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## T-CELL LYMPHOMAS : NEW THERAPEUTIC APPROACHES

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## DISCLOSURE

- <u>Relevant Financial Relationship(s)</u>
  - Speakers bureau Seattle Genetics
  - Advisory board for Celgene and Spectrum
- Off Label Usage
  - Lenalidomide, 5 Azacitidine, Mogamulizumab, Alisertib, Duvelisib, ADC-301, Venetoclax

## BACKGROUND

- PTCLs have a poor outcomes with current therapies
- 5 year survival remains at around 30% for most histologies with the exception of alk+ALCL with low IPI
- High dose therapy and ASCT is recommended
  - Consolidation in CR1 in eligible patients- recommended by NCCN, ABMTR
  - Relapsed disease in chemo sensitive relapse if the patient has not had a prior transplant. ABMTR strongly recommends considering an allo transplant in this setting.

## **OPTIMAL UPFRONT THERAPY**

- CHP+Brentuximab Vedotin Only approved strategy in 2019 is Brnetuximab Vedotin + CHP for CD30 expressing T cell lymphomas
- CHOP based therapies remain the back bone of upfront therapy for non CD30 expressing lymphomas
- Role of Etoposide if the upfront regimen continues to be debated. Best data is by Schimdt, et al.
  <60, normal LDH, improved OS. CHOEP followed by high dose ASCT has been used by several groups.</li>
- CHOP+Romdepsin (Ro-CHOP) Initial results ORR 78% including 66% CR. Randomized phase 3 ongoing.
- CHOP+Belinostat ORR 86%, CR 67%, PR 19%
- CHOP+Pralatrexate ORR 89%, CR 67%
- CHOEP+Revlimid ORR 88% and CR 38%. Len maintenance arm

## SELECT CLINICAL TRIALS (UPFRONT THERAPY FOR PTCL)

- CHEP + BV ongoing at COH and other sites (CD30 expressing)
- Romidepsin + lenalidomide- Northwestern (elderly or frail)
- Nivo + DAEPOCH- sponsored by University of Colorado
- Epigenetic platforms- (AITL, TET2 mutations may have a higher response rate to hypomethylating agents)

## **EFFECT OF UPFRONT TRANSPLANT IN PTCL**

	ALCL ALK+	ALCL ALK-	PTCL-NOS	AITL	NK/T
5 yr OS rate%- Int T- cell Project	70	49	32	32	32
5 year OS rate % Abouyabis et al	56 ( all subtypes		34	36	48
3 year OS 88.8 Schmitz et al		63	53	56	49
5 year OS % D'Amore et al	Not included	70	47	52	44

### APPROVED AGENTS FOR THE TREATMENT OF RR PTCL

	AGENT	Histology	ORR/CR	ORR/CR	
	Pralatrexate 2009	PTCL- all subtypes	29%/11%	PTCL- nos 32% sALCL- 35% AITL- 8% other – 38%	DOR = 10.1 months ( ,1- 22.1)
	Romidepsin 2009	PTCL- all subtypes	25%/15%	PTCL- nos—29/14 AITL- 30/19 Alk-ve ALCL -24/19	DOR 28 months (1-48) Median OS= 11.3 months Time to CR =3.7months
	Belinostat 2014	PTCL- all subtypes	26%/11%	PTCL-nos-23% AITL-46%/18% ALCL- 15% ENKTCL-50%	DOR= 13.6 months (4.5- 29.4)
	Brentuximab Vedotin 2011	sALCL	86%/59%	Highest responses in ALCL- other subtypes much less	DOR = 13.2 (5.7-26.3) OS- 70% at 1 yr. 64% at 4 yrs
	Mogamulizumab 2012	ATLL	50/31	Approved for CTCL in the US, ATLL and CCR4 expressing PTCL in Japan	Median PFS 5.2 months
the <b>MIRACLE</b>	Chidamide 2014	PTCL	28/14	Approved in China	Median PFS 2.1 month, OS 21.4 months

