Society for Hematopathology 2017

Session 2

Genetic Testing in the Diagnosis of Lymphoid Neoplasms

Session Chairs:

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Session 2 Overview

- Focus on genetic testing utilized either to:
  - Aid in diagnosing or classifying lymphoma (and histiocytic neoplasms)
  - Predict prognosis within a diagnostic category
  - Guide therapy selection

- 42 cases
- 7 oral presentations

- Cases focusing on genetic testing (often NGS) utilized to better understand the biology of lymphoid neoplasms will be discussed in Session 8

B cell lymphomas/LPDs	Large/high grade	DLBCL	Large BCL with *IRF4* rearr.	341, 172
			ALK+ LBCL	161
			Primary cutaneous DLBCL, leg type	191
			PMBL	378
			EBV+ DLBCL	228
		High Grade	HGBL with *MYC* and *BCL2* or *BCL6* rearr.	160, 206
		Burkitt	Burkitt with *MYC-IGH* and *ID3* mutation	287
			Burkitt with 11q abnl	137, 43, 58, 356
	Small/low grade	Follicular	Pediatric type	260
			Adult type	334, 154, 204
		Mantle cell		33
		Marginal zone		46?
		LPL		127, 112
		Splenic and Hairy cell		22, 95, 198, 208,162
T cell lymphomas/LPDs	ALCL	ALK+		153, 132
		DUSP22+		277, 270
	AITL			377
	Aggressive NK			179, 331
	T LGL			111, 179, 190,
	Other T cell LPD			114, 115, 326
Histiocytic neoplasms	Langerhans cell			135, 336, 368
	Erdheim-Chester			336
	ALK+			380

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B cell lymphomas/LPDs	Large/high grade	DLBCL	Large BCL with *IRF4* rearr.	341, 172	*IRF4*
			ALK+ LBCL	161	*ALK1*
			Primary cutaneous DLBCL, leg type	191	*MYD88*
			PMBL	378	*IKZF1, JAK2, PDCD1LG2, SOC1, TNFAIP3, STAT6*
			EBV+ DLBCL	228	
		High Grade	HGBL with *MYC* and *BCL2* or *BCL6* rearr.	160, 206	*BCL2, MYC*
		Burkitt	Burkitt with *MYC-IGH* and *ID3* mutation	287	*IDH3, 11q*
			Burkitt with 11q abnl	137, 43, 58, 356	
	Small/low grade	Follicular	Pediatric type	260	1p36
			Adult type	334, 154, 204	
		Mantle cell		33	*CCND1*
		Marginal zone		46?	*MYD88*
		LPL		127, 112	*MYD88*
		Splenic and Hairy cell		22, 95, 198, 208,162	*BRAF, IGHV4-34, IDH2*
T cell lymphomas/LPDs	ALCL	ALK+		153, 132	*ALK*
		DUSP22+		277, 270	*DUSP22*
	AITL			377	*TET2, DNMT3A, RHOAG17V*
	Aggressive NK			179, 331	
	T LGL			111, 179, 190	*STAT3*
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Histiocytic neoplasms	Langerhans cell			135, 336, 368	*BRAF*
	Erdheim-Chester			336	*BRAF*
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2016 WHO Classification of mature lymphoid, histiocytic and dendritic cell neoplasms

