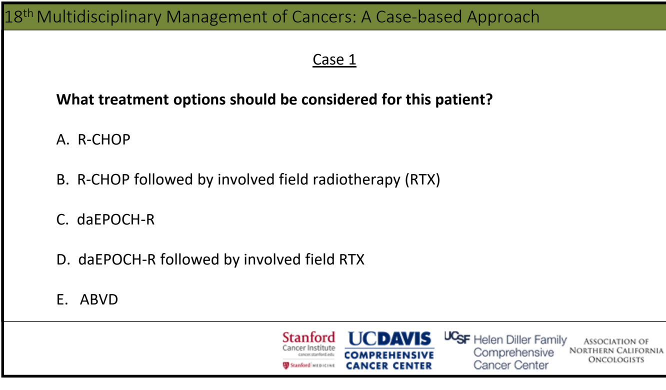
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Case 1
What treatment options should be considered for this patient?
A. R-CHOP
B. R-CHOP followed by involved field radiotherapy (RTX)
C. daEPOCH-R
D. daEPOCH-R followed by involved field RTX
E. ABVD
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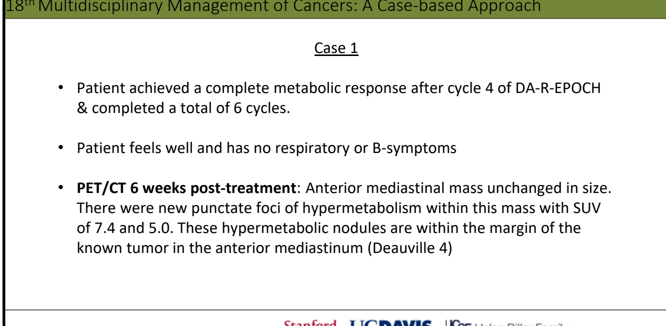
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Case 1
Patient achieved a complete metabolic response after cycle 4 of DA-R-EPOCH & completed a total of 6 cycles.
Patient feels well and has no respiratory or B-symptoms
PET/CT 6 weeks post-treatment: Anterior mediastinal mass unchanged in size. There were new punctate foci of hypermetabolism within this mass with SUV of 7.4 and 5.0. These hypermetabolic nodules are within the margin of the known tumor in the anterior mediastinum (Deauville 4)
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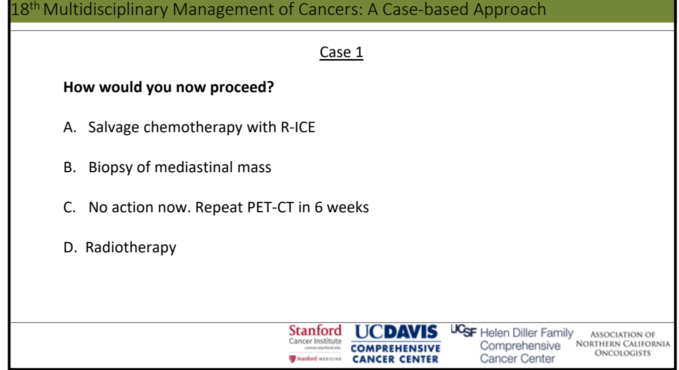
18th Multidisciplinary Management of Cancers: A Case-based Approach
Case 1
How would you now proceed?
A. Salvage chemotherapy with R-ICE
B. Biopsy of mediastinal mass
C. No action now. Repeat PET-CT in 6 weeks
D. Radiotherapy
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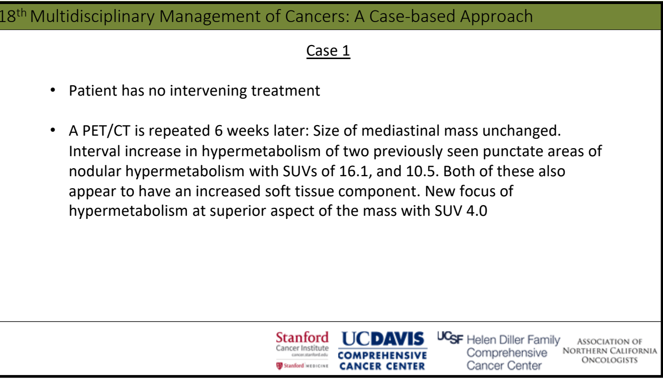
18th Multidisciplinary Management of Cancers: A Case-based Approach
Case 1
Patient has no intervening treatment
A PET/CT is repeated 6 weeks later: Size of mediastinal mass unchanged. Interval increase in hypermetabolism of two previously seen punctate areas of nodular hypermetabolism with SUVs of 16.1, and 10.5. Both of these also appear to have an increased soft tissue component. New focus of hypermetabolism at superior aspect of the mass with SUV 4.0
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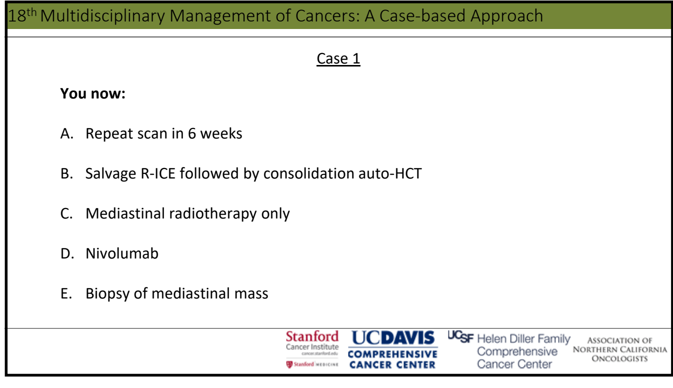
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Case 1
You now:
A. Repeat scan in 6 weeks
B. Salvage R-ICE followed by consolidation auto-HCT
C. Mediastinal radiotherapy only
D. Nivolumab
E. Biopsy of mediastinal mass
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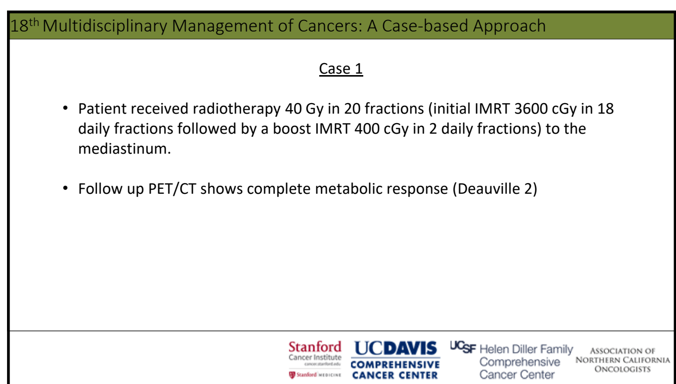
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Case 1
• Patient received radiotherapy 40 Gy in 20 fractions (initial IMRT 3600 cGy in 18 daily fractions followed by a boost IMRT 400 cGy in 2 daily fractions) to the mediastinum.
• Follow up PET/CT shows complete metabolic response (Deauville 2)
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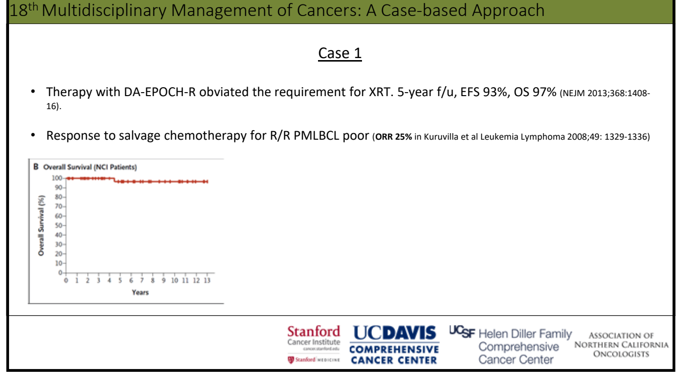
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Case 1
• Therapy with DA-EPOCH-R obviated the requirement for XRT. 5-year f/u, EFS 93%, OS 97% (NEJM 2013;368:1408-16).
• Response to salvage chemotherapy for R/R PMLBCL poor (ORR 25% in Kuruvilla et al Leukemia Lymphoma 2008;49: 1329-1336)
B Overall Survival (NCI Patients)
Overall Survival (%)
Years
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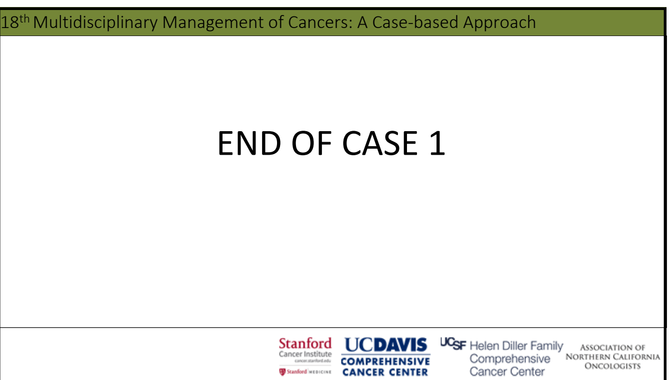
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END OF CASE 1
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Case 2