### SELECTED AGENTS FOR R/R PTCL

	AGENT	N	HISTOLOGICA L subtypes n	ORR/CR (5)	Response by histology ORR/CR	Outcomes	COMMENTS
	ICE	40	PTCL	70/35		Median PFS= 6 months	68% went to transplant 83% relapsed at 3 years
	ESHAP	22	All PTCL	32/18		Median PFS= 2.5 months	
	Bendamsutine	58	AITL- 32 PTCL- nos 23 ALCL- 2 EATL- 1	50/28		Median DOR= 3.5 ( 1-21)	Median OS 6.3 months
	Gem/Dex/Cispl atin	51	PTCL	69/19		Median PFS= 4 months	72% went to auto or stem cell transplant
	Alemtuzumab	PTCL-nos 10 AITL – 4	2(1-4)	36/21			
the <b>MIRACLE</b>	Crizotinib	Alk+ ALCL=9		89/78		NR	

## SINGLE VS COMBINATION CHEMOTHERAPY COMPLETE REGISTRY

Combination CTX	N=26	
CHOP/CHOEP	1	
DHAP	1	
Gemcitabine based	10	
Platinum based	4	
Other	3	
Single agent	N=31	
Pralatrexate	5	
Romidepsin	8	
Brentuximab Vedotin	12	
Denileukin Diftitox	1	
Lenalidomide	1	
Alisertib	3	
Bendamustine	1	

	Combinatio n =26	Single =29	P value
CR <	5 (19 %)	12( 41%)	0.0195
PR	7 (26%)	5 (17%)	
None	8 (30%)	1 (3 %)	
PD	3 (12%)	9 (31%)	
Not evaluable	3 (12%)	2(7%)	
Median duration of treatment	1.5 mo	3.3 mo	0.06
Transplant	2/2	4/8	0.19

Stuver et al- in publication

## SINGLE VS COMBINATION THERAPY FOR RR PTCL (COMPLETE DATA)

- 57 patients retreated
- 26 combination chemotherapy, 31 single agent
- Median fu 2 years
- Increased CR with single vs combination (41% vs 19%)
- Median OS single vs combination (38.9 vs 17.2 months)
- Median PFS- single vs combination (11.2 vs 6.7 months)
- Stem cell transplants single vs combination (25% vs 8%)
- Adverse events more common with combination chemotherapy

Stuver et al- in publication

### **FREQUENTLY MUTATED GENES IN PTCL**



## POTENTIAL THERAPEUTIC TARGETS FOR PTCL





## HAVE WE MADE AN IMPACT ON TREATMENT OUTCOMES





"The good news is, we did as well as expected last quarter. The bad news is, we didn't expect to do too well."

## **CD30 TARGETED ADC BRENTUXIMAB VEDOTIN**



Approved for upfront treatment of CD30 expressing PTCL in combination with CHP

Approved for relapsed ALCL as a single agent

Approved for the treatment of relapsed CTCL with CD30 expression

## ECHELON-2- UPFRONT TREATMENT OF CD30 EXPRESSING PTCL



• G-CSF primary prophylaxis was administered to 34% of A+CHP patients and 27% of CHOP patients<sup>2</sup>

Horwitz et al- Lancet 2019

### **PATIENT CHARACTERISTICS**

	A+CHP (N = 226)	CHOP (N = 226)
Age in years, median (IQR)	58 (45-67)	58 (44-67)
PTCL subtype		
sALCL	162 (72)	154 (68)
ALK+	49 (22)	49 (22)
ALK-	113 (50)	105 (46)
PTCL-NOS	29 (13)	43 (19)
AITL	30 (13)	24 (11)
ATLL	4 (2)	3 (1)
EATL	1 (<1)	2 (1)
ECOG PS		
0	84 (37)	93 (41)
1	90 (40)	86 (38)
2	51 (23)	47 (21)
Disease stage		
III	57 (25)	67 (30)
IV	127 (56)	113 (50)
Baseline IPI score	, , ,	
0-1	53 (24)	48 (21)
2	74 (33)	78 (35)
3	66 (29)	66 (29)
4-5	33 (15)	34 (15)