Table 1. 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms

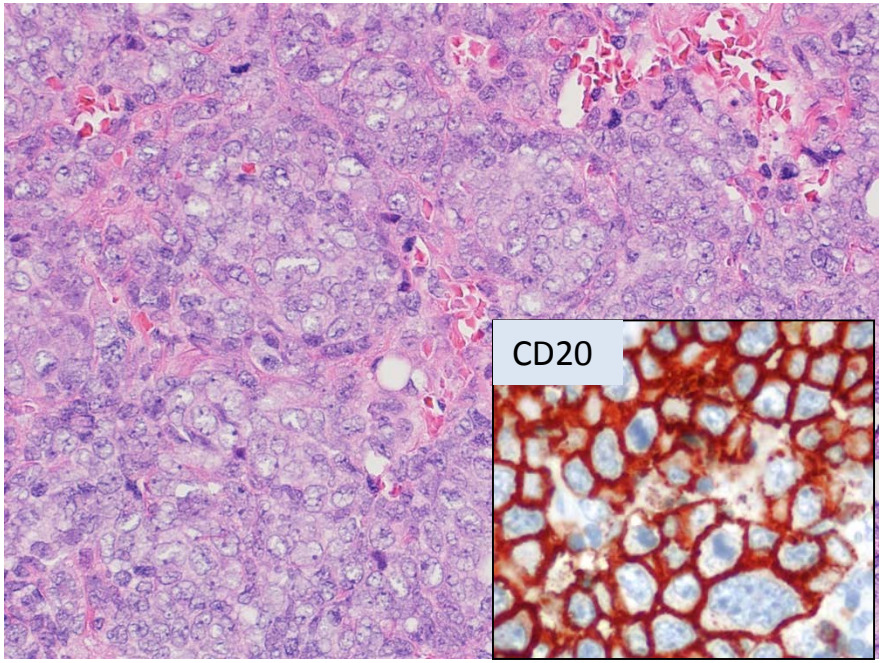
Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis*
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM*
μ heavy-chain disease
γ heavy-chain disease
α heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases*
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
In situ follicular neoplasia*
Duodenal-type follicular lymphoma*
Pediatric-type follicular lymphoma*
*Large B-cell lymphoma with IRF4 rearrangement**
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia*
Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal center B-cell type*
Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV$^+$ DLBCL, NOS*
*EBV$^+$ mucocutaneous ulcer**
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK$^+$ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
*HHV8$^+$ DLBCL, NOS**
Burkitt lymphoma
*Burkitt-like lymphoma with 11q aberration**
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
High-grade B-cell lymphoma, NOS*
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma**
*Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK$^-$*
*Breast implant–associated anaplastic large-cell lymphoma**
Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma
Posttransplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD*
Polymorphic PTLD
Monomorphic PTLD (B- and T-/NK-cell types)
Classical Hodgkin lymphoma PTLD
Histiocytic and dendritic cell neoplasms
Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Indeterminate dendritic cell tumor
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor
Disseminated juvenile xanthogranuloma
Erdheim-Chester disease*

Provisional entities are listed in italics.
*Changes from the 2008 classification.

Swerdlow SH et al. Blood, 19 May 2016. Vol 127, 20.

The good old days of ~~medicine~~?