- 67 yo female who presented with cervical adenopathy and fatigue.
- Physical Exam: bilateral palpable cervical lymphadenopathy
- Labs: LDH 360 U/L, WBC 19 x 10^9/L, ANC 9.4 x 10^9/L , Hgb 10.2 g/dL, Plts 148 x 10^9/L, acid 3.2 mg/dL.
- Bone marrow biopsy negative.

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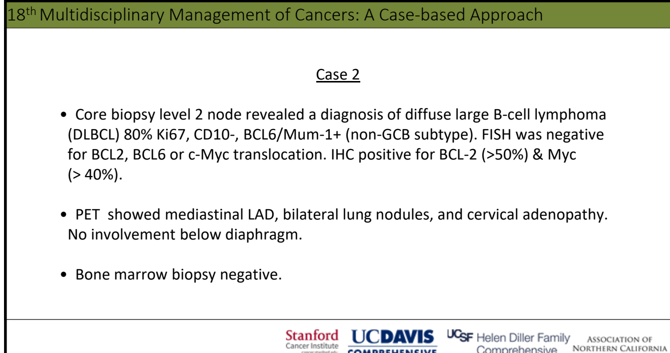

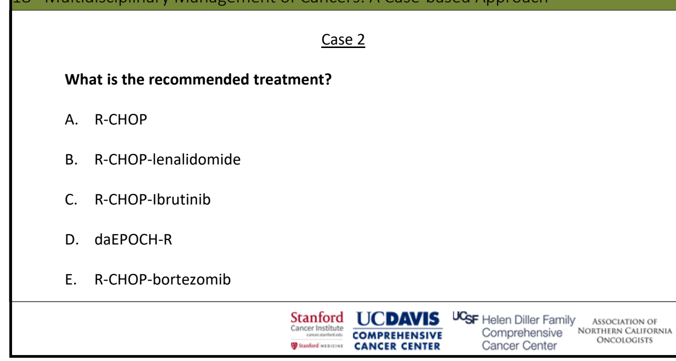

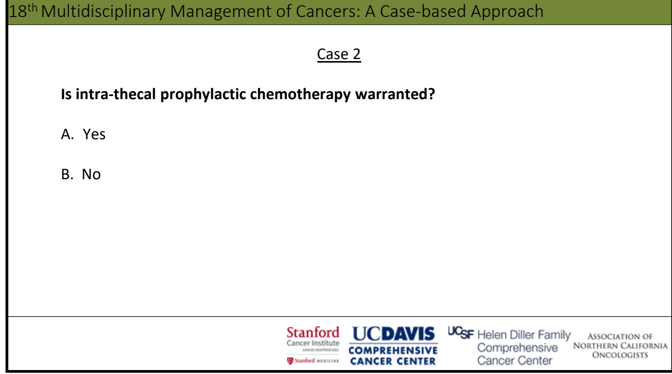

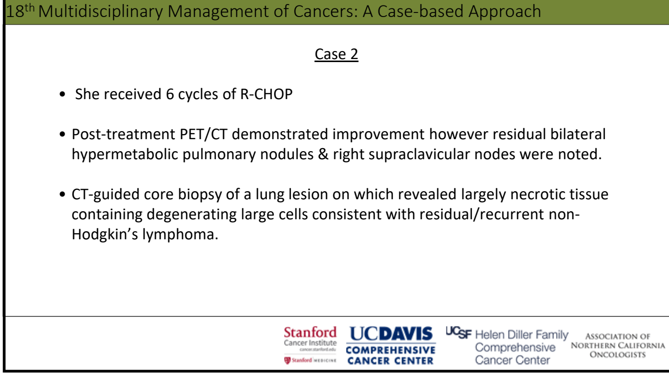
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Case 2
She received 6 cycles of R-CHOP
Post-treatment PET/CT demonstrated improvement however residual bilateral hypermetabolic pulmonary nodules & right supraclavicular nodes were noted.
CT-guided core biopsy of a lung lesion on which revealed largely necrotic tissue containing degenerating large cells consistent with residual/recurrent non-Hodgkin's lymphoma.
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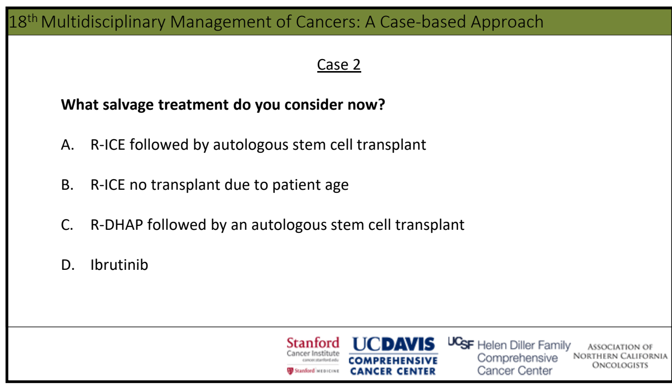
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Case 2
What salvage treatment do you consider now?
A. R-ICE followed by autologous stem cell transplant
B. R-ICE no transplant due to patient age
C. R-DHAP followed by an autologous stem cell transplant
D. Ibrutinib
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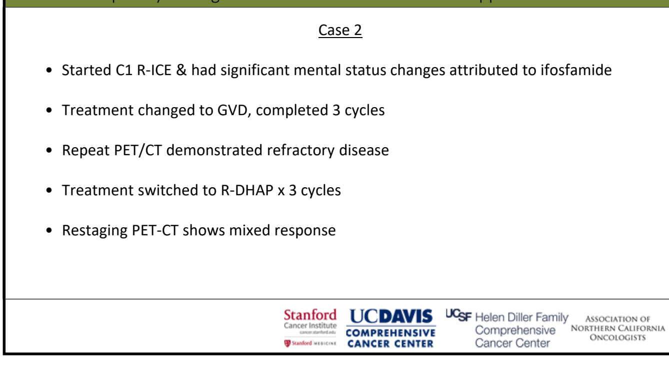
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Case 2
Started C1 R-ICE & had significant mental status changes attributed to ifosfamide
Treatment changed to GVD, completed 3 cycles
Repeat PET/CT demonstrated refractory disease
Treatment switched to R-DHAP x 3 cycles
Restaging PET-CT shows mixed response
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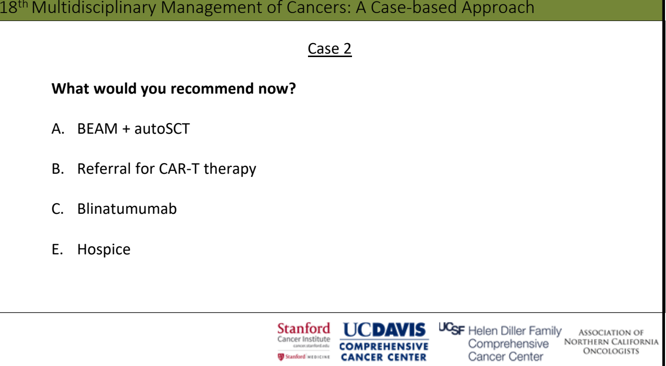
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Case 2
What would you recommend now?
A. BEAM + autoSCT
B. Referral for CAR-T therapy
C. Blinatumumab
E. Hospice