## **PFS IMPROVED WITH A+CHP**



- A+CHP demonstrated superior PFS vs CHOP with a 29% reduction in risk of PFS event
- A+CHP more than doubled median PFS vs CHOP (48.2 vs 20.8 months)

Horwitz et al : Lancet 2019

## **IMPROVED OS**



Median OS follow-up of 42.1 months with A+CHP and CHOP Median OS not reached in either arm

## **HIGHER CR RATES**



# SECONDARY EFFICACY ENDPOINTS

Response rates in intent-t	o-treat population at EOT	A+CHP (n = 226) %	CHOP (n = 226) %	
	% (95% CI)	83 (78,88)	72 (66,78)	
IRF-assessed ORR	P-value	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	003	
	n	163	151	
IRF-assessed PFS for	Median PFS, months (95% CI)	55.7 (48.2- NE)	54.2 (13.4, NE)	
patients with SALCE	Hazard ratio (95% CI)	0.59 (0.42, 0.84)		
	P-value	0.003		

Fewer A+CHP needed subsequent anticancer chemotherapy to treat residual or progressive disease as a PFS event compared to the CHOP arm (5% vs 9%, respectively)<sup>1</sup>

### LONG TERM FOLLOW UP OF PHASE I STUDY OF BV+ CHP



Fanale et al : 2018

# **CD30 EXPRESSING CAR-T**

- Treating CD30 positive lymphomasrelapsed /refractory
- Preventing relapse after high dose therapy and stem cell transplant in CD30+ lymphoma



### **OTHER CD30 DIRECTED STRATEGIES**

#### CD16A platform NK cell recruitment



#### **CD30-Positive Lymphoma**

#### Trial:

- Investigator-sponsored\*, translational study to evaluate immunological effects and preliminary efficacy of AFM13 monotherapy in R/R CD30+ lymphoma with cutaneous presentation
- 9 patients treated in 3 dose cohorts

#### Overview\*\*:

- AFM13 monotherapy is active post-Brentuximab vedotin failure
- Biomarker data: possible correlation between response and tumor NK cell infiltration pre-therapy

Results									
Cohort	Disease	Toxicity	Response						
	S-ALCL, Alk (-)	No AE	PR						
4	T-MF	No AE	POD						
1	C-ALCL	Rash (G4) Skin infection (G3)	CR						
	MF	IRR (G1)	SD						
2	T-MF	IRR (G1)	SD						
2	T-MF	Skin infection (G3) IRR (G1)	Not assessed						
	T-MF	No AE	PR						
3	S-ALCL, Alk (-)	No AE	PR						
	MF	No AE	POD						
	• 44% ORR incl	uding 1 CR and 3 PR	s						

#### 

#### Sawas et al: ASH abstract 2018

## **UPDATES IN EPIGENETIC THERAPY**

	AITL	Other PTCL*	p
	12	7	
Median age, y	71 [39 - 85]	59 [32 - 83]	0,09
Male/Female	7/5	5/2	0,65
IPI at diagnosis			
- 1-2	3	1	1
- 3	3	2	1
- 4-5	6	4	
PIT at diagnosis			
- <3	3	3	0,62
- 3-4	9	4	
Ann Arbor stage III-IV	12	7	1
LDH level > ULN	9	7	0,26
PS≥2	6	6	0,17
Previous ASCT	2	1	1
Median number of previous therapy	2	3	0,12
TET2 mutation	8/10 (80%)	1/4 (25%)	0,09
ORR	9 (75%)	1 (15%)	0,0198
CR	5 (41%)	0 (0%)	0,106

Common epigenetic mutations in PTCL

	AITL	PTCL with TFH	PTCL-nos	Alk+ALCL	ALK-ve ALCL	ATLL
RHOAG17V	70%		25%			Present
TET2	33-82%		20-49%	1	50%	~
IDH2 –	13-32%		7%	1	60	44
R172						
DNMT3	23-38%		36		16	

Results of 5-Azacytidine (5-AZA) treatment in 19 R/R PTCL patients-Median number of cycles was 3

\* ATLL: 3 patients, EATL: 1 patient, PTCL-NOS: 2 patients, transformed MF: 1 patient

the MRichard Delarue et al. Blood 2016;128:4164 OUL X Cityof Hope.