Hematopathology

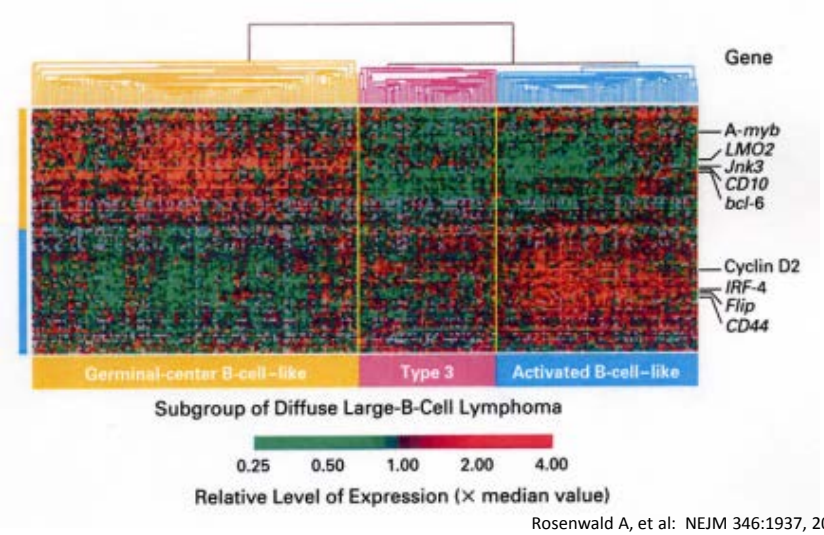


WHO 2016: Cell of Origin in DLBCL

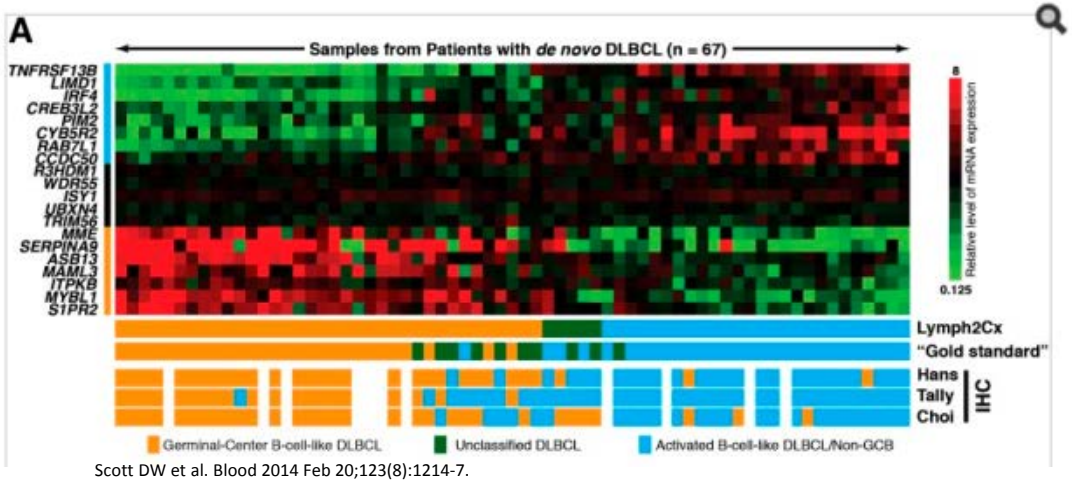
- GCB and ABC DLBCL are different diseases
  - ABC: NFκB and BCR signaling
  - GCB: Histone modification (*EZH2*), *BCL2* rearr., *MYC* rearr.

- WHO requires cell-of-origin
  - Perform CD10, BCL6, MUM1 IHC

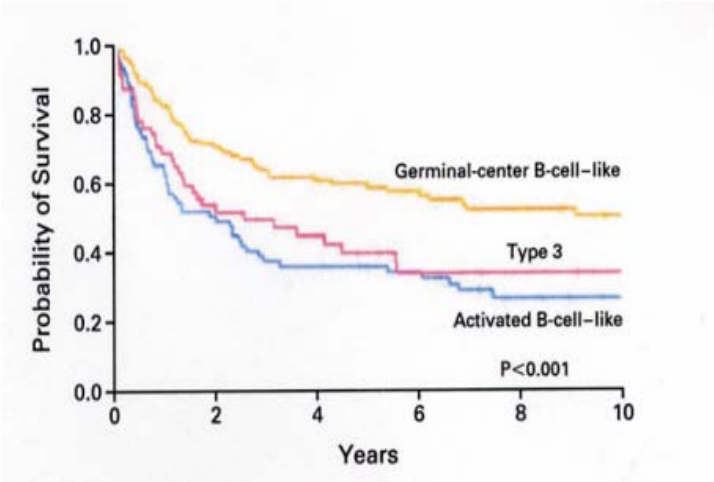
  or
  - Gene expression profiling



Rosenwald A, et al: NEJM 346:1937, 2002



Scott DW et al. Blood 2014 Feb 20;123(8):1214-7.

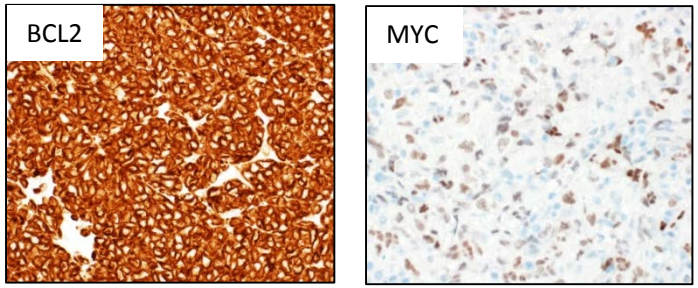


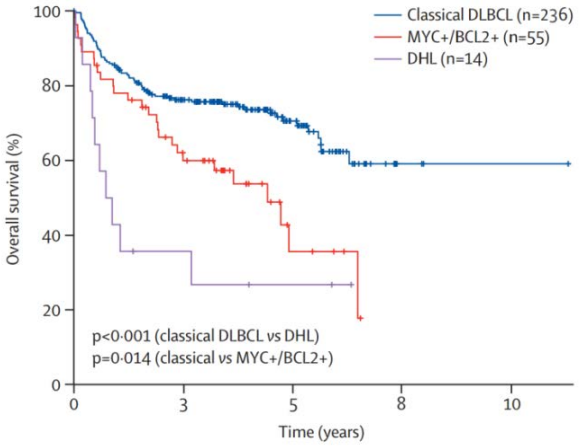
WHO 2016: MYC in DLBCL

- Requires distinction between:
  - DLBCL, NOS

    and
  - High grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* translocations (double-hit/triple-hit) (Case 160)
    - Regardless of morphology (high grade vs. DLBCL)
    - Requires FISH for *MYC* (*BCL2* and *BCL6*)