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Case 2

- The patient is enrolled in a CD19 CAR-T cell clinical trial
- However, patient developed progression and is in need of disease control before proceeding to CART.
- Options offered: R-Bendamustine-carfilzomib; lenalidomide-blinatumumab, R- or G-Bendamustine

Case 2

- Double expressor DLBCLs have unfavorable outcome, higher CNS relapse risk (Savage et al JCO.2016;127: 2182) no clear benefit from DA EPOCH-R. (CALGB 50303 data pending).
- Addition of bortezomib to R-CHOP failed to show benefit in non-GCB DLBCL in two trials (Leonard JM. Blood. 2015;126(23):811 / Davies AJ. Ann Oncol. 2017;35(Suppl 2):130-131)
- Randomized trial of R-CHOP +/- ibrutinib (PHOENIX) for non-GCB fully enrolled.
- R^2-CHOP active but not clearly better. (J Clin Oncol. 2015;33(3):251, Lancet Oncol 2014;15:730-37. Randomized trial in progress (ECOG E1412)
- Patients who fail to respond to a first salvage regimen outcomes very poor (Elstrom R et al *Clin Lymphoma Myeloma Leuk.* 2010;10:192-196.)
- Commercial CART (axicabtagene) eligibility: falure to respond to two lines of therapy

ZUMA-1 Pivotal Trial Met Primary Endpoint of ORR At the Interim Analysis (P<0.0001)*

Best Overall Response in Patients with ≥3 Month Follow-up

Subgroup	n	ORR	CR
DLBCL	51	76%*	47%
TFL / PMBCL	11	91%	73%
Total	**62**	**79%**	**52%**

*$P<0.0001$ (exact binomial test comparing observed ORR to a historical control assumption of 20%)

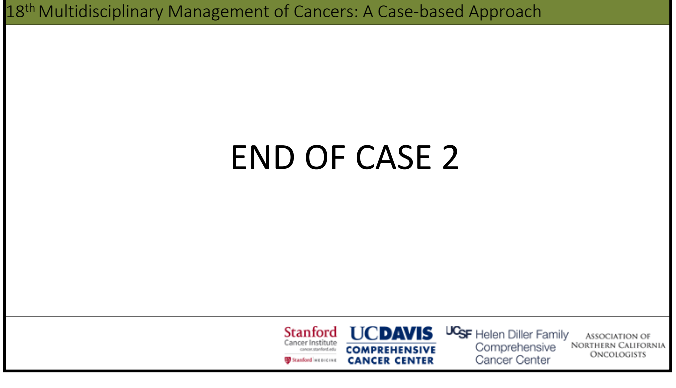
- At month 3 assessment the CR rate was 39%
- 7 patients with SD/PR at 1 mo converted to CR at 3 mo
- Complete Response in key subgroups:
  - 75% (n=9/12) CR relapsed post-ASCT
  - 47% (n=23/49) CR refractory to ≥2nd line

JULIET: Primary Endpoint

Response Rate, %	Best Overall Response Rate (N = 81)	Response at 3 Months (N = 81)	Response at 6 Months (n = 46)
ORR (CR + PR)	53[a]	38	37
CR	40	32	30
PR	14	6	7

* $P < .0001$ (95% CI, 42%-64%). Null hypothesis of ORR ≤ 20%.