## EPIGENETIC TARGEGING THERAPY IN PTCL PATIENTS.



### **Targeting CD25**

CD25 (identified by Tac monoclonal antibody) is differentially expressed in PTCL and is a therapeutic target

Monoclonal anti - Tac antibodies (Basiliximab, Dacluzimab) can be linked to:

- Radioisotope i.e. <sup>212</sup> bismuth and <sup>90</sup> Yttrium
- Toxic proteins like diphtheria toxin (denileukin diftitox) or pseudomonas endotoxin
- Cytotoxic agents- PBD (ADC-301)



Table: Best overall responses* at each Cami-T dose (efficacy analysis set; patients with NHL)											
	Dose (µg/kg)										
Response		B-cell ly	ymphoma	(n=22)			T-cell ly	mphoma	(n=15)		
(n, %)	≤45	60	80	≥100	Total	≤45	60	80	≥100	Total	
	(n=6)	(n=6)	(n=7)	(n=3)	(n=22)	(n=5)	(n=4)	(n=5)	(n=1)	(n=15)	
CR	0	1 (17)	1 (14)	1 (33)	3 (14)	0	0	0	0	0	
PR	0	1 (17)	1 (14)	0	2 (9)	0	1 (25)	3 (60)	1 (100)	5 (33)	
SD	0	0	1 (14)	0	1 (5)	0	1 (25)	0	0	1 (7)	
PD	6 (100)	4 (67)	4 (57)	1 (33)	15 (68)	5 (100)	2 (50)	1 (20)	0	8 (53)	
NE	0	0	0	1 (33)	1 (5)	0	0	1 (20)	0	1 (7)	
ORR (CR+PR)	0	2 (33)	2 (29)	1 (33)	5 (22)	0	1 (25)	3 (60)	1 (100)	5 (33)	
*Best visit r	esponse b	ased on th	ne 2014 Lu	gano Clas	sification	criteria (a	nd Global	Response	Score Gra	ading	

"Best visit response based on the 2014 Lugano Classification criteria (and Global Response Score Gradin Scales for Modified Severity-Weighted Assessment Tool for cutaneous T-cell lymphoma) CR, complete response; NE, not evaluable; NHL, non-Hodgkin Lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease

Collins et al: ASH 2018



## **ANTI-TAC THERAPY FOR T-CELL MALIGNANCIES**

- Unlabeled murine anti-CD25 mab relapsed HTLV1 associated ATLL- 6/19 responses noted
- Phase I/II <sup>90</sup> yttrium radio-labelled murine antibodies dose of 5-19 mCi in ATLL
- Denileukin Diftitox (immunoconjugate) for CTCL 30% RR
- <sup>90</sup>Y-labelled Dacluzimab in ATLL. Phase I/II trial of hematologic malignancies ORR 56% in ATLL
- CD25 antibody conjugates in clinical trials for the treatment of PTCL . E777, ADCT-301

Waldmann, et al. Blood. 1993 Waldmann et al. Blood. 1995 Duvic, et al. 2008 Janik, et al. PNAS. 2015

### PHASE I STUDY OF <sup>90</sup> YTTRIUM LABELLED BASILIXIMAB WITH BEAM FOR ASCT A-TAC BEAM

- All patients with a diagnosis of PTCL being considered for ASCT
- Day -21--- Cold Basiliximab infusion followed by 5miC of <sup>111</sup> In-Basiliximab/DOTA infusion – Indium scan to determine bio distribution. Off study if lung uptake
- Day -14--- Cold Basiliximab infusion followed by 5miC of <sup>111</sup> In-Basiliximab/DOTA infusion with <sup>90</sup> Y- Basiliximab/DOTA dosed to deliver 0.4miC/kg, 0.5miC/kg. 0.6miC/kg (max 60miC) of radiation– Indium scan
- **Day -8**--- admit for standard BEAM based conditioning and transplant
- Day 30, Day 100, Day 180, 1 year, 1.5 year, 2 year follow up