- Recommends identification of "double expressors"
  - Perform MYC and BCL2 by IHC





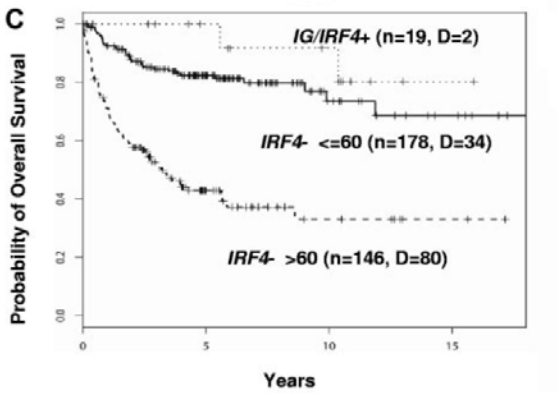
Sarkozy et al. Lancet Oncol. 2015 Nov;16(15):e555-67

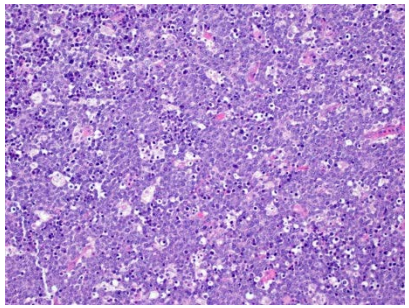
Genetic testing to consider in large/high grade B cell lymphomas

- *MYD88* L265P
  - Extranodal disease, ABC type, unfavorable prognosis
  - Primary DLBCL of the CNS (60%)
  - DLBCL involving the testes (77%)
  - Primary cutaneous DLBCL, leg type (40-75%)
    - Shorter survival with *MYD88* L265P mutation

- Large B cell lymphoma with *IRF4* rearr. (Case 341)
  - Young patients, GCB type/FL, favorable prognosis

- Burkitt-like lymphoma with 11q rearr. (Case 137)
  - Lack *MYC* rearr.
  - Clinicopathologic features similar to *MYC* rearr. Burkitt





Lee et al. Sci Rep. 2017 May 11;7(1):1785
Pham-Ledard A. JAMA Dermatol. 2014 Nov;150(11):1173-9.
Rovira et al. Clin Cancer Res. 2016 Jun 1;22(11):2755-64.
Salaverria et al. Blood. 2011 Jul 7;118(1):139-47
Salaverria et al. Blood. 2014 Feb 20;123(8):1187-98

Genetic testing in small/low grade B cell lymphomas

- Lymphoplasmacytic lymphoma
  - *MYD88* (90%+)
  - *CXCR4* (30%)
- Hairy Cell Leukemia
  - *BRAF* V600E
  - *MAP2K1* with IGVH-34 usage
- Follicular lymphoma
  - Diffuse FL with 1p36 deletion/*TNFRSF14* (Case 334)
  - *STAT6* mutation

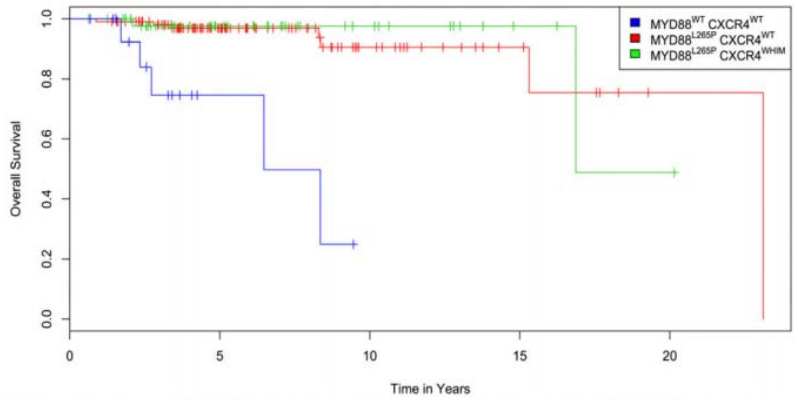
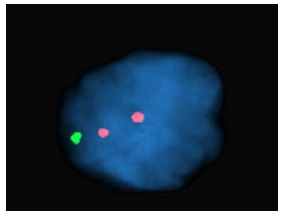


Figure 2. Kaplan-Meier plot for overall survival of 175 WM patients from time of diagnosis stratified by MYD88 and CXCR4 mutation status. Differences in survival curves based on CXCR4 and MYD88 mutation status were significant ($P < .0001$), as was the analysis based on MYD88 status alone ($P < .0001$) by Fleming-Harrington log-rank analysis.