CR, complete response; ORR, overall response rate; PR, partial response.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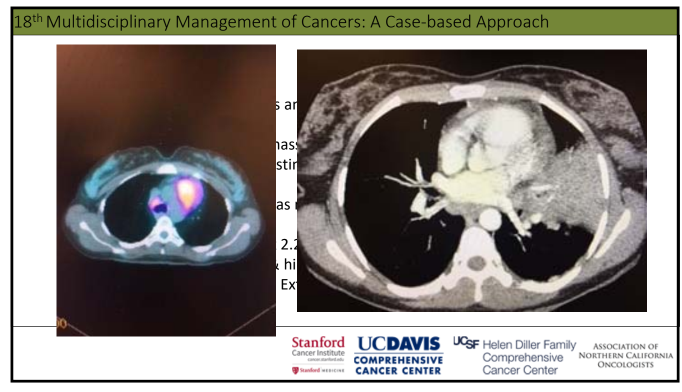
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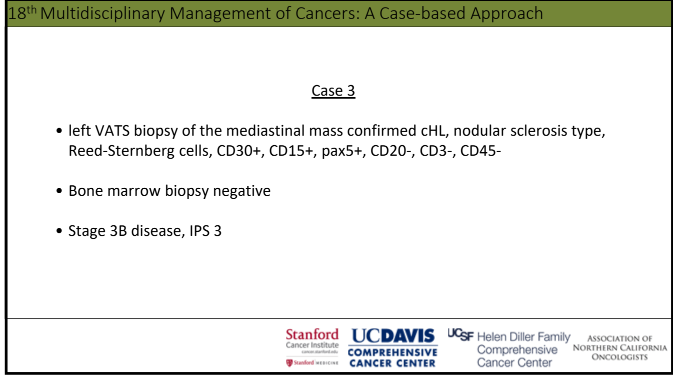
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Case 3
• left VATS biopsy of the mediastinal mass confirmed cHL, nodular sclerosis type, Reed-Sternberg cells, CD30+, CD15+, pax5+, CD20-, CD3-, CD45-
• Bone marrow biopsy negative
• Stage 3B disease, IPS 3
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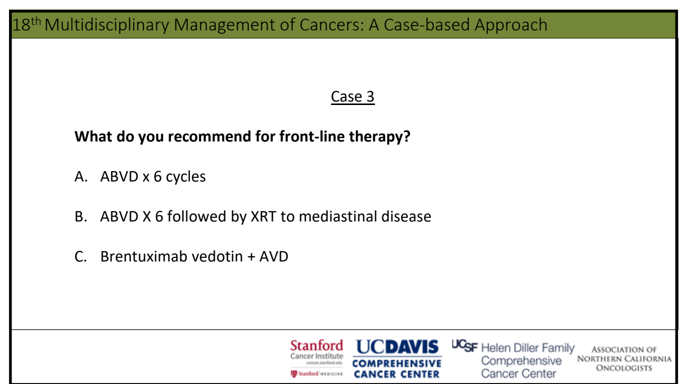
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Case 3
What do you recommend for front-line therapy?
A. ABVD x 6 cycles
B. ABVD X 6 followed by XRT to mediastinal disease
C. Brentuximab vedotin + AVD
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Case 3

- Patient receives 2 cycles ABVD
- Re-staging PET/CT after cycle 2 demonstrated a CMR, Deauville 2
- She goes on to receive 4 additional cycles of ABVD
- Re-staging PET/CT demonstrated increased size of the mediastinal mass ,now extending across the midline measuring 4.4 x 8.0 cm, SUV 8.4, confluent subcarinal, pretracheal, paraesophageal, & hilar LAD all increased, multiple new pulmonary nodules, a lingular mass 4.4 x 4 cm SUV 13.1 and new bilateral pleural effusions. Repeat bx + recurrent cHL

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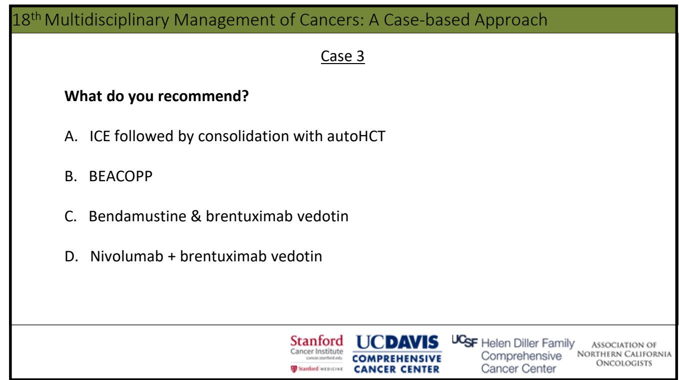

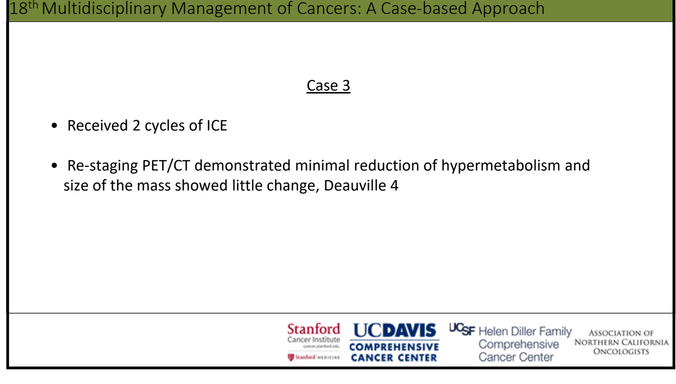

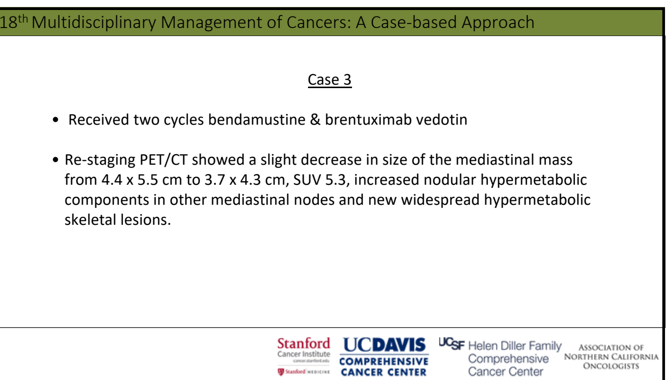

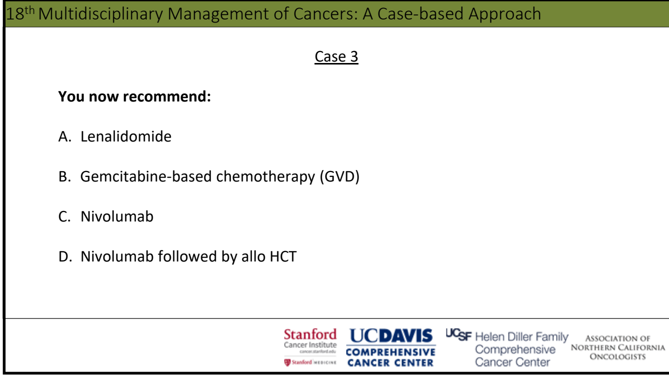

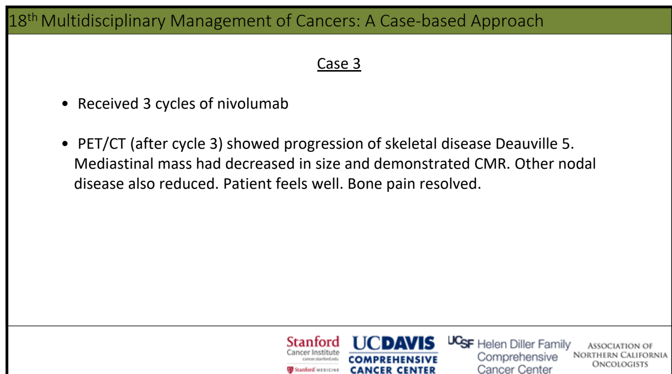

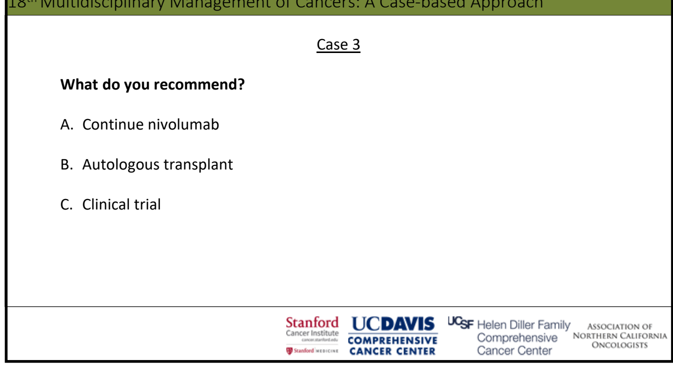

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Case 3

- Went on to receive total 7 cycles of nivolumab
- PET/CT demonstrated a mixed response and new carinal, hilar LAD, increased periportal LAD, all hypermetabolic, deauville 5
- Receives 2 cycles GVD
- PET/CT 3/23/16 demonstrated a CMR in mediastinum and significant decrease in retroperitoneal LAD and skeletal lesions.
- Receives BEAM-auto HCT but relapses 4 months post-auto. Elects hospice care

