Lymphoma Management: Updates for 2021

UNC Lineberger Cancer Network Lecture
9/22/2021

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Diffuse Large B Cell Lymphoma patient

- 29yo male diagnosed in 3/2020 with Primary mediastinal DLBCL
  - PMHx – non-contributory
  - Fam Hx: sibling with Hodgkin lymphoma
- **4/2/20** - DA-R-EPOCH x 6 cycles- ending 7/20/20 with one residual area of biopsy proven disease
- **9/21/20-10/29/20:** consolidative radiotherapy with 36 Gy to the CT residual abnormality followed by a 9 Gy boost (45 Gy total) to PET avid disease. complicated by pericarditis
- **1/8/21 -** PET scan showed evidence of progressive disease outside of the radiation field

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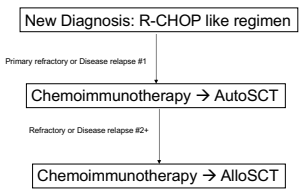
Management DLBCL



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- **1/8/21** - PET scan showed evidence of progressive disease outside of the radiation field
- **1-4/2021** - Gemcitabine/cisplatin/dexamethasone
- **4/20/21** - PET scan showed stable disease (chest nodes increased in size but not by 50%)

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Drugs approved for Rel/Ref DLBCL

- 2017: First CAR-T therapy FDA approved
  - Tisagenlecleucel (Kymriah)
  - Axicabtagene ciloleucel (Yescarta)
- 2019: Polatuzumab vedotin + bendamustine + rituximab
- 2020:
  - Tafasitamab + lenalidomide
  - Selinexor
- 2021:
  - Loncastuximab tesirine
  - Lixocabtagene maraleucel (breyanzi)

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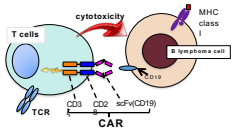
CAR-T: Chimeric Antigen Receptor T Cells

- Modifies the patients own immune cells to try to better target the cancer cells in their bodies.



Amended Courtesy of Keiya Ozawa, Professor, Div. Genetic Therapeutics at the University of Tokyo
From the 6th International Hematologic Malignancies Conference

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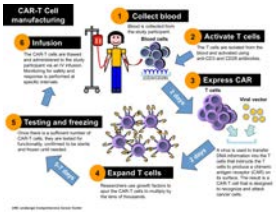
Chimeric Antigen Receptor T-Cells: What is the process?



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Three CAR-T Cell Products FDA approved for

	Axicabtagene ciloleucel (ZUMA-1 Trial)	Tisagenlecleucel (Juliet Trial)	Lisocabtagene maraleucel (TRANSCEND)
Approved for	DLBCL, tFL, PMBL ≥2 lines prior therapy	DLBCL ≥2 lines prior therapy	DLBCL ≥2 lines prior therapy
ORR	82% (n=111)	52% (n=81)	73% (n=269)
Best CR	58%	40%	53%
≥3 CRS	13%	22%	2%
≥3 Neurotoxicity	28%	12%	10%

Neelapu et al. NEJM 2017 377:2531-2544.
Schuster et al NEJM 2019; 380:45-56
Abramson et al Lancet 2020;396:839-852.

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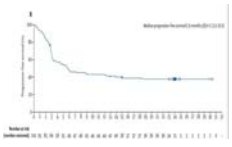
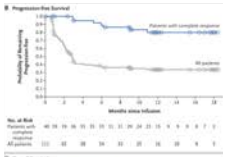
Durable CAR-T Responses

Juliet Trial: Tisagenlecleucel



Zuma 1: Axicabtagene ciloleucel



Schuster et al NEJM 2019; 380:45-56
Locke FL et al. Lancet Oncol 2019:20:31-42.

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The CAR-T Results in Context

	Cytotoxic Chemotherapy Trials in rel/ref DLBCL				CAR-T Trial
	CORAL (n=619) 2nd line Therapy		CCTG LY12 (n=396) 2nd Line Therapy		ZUMA-1 (n=111) ≥2nd Line Therapy
Chemo regimen	DHAP (dex/cytarabine/cis)	GDP (gem/dex/cis)	R-ICE (ritux/ifos/carbo/etop)	R-DHAP (ritux/dex/cytarabine/cis)	Axicabtagene ciloleucel
ORR (%)	44.0	46.1	62.5	62.8	82
CR/CRu (%)	14.3	11.5	36	40	54

Crump M et al. JCO 32:3490-3496, 2014.
Gisselbrecht C et al. JCO 28:4184-4190, 2010.