# RESULTS

	Dz status at day100	Dz status at day 180	Dz status at 1 year	Dz status at 1.5 years	Dz status at 2 years	Alive	Cause of death	Days from HCT to relapse	RFS/PFS Days	OS Days pos tx	Treatment After relapse
1	CR	CR	CR	CR	CR	Yes		NA	796	796	NA
2	CR		RL			No	POD	307	307	527	Belinostat
3	CR	CR	CR	CR	CR	Yes		NA	511		NA
4	CR	CR	CR	CR	CR	Yes		NA	785	785	NA
5	CR	CR	CR	CR	CR	Yes		NA	743	743	NA
6	CR	CR	CR	CR	CR	Yes		NA	717	717	NA
7	CR	RL				No	POD	218	218	323	pembrolizumab
8	CR	CR	CR	CR	CR	Yes		NA	583	734	NA
9	CR	CR	CR	CR					514	514	
10	CR	CR	CR	CR				504	385	385	NA
11	RL					Yes		108	108	434	Romidpesin, Gemcitabine , clinical trial
12	CR	CR	CR			Yes		NA	387	387	NA
13	RL					No	POD	105	`105	180	BV x1,pralatrexate, Gem OX,
14	CR	RL				Yes		182	118	28	
15											

Zain et al-ASH 2018

## **TARGETING CCR4- MOGAMULIZUMAB**



## **MAVORIC TRIAL- MOGAMULIZUMAB VS VORINOSTAT**



Kim et al: Lancet 2018

# **NOVEL SINGLE AGENTS FOR PTCL**

Agent	Mechanism of action	RR	N	ORR	CR	PFS/OS
Alisertib	Aurora A inhibitor	PTCL	37	30%	14%	3 months
Crizotinib	ALK inhibitor	ALK+ALCL	9	100%	100%	
Duvelisib	PI3K-δ inhibitor	16	19	50		8.4 months
Tenalisib	PI3Kγ δ Inhibitor	PTCL/CTCL	50	56%	25%	
Ruxolitinib	Jak1/2 inhibitor	PTCL	25	38%		
Cerdulatinib	JAK and SYK inhibitor	PTCL/CTCL	38	35%	31%	

## **DOUBLETS AND TRIPLETS**

Combination	n	Results	Main toxicity/DLT
Pralatrexate + Romidepsin	14	ORR 71%	Mucositis, thrombocytopenia
Duvelisib+Romi		ORR 50%	
Duvelisib + Boretezomib		ORR 53%	
Alisertib + Romidepsin	3	ORR 25%	Hematologic, fatigue, infection
Chidamide+thalidomide+Cyclophosphamie	12	ORR 83%,CR41%, PR33%	
Romidepsin+ Azacitidine	5	ORR80%,CR40%	Neutropenia, thrombocytopenia
Lenalidomide+vorinostat	8	ORR 25%	hematologic
Romidepsin plus lenalidomide	11	ORR 50%	Neutropenia, thrombocytopenia
Romidepsin+lenalidomide+carflizomab	16	ORR 45%, CR 36%, PR 9%	Hematologic, DVT, infection
Panobinostat + boretezomib	23	ORR 43%	Thrombocytopenia, diarrhea, neuropathy

### **ENROLLING MACROPHAGES IN THE FIGHT AGAINST LYMPHOMA**

Binds to CD47 with nanomolar affinity

Disrupts the interaction of CD47 with

Enables macrophage-mediated killing

Exhibits potent in vivo anti-leukemic

activity in AML xenograft models

Is in pre-clinical development as a

cell surface SIRPa

of tumor cells in vitro

therapy for AML

#### Blocking the CD47 "Do Not Eat" Signal with SIRPαFc

SIRP@Fc:

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CD47 on tumor cells delivers a stop signal to macrophages to suppress phagocytosis

The CD47 stop signal is blocked by SIRPaFc, allowing macrophages to phagocytose tumor cells



\* Patients received maximally 2 weeks of study treatment (induction phase)

Roschewski, M.D., Ann LaCasce, M.D., Graham P. Collins, M.D., Thu Tran, B.S., Judith Lynn, M.B.A., et al.