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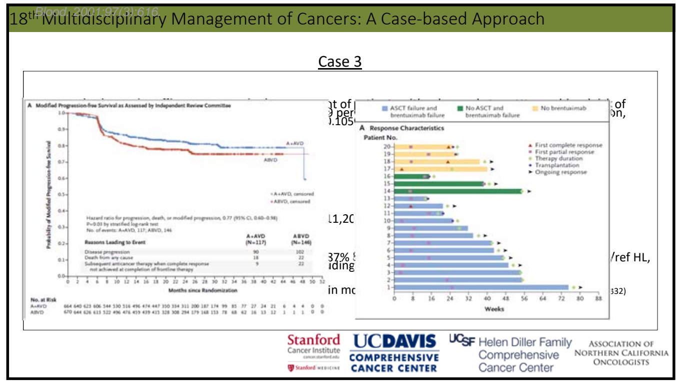
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Case 3
A Modified Progression-free Survival as Assessed by Independent Review Committee
A+AVD
ABVD
Reasons Leading to Event
Disease progression
Death from any cause
Months since Randomization
No. at Risk
ASCT failure and brentuximab failure
No ASCT and brentuximab failure
No brentuximab
A Response Characteristics
Patient No.
First complete response
First partial response
Therapy duration
Transplantation
Ongoing response
Weeks
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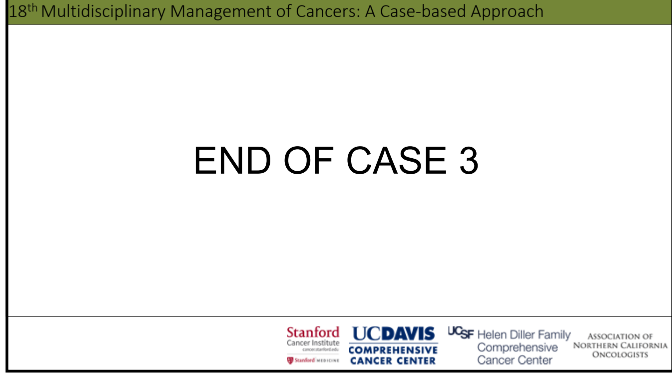
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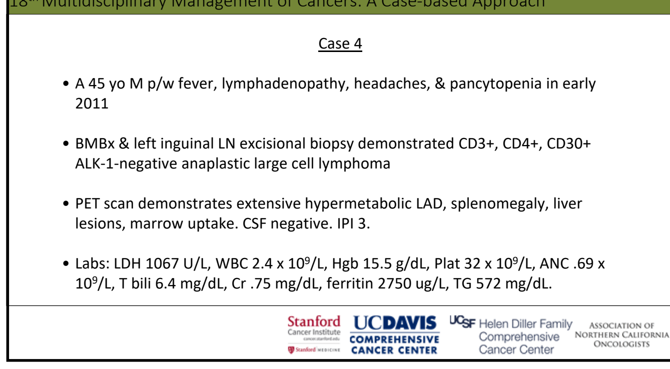
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Case 4
• A 45 yo M p/w fever, lymphadenopathy, headaches, & pancytopenia in early 2011
• BMBx & left inguinal LN excisional biopsy demonstrated CD3+, CD4+, CD30+ ALK-1-negative anaplastic large cell lymphoma
• PET scan demonstrates extensive hypermetabolic LAD, splenomegaly, liver lesions, marrow uptake. CSF negative. IPI 3.
• Labs: LDH 1067 U/L, WBC 2.4 x 10^9/L, Hgb 15.5 g/dL, Plat 32 x 10^9/L, ANC .69 x 10^9/L, T bili 6.4 mg/dL, Cr .75 mg/dL, ferritin 2750 ug/L, TG 572 mg/dL.
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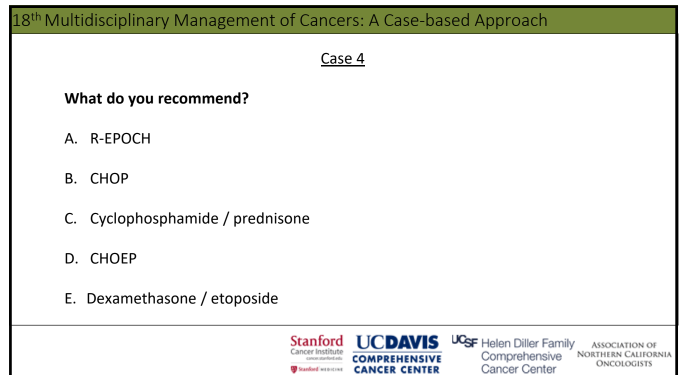
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Case 4
What do you recommend?
A. R-EPOCH
B. CHOP
C. Cyclophosphamide / prednisone
D. CHOEP
E. Dexamethasone / etoposide
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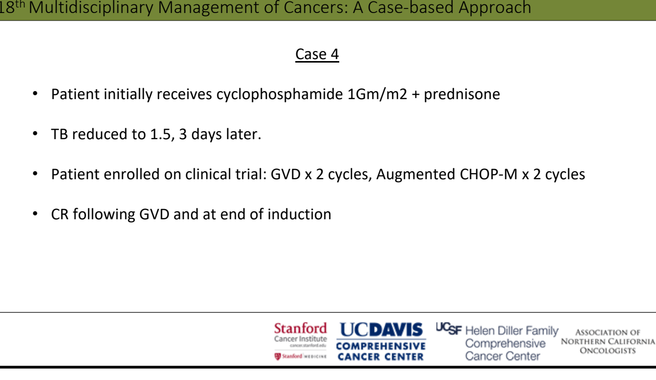
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Case 4
• Patient initially receives cyclophosphamide 1Gm/m2 + prednisone
• TB reduced to 1.5, 3 days later.
• Patient enrolled on clinical trial: GVD x 2 cycles, Augmented CHOP-M x 2 cycles
• CR following GVD and at end of induction
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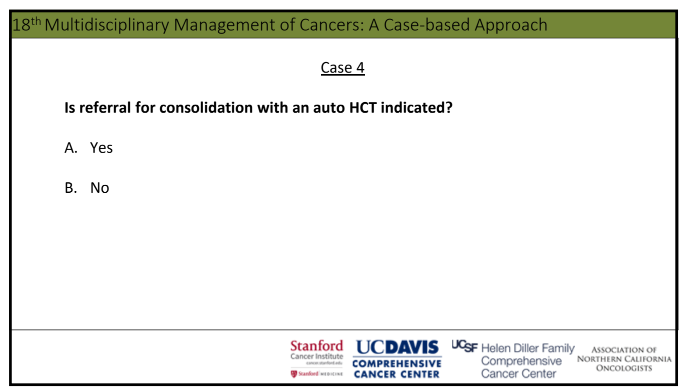
18th Multidisciplinary Management of Cancers: A Case-based Approach