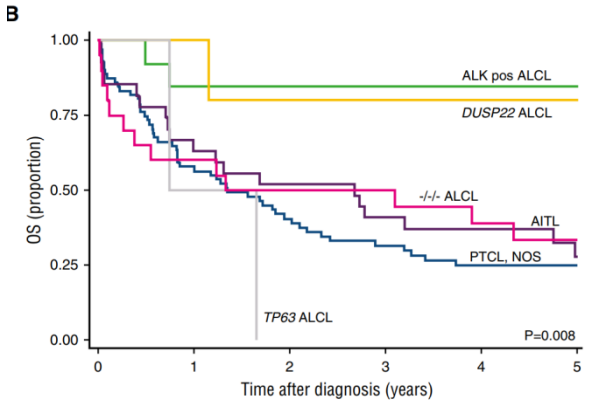


1p36 del
(SRD) Green/1q21 (CKS1B) Orange

Treon et al. 2012 Aug 30;367(9):826-33
Treon et al. Blood. 2014 May 1;123(18):2791-6
Waterfall et al. Nat Genet. 2014 Jan;46(1):8-10.
Tiacci et al. N Engl J Med. 2011 Jun 16;364(24):2305-15.
Katzenberger et al Blood, 113; 5. 2009
Siddiqi et al. Mod Pathol. 2016 Jun;29(6):570-81

Genetic testing in T/NK cell lymphomas

- Anaplastic large cell lymphoma, ALK-negative
  - *DUSP22 rearrangement:* Favorable prognosis, similar to ALK+ (Case 277)
  - *TP63 rearrangement:* Very unfavorable prognosis



- Large granular lymphocytic leukemia(T and NK)
  - *STAT3: 30-40%;* can be useful in diagnostically challenging cases (Case 111)
  - *STAT5B:* 2%, aggressive course

- Angioimmunoblastic T cell lymphoma (Case 377)
  - *RHOA, IDH2, TET2, DNMT3A*, others
  - Use in clinical setting evolving

Pedersen MB….et al. Feldman AL. Blood. 2017 Jul 27;130(4):554-557.
Koskela et al. N Engl J Med. 2012 May 17;366(20):1905-13
Rajala et al. Blood. 2013 May 30;121(22):4541-50.
Yoo et al. Nat Genet. 2014 Apr;46(4):371-5.
Wang et al. Blood. 2015 Oct 8;126(15):1741-52.

Thank you for your attention!

Session 2: Oral Presentations

1	1:40-1:50	Williams	SH2017-0160	Whole exome sequencing of high grade B cell lymphoma with BCL2/MYC rearrangements reveals actionable mutations and antecedent follicular lymphoma
2	1:52-2:02	Huettl	SH2017-0137	An Aggressive Burkitt-like Lymphoma with 11q Aberration
3	2:04-2:14	Aggarwal	SH2017-0341	Large B-cell lymphoma with IRF4 rearrangement in a 63 year old male.
4	2:16-2:26	Khattar	SH2017-0334	t(14:18) negative follicular lymphoma (FL) with 1p36 deletion associated with in situ follicular neoplasia (ISFN) with t(14:18) translocation.
5	2:28-2:38	Wu	SH2017-0111	STAT3 mutated T-LGL, donor derived, post-cord transplant for T lymphoblastic leukemia
6	2:40-2:50	Ho	SH2017-0277	Comprehensive Molecular Profiling of an ALK-Negative, Anaplastic Large Cell Lymphoma with DUSP22 rearrangement
7	2:52-3:02	Gaulard	SH2017-0377	Clonal evolution of a TET2 mutated-angioimmunoblastic T-cell lymphoma towards an EBV-associated TFH PTCL