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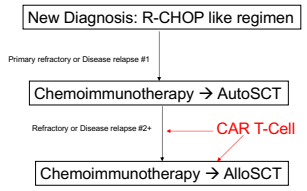
Management DLBCL



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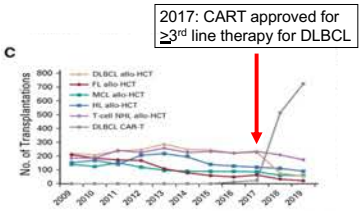
CAR-T Instead of Allogeneic SCT



Shah NN and Hamadani M. JCO 2021 39:487-498.

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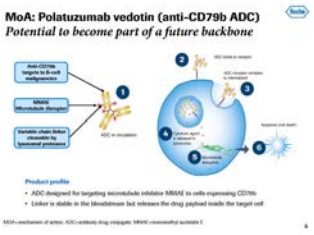
Polatuzumab Vedotin

- Anti-CD79 Antibody drug conjugate



Polatuzumab-vedotin-MOA_Page_02.png (2000×1500) (novelarrets.com) accessed 8/30/2021

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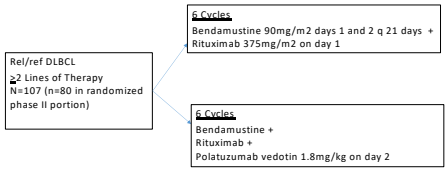
Phase Ib/Randomized Phase II Trial of Polatuzumab



Sehn LH et al. JCO 2020;38:155-165.

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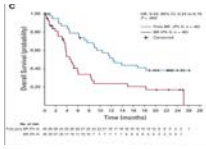
Significantly Superior Complete Response Rate in the Polatuzumab Arm

	Pola BR	BR
ORR	45%	17.5%
CR (p=0.026)	40%	17.5%
Median PFS, months (<0.01)	9.5 (6.2-13.9)	3.7 (2.1-4.5
Median OS, Months	12.4	4.7
Median follow up 22.3 months		



Overall Survival (p=0.02)

Sehn LH et al. JCO 2020;38:155-165.

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Adverse Events Relatively Similar Between the Two Arms

	Pola-BR	BR
RBC Transfusions	25.6%	20.5%
Platelets Transfusions	15.4%	15.4%
Gr 3-4 Infections	23.1%	20.5%

Sehn LH et al. JCO 2020;38:155-165.

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L-MIND phase 2 Study: Tafasitimab + Lenalidomide

- Anti-CD19 Monoclonal Antibody
- N=80
- Rel/ref DLBCL
- 1-3 prior treatment regimens (median 2)

12 Cycles:
Lenalidomide: 25 mg po on days 1-21 of a 28 day cycle

Tafasitamab IV 12mg/kg over 2 hours
- days 1, 8, 15 and 22 of cycles 1-3
- Days 1 and 15 of cycles 4-12
- Premed w/ antipyretics, H1 and H2 blockers, glucorticoids

→ Tafasitamab q 14 days until PD

Salles G et al. Lancet Oncol 2020;21:978-988.

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Initial Results Encouraging

- Median f/up 13.2 months
  - 37% of 80 patients had completed 12 cycles of doublet and were on monotherapy
- ORR 60% (CR 43%)
- Median time to response 2.0 months
- Median DOR 21.7 months

Salles G et al. Lancet Oncol 2020;21:978-988.

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Generally Well Tolerated

Doublet		
	Grade 3	Grade 4
Neutropenia	27%	17%
Febrile Neutropenia	10%	2%
Thrombocytopenia	12%	5%
Rash (grade 1-2 in 27%)	9%	0%
Diarrhea (grade 1-2 in 32%) Median Duration 8 days	1%	0%
46% had ≥1 lenalidomide dose reduction but 78% maintained a dose ≥20mg		
Tafasitimab (cycle 13+)		
Neutropenia	3.9%	7.8%
No grade ¾ febrile neutropenia, diarrhea or thrombocytopenia		

Salles G et al. Lancet Oncol 2020;21:978-988.

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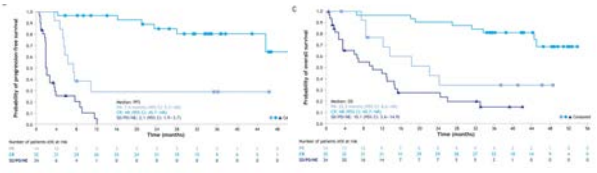
Long Term Results (≥ 35 months) of L-MIND study of tafasitamab + lenalidomide

- Median DOR 43.9 months
- Median PFS 11.6 months

Median OS 33.5 months



Duell et al. Haematologica 2021.

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LOTIS-2 Phase II study:
Loncastuximb Tesirine: Anti-CD19 antibody drug conjugate

- Rel/ref DLBCL (n=145)
- ≥ 2 prior lines of therapy (median of 3)

Loncastuximab tesirine
- 150ucg/kg on day 1 of 21 day cycle for 2 cycles
- 75mcg/kg on day 1 of 21 day cycle for up to a year

Caimi et al. Lancet Oncol 2021; 22:790-800.