Case 4
Is referral for consolidation with an auto HCT indicated?
A. Yes
B. No
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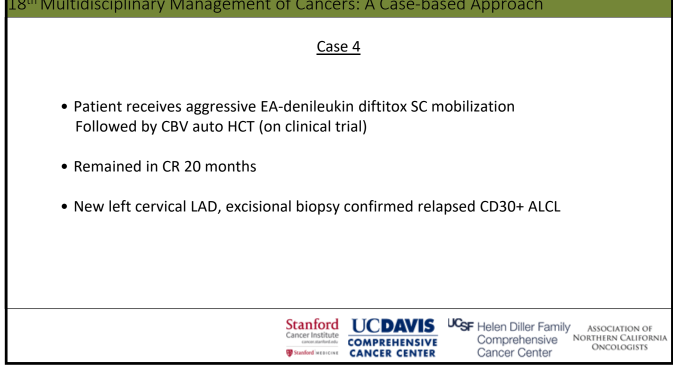
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Case 4
• Patient receives aggressive EA-denileukin diftitox SC mobilization
Followed by CBV auto HCT (on clinical trial)
• Remained in CR 20 months
• New left cervical LAD, excisional biopsy confirmed relapsed CD30+ ALCL
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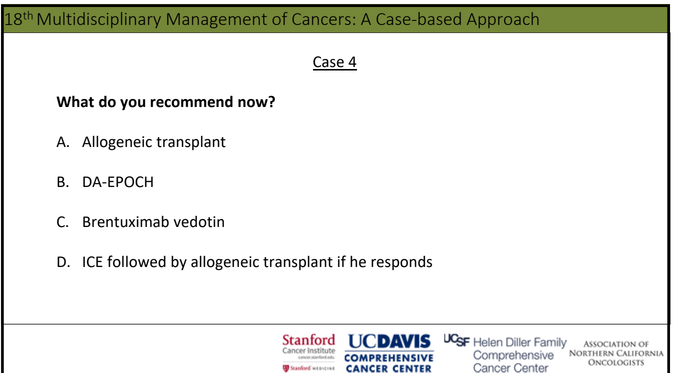
18th Multidisciplinary Management of Cancers: A Case-based Approach
Case 4
What do you recommend now?
A. Allogeneic transplant
B. DA-EPOCH
C. Brentuximab vedotin
D. ICE followed by allogeneic transplant if he responds
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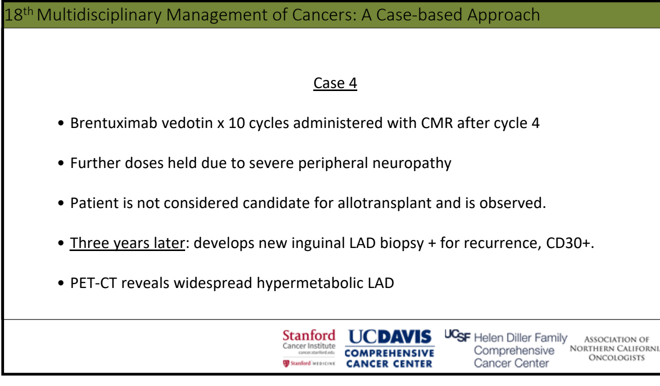
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Case 4
• Brentuximab vedotin x 10 cycles administered with CMR after cycle 4
• Further doses held due to severe peripheral neuropathy
• Patient is not considered candidate for allotransplant and is observed.
• Three years later: develops new inguinal LAD biopsy + for recurrence, CD30+.
• PET-CT reveals widespread hypermetabolic LAD
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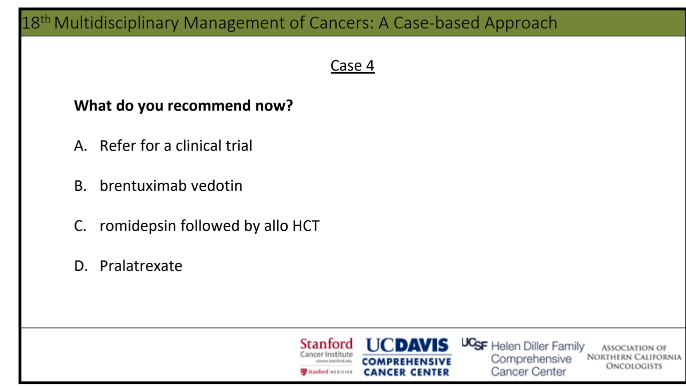
18th Multidisciplinary Management of Cancers: A Case-based Approach
Case 4
What do you recommend now?
A. Refer for a clinical trial
B. brentuximab vedotin
C. romidepsin followed by allo HCT
D. Pralatrexate
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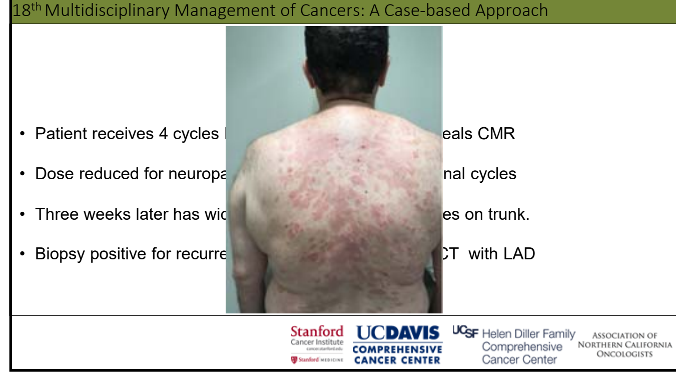
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• Patient receives 4 cycles
eals CMR
• Dose reduced for neuropa
nal cycles
• Three weeks later has wid
es on trunk.
• Biopsy positive for recurre
CT with LAD
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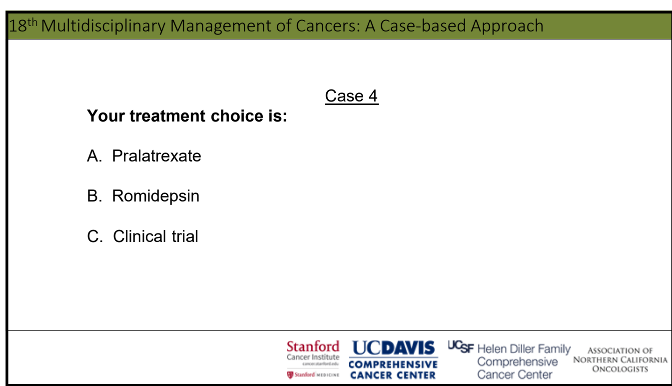
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Case 4
Your treatment choice is:
A. Pralatrexate
B. Romidepsin
C. Clinical trial