<sup>+</sup> Response assessments beyond day 14 are provided if patients have not progressed or continued onto another therapy

# The first patient treated obtained a CR of the injected lesion that is ongoing after 52+ weeks

Intratumoral injection

## **MAJOR TURNING POINT IN NK/T-CELL LYMPHOMAS**



#### Annals of Hematology

Authors

January 2018, Volume 97, <u>Issue 1</u>, pp 193–196 <u>Cite as</u>

PD1 blockade with low-dose nivolumab in NK/T cell lymphoma failing L-asparaginase: efficacy and safety

Authors and affiliations

Thomas S. Y. Chan, Jamilla Li, Florence Loong, Pek-Lan Khong, Eric Tse, Yok-Lam Kwong 🖂



- High expression of PD1 seen in NK/T-cell lymphomas driven by EBV
- High response rates to PD1 blockade in RR disease
- Disappearance of EBV from responding tumors
- Treatment was safe even in post allogenic transplant patients

Kwong, et al. 2017. Blood.

## TARGETING EBV FOR THE TREATMENT OF NK/T CELL LYMPHOMAS

- Autologous Cytotoxic T cells targeting EBV viral latent proteins
- Expansion of LMP- cytotoxic TL using autologous dendritic cells
- 50 patients received these cells including 11 NK/T
- 39 (9/11) achieved and maintained remission
- Phase II study is ongoing



the MIRACLE of SCIENCE with SOUL X Cityof Hope.

## CAR-T CELL

Targeting T-cell malignancies using anti-CD4 CAR NK-92 cells

### Autolus Therapeutics Announces Update on its Novel CAR T Cell Program for Peripheral T Cell Lymphoma (PTCL)

-First patient dosed in Phase 1/2 trial of AUTO4 in TRBC1-positive peripheral T cell lymphoma-

-Preclinical data for AUTO5 targeting TRBC2-positive peripheral T cell lymphoma presented at the 60th Annual American Society of Hematology (ASH) Meeting-





Pinz et al – 2018 Pule et al -2017

### **CD38 directed therapies for NK/T cell LYMPHOMA**

- CD38 expression can be seen in NK/T cell lymphomas and may have prognostic significance
- Daratumumab targets CD38
- Induces ADCC
- Promising activity in NK/TCL



Figure 1. Flow-Cytometric Analysis of a Peripheral-Blood Sample in a Patient with a Recurrence of Leukemic Extranodal Natural Killer (NK) Cell–T-Cell Lymphoma (Nasal Type).

Aberrant NK cells (red) were positive for CD2, CD16 (dim), CD38, and CD56 (bright) and negative for surface CD3, CD4, CD5, CD7, and CD8. Normal NK cells (cyan), T cells (green), and B cells (blue) are shown for comparison. Both normal and abnormal NK cells are negative for surface light chains (kappa and lambda).

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## **FUTURE DIRECTIONS**

- Collaborative efforts between centers T cell consortium
- Tissue banking (tumor, peripheral blood)- effort led by John Chan
- Genetic and mutational analysis to establish biomarkers to predict response collaboration with T-Gen, COH sequencing lab to have panels specific to tumor types
- Develop targeted therapies to match individual tumor characteristic for a more personalized approach to anti- lymphoma therapy
- Enhance outcomes of transplants and reduce complications- COH is a leading transplant center
- Develop cellular therapies for a lasting immune response to tumors

## **CLINICAL TRIALS AT COH FOR PTCL**



# **THANK YOU**



### OS AND PFS AFTER FIRST RETREATMENT FOR RR PTCL