22

Loncastuximab Tesirine Efficacy

- ORR 48.3% (CR 24%)
- Median time to first response was 41 days
- Median number of cycles 3

	All Enrollees	CR	PR
Median DOR, months	10.3	13.4	5.7

Caimi et al. Lancet Oncol 2021; 22:790-800.

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Loncastuzimab Adverse Events

≥ Grade ¾ neutropenia	26%
≥ Grade ¾ thrombocytopenia	18%
Infusion related reactions (any grade)	5%
Peripheral edema, grade 1-2	19%
Rash, grade 1-2	12%
Pleural effusion, grade 1-2	8% (2% grade 3)
Liver enzyme abnormalities	51%

Caimi et al. Lancet Oncol 2021; 22:790-800.

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SADAL phase 2 trial: Selinexor

- Oral selective inhibitor of XPO1-mediated nuclear export (SINE)
- Rel/ref DLBCL (n=127)
- 2-5 prior lines of therapy
- Selinexor po on days 1 and 3 each week until PD
- ORR 28% (CR 17%)
- Median DOR 9.3 months

	Grade 3	Grade 4
Thrombocytopenia	31%	15%
Neutropenia	15.7%	8.7%
Diarrhea, any grade: 35% Fatigue, any grade: 47% Vomiting, any grade: 29%		

Kalakonda et al. Lancet Haematol 2020;7:e511-e522.

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Questions for DLBCL Management

- How do we chose which treatment to use?
- Does it matter what order we use the treatments in?
- Will CAR-T or these other options move into earlier lines of therapy?

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CAR-T Therapy FDA Approved for More Indications

Follicular Lymphoma
Mantle Cell Lymphoma

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ZUMA-5: CAR-T Axicabtagene Ciloleucel
FDA approved for Follicular lymphoma in 2021

- Phase II trial of 146 patients (124 FL, 22 MZL)
- After ≥ 2 prior lines of therapy (median of 3)

Adverse Events

- Grade ≥3 CRS 7%
- Grade ≥3 Neurologic event 19%
  - 15% in FL
  - 41% in MZL
- Almost all had resolved by data cutoff

Jacobson et al. Blood 2020; 130 (supplement 1): 40-41.

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ZUMA-5:
Axicabtagene Ciloleucel FDA approved for Follicular lymphoma in 2021

Response Rates

- Follicular lymphoma (n=84): ORR 94% and CR 80%
- Marginal zone lymphoma (n=20): ORR 85% and CR 60%

Durability of Response (12-month estimated rates)

- PFS 74% (95% CI, 63-82)
- OS 93% (95% CI, 86-97)

Jacobson et al. Blood 2020; 130 (supplement 1): 40-41.

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ZUMA-2: Brexucabtagene Autoleucel CAR-T
FDA Approved for Mantle Cell Lymphoma in 2020

- Rel/ref MCL after 1-5 prior therapies (median 3)
  - Prior BTK therapy (100%)
  - Prior auto SCT (43%)
- ≥Grade 3 neurologic toxicity 31%
- ≥Grade 3 CRS 15%
- 60 patients assessable for response
  - ORR 93% (CR 67%)

Wang et al. N Engl J Med 2020;382:1331-1342.

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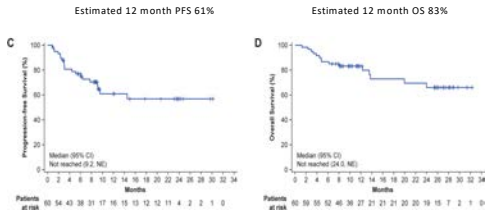
Durable Remissions for CAR-T in MCL Patients



Wang et al. N Engl J Med 2020;382:1331-1342.

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In Summary

- Many advances and new therapies FDA approved for rel/ref DLBCL in the past 5 years
- CAR-T options now available for rel/ref follicular lymphoma and mantle cell lymphoma

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My 24 yo Patient with rel/ref DLBCL

- CAR-T therapy on 6/14/21
- Worsening pain and Disease progression!
  - 6/30/21: CT with contrast abdomen and pelvis showed on mass was 5.8 x 5.4 x 7.1 cm, previously 3.1 x 2.8 cm and a 2nd mass 4.6 x 4.3 cm, previously 2.1 x 2.7 cm

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- Maybe it was pseudoprogression (We hope)
  - 7/30/21 CT chest/AP with contrast showed moderate interval decrease in size of right retrocrural mass (2.9 x 2.5 cm) and Interval decrease in size of anterior mediastinal mass (3.9 x 2.4 cm)
- Plan for repeat imaging in October

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Thanks for your Time

Any Questions?

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