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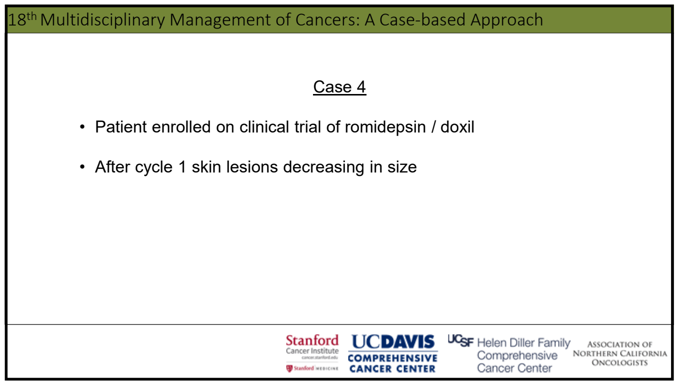
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Case 4
• Patient enrolled on clinical trial of romidepsin / doxil
• After cycle 1 skin lesions decreasing in size
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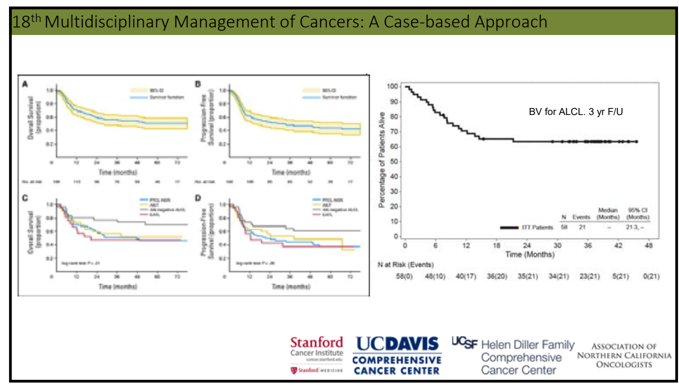
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BV for ALCL. 3 yr F/U
Percentage of Patients Alive
Time (Months)
ITT Patients
N at Risk (Events)
58(0) 48(10) 40(17) 36(20) 35(21) 34(21) 23(21) 5(21) 0(21)
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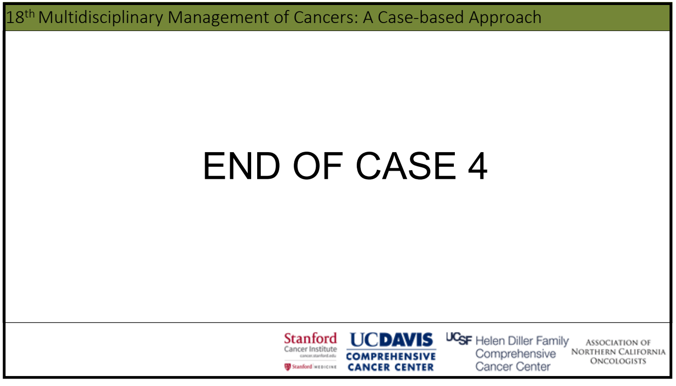
18th Multidisciplinary Management of Cancers: A Case-based Approach
END OF CASE 4
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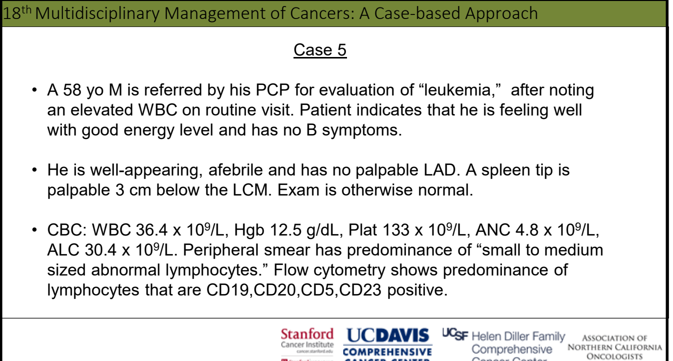
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Case 5
• A 58 yo M is referred by his PCP for evaluation of "leukemia," after noting an elevated WBC on routine visit. Patient indicates that he is feeling well with good energy level and has no B symptoms.
• He is well-appearing, afebrile and has no palpable LAD. A spleen tip is palpable 3 cm below the LCM. Exam is otherwise normal.
• CBC: WBC 36.4 x 10^9/L, Hgb 12.5 g/dL, Plat 133 x 10^9/L, ANC 4.8 x 10^9/L, ALC 30.4 x 10^9/L. Peripheral smear has predominance of "small to medium sized abnormal lymphocytes." Flow cytometry shows predominance of lymphocytes that are CD19,CD20,CD5,CD23 positive.
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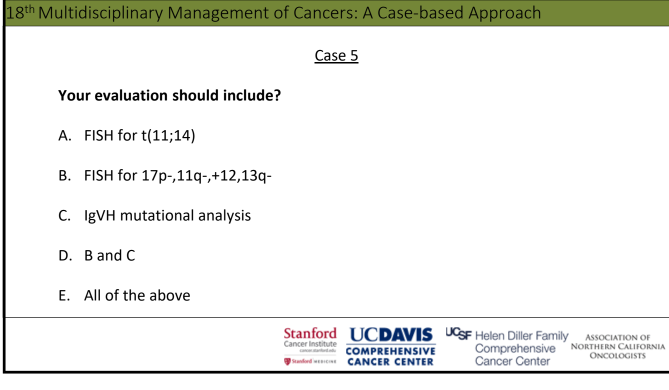
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Case 5
Your evaluation should include?
A. FISH for t(11;14)
B. FISH for 17p-,11q-,+12,13q-
C. IgVH mutational analysis
D. B and C
E. All of the above
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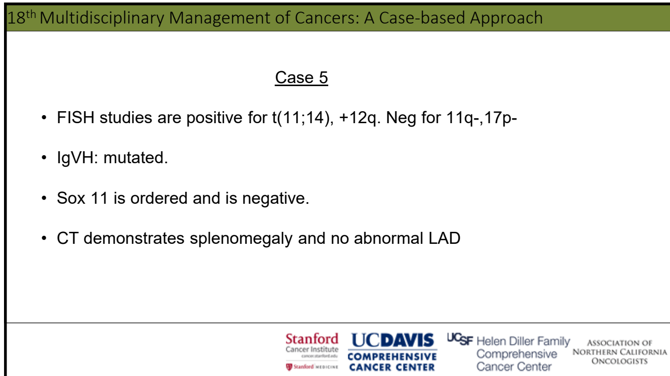
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Case 5
FISH studies are positive for t(11;14), +12q. Neg for 11q-,17p-
IgVH: mutated.
Sox 11 is ordered and is negative.
CT demonstrates splenomegaly and no abnormal LAD
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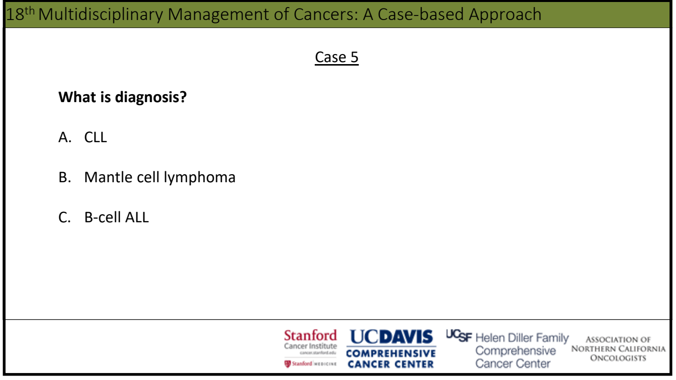
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Case 5
What is diagnosis?
A. CLL
B. Mantle cell lymphoma
C. B-cell ALL
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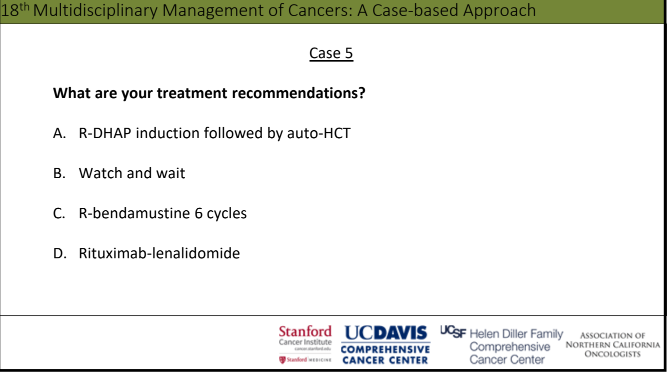
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Case 5
What are your treatment recommendations?
A. R-DHAP induction followed by auto-HCT
B. Watch and wait
C. R-bendamustine 6 cycles
D. Rituximab-lenalidomide
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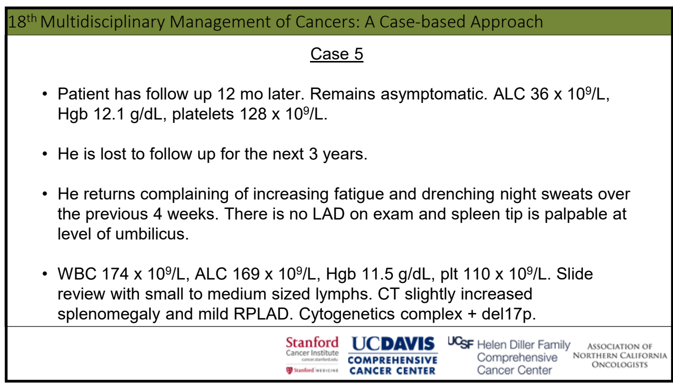
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Case 5
• Patient has follow up 12 mo later. Remains asymptomatic. ALC 36 x 10⁹/L, Hgb 12.1 g/dL, platelets 128 x 10⁹/L.
• He is lost to follow up for the next 3 years.
• He returns complaining of increasing fatigue and drenching night sweats over the previous 4 weeks. There is no LAD on exam and spleen tip is palpable at level of umbilicus.
• WBC 174 x 10⁹/L, ALC 169 x 10⁹/L, Hgb 11.5 g/dL, plt 110 x 10⁹/L. Slide review with small to medium sized lymphs. CT slightly increased splenomegaly and mild RPLAD. Cytogenetics complex + del17p.
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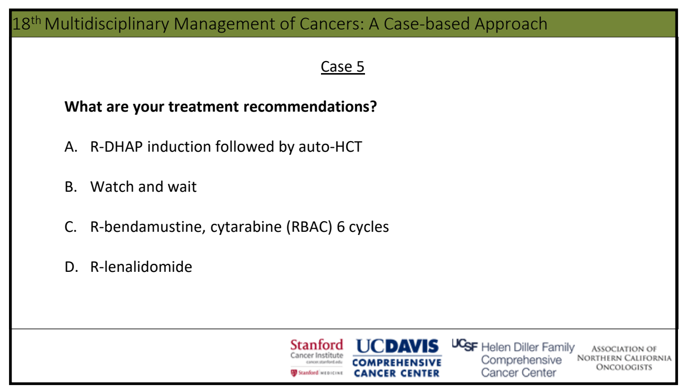
18th Multidisciplinary Management of Cancers: A Case-based Approach
Case 5
What are your treatment recommendations?
A. R-DHAP induction followed by auto-HCT
B. Watch and wait
C. R-bendamustine, cytarabine (RBAC) 6 cycles
D. R-lenalidomide
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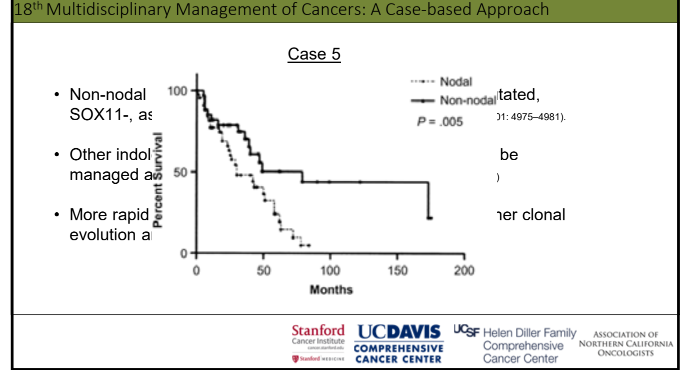
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Case 5
• Non-nodal
SOX11-, as
• Other indol
managed a
• More rapid
evolution a
tated,
be
ner clonal
Nodal
Non-nodal
P = .005
Percent Survival
100
50
0
0
50
100
150
200
Months
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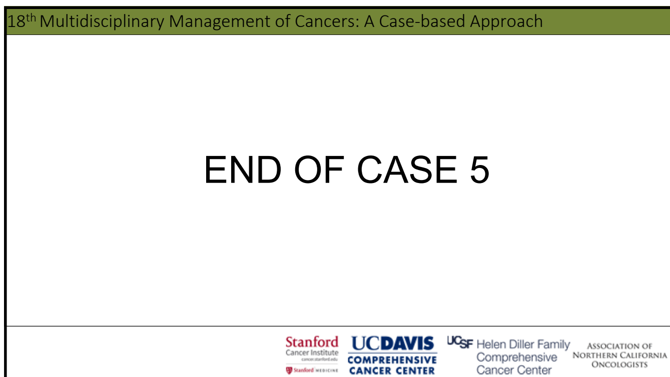
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END OF CASE 5
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