Need for further cooperation in T cell Lymphoma

T cell Registries

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TCP & COMPLETE Collaboration

- The TCP and the COMPLETE Registry have collaborated closely from the start
  - Steering committee/executive committee members in common
  - Studies were designed to complement one another
    - The aims, design and level of data collection for each study are distinct
  - Sites participating in one study were actively encouraged to participate in the other
  - Joint/parallel abstracts to ASH and Lugano meetings
- Findings of each study will advance the knowledge of PTCL in different and important ways
- Given the rarity of PTCL, we need more of these kinds of collaborations!

Comprehensive **O**ncology **M**easures for **P**eripher**a**l T-C**e**ll Lymphoma **T**r**e**atment (COMPLETE)

Treatment Registry for Patients with Newly Diagnosed Peripheral T-Cell Lymphoma (PTCL)

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Study Rationale

- Knowledge of PTCL comes principally from small, disparate clinical trials
- Registries can be invaluable in providing 'real world' data on a population of patients
- Existing T-cell lymphoma registries focus primarily on accuracy of diagnosis and prognosis or are institution specific
- COMPLETE is designed to extend current cancer registries by providing:
  - Detailed data on cancer therapy received
    - COMPLETE is non-drug specific
  - Information on treatment-related morbidity
  - Longitudinal follow-up

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Study Design

- Prospective, multicenter, observational
- US
- Sample size: ~500
- Number of sites activated: 69
  - Academic and community practices
- Duration: Approximately 6 years (initial duration)
- Analyses: primarily descriptive in nature

Study is sponsored by Spectrum Pharmaceuticals, Inc.

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Study Objectives

- Primary
  - Describe, in detail, patterns of care for patients with PTCL, by treatment setting
- Secondary
  - Document outcome (best response, duration of response, progression-free survival, overall survival): overall and by treatment regimen
  - Identify factors influencing treatment decisions
  - Determine incidence and severity of selected treatment toxicities:
    - Myelosuppression (neutropenia, thrombocytopenia, anemia), febrile neutropenia, fatigue, nausea and mucositis
  - Identify supportive care received for managing selected toxicities

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Patient Eligibility: Inclusion Criteria

- Newly diagnosed, histologically/cytologically confirmed PTCL:
  - Aggressive natural killer (NK)-cell leukemia
  - Adult T-cell lymphoma/leukemia (human T-cell leukemia virus [HTLV] 1+)
  - Angioimmunoblastic T-cell lymphoma
  - Anaplastic large cell lymphoma (ALCL), primary systemic type
  - PTCL – not otherwise specified
  - T/NK-cell lymphoma, nasal type
  - Enteropathy-type intestinal lymphoma
  - Hepatosplenic T-cell lymphoma
  - Subcutaneous panniculitis T-cell lymphoma
  - Transformed mycosis fungoides (at diagnosis of transformation)
  - T-cell prolymphocytic leukemia (T-PLL)
  - Cutaneous γ/δ T-cell lymphoma
  - Cutaneous aggressive CD8+ T-cell lymphoma
  - Hematodermic neoplasms (blastic plasmacytoid dendritic cell neoplasms)
  - Systemic Epstein Barr Virus (EBV)+ lymphomas(T-cell lymphoproliferative disorders of childhood)
  - Other T-Cell lymphomas not excluded
- Written informed consent

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Patient Eligibility: Exclusion Criteria

- Diagnosis of other T- or NK-cell malignancies including:
  - Precursor T/NK neoplasms
  - T-cell large granular lymphocytic leukemia
  - Mycosis fungoides, other than transformed mycosis fungoides
  - Sézary syndrome
  - Primary cutaneous CD30+ disorders: ALCL and lymphomatoid papulosis

Registry participation does not exclude participation in clinical trials.

Both adults and children are eligible to participate (no age limit).

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Data Collection

- Patients evaluated according to treating physician's standard practice
- No specific evaluations or visits required for the Registry
- Data captured in the Registry reflects what is routinely collected for patients with PTCL
- Schedule of data collection is reflected below

Following written IC	Baseline	Initial Treatment	Follow-Up/Re-Treatment* Year 1	Year 2	Year 3
	X	X	X	X	X

*Re-treatment information is collected for patients with progressive/recurrent disease

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Study Oversight

COMPLETE is led by an international group of experts in diagnosis and treatment of PTCL whose role is to guide the design, conduct, analysis and reporting of the Registry

Name	Affiliation
Francine Foss, MD (Chair)	Yale University
Massimo Federico, MD	University of Modena, Italy
Christian Gisselbrecht, MD	Hôpital Saint Louis, Paris, France
Eric Hsi, MD	Cleveland Clinic
Steven Horwitz, MD	Memorial Sloan-Kettering Cancer Center
Lauren Pinter-Brown, MD	UC Irvine
Barbara Pro, MD	Northwestern University
Steven Rosen, MD	City of Hope
Andrei Shustov, MD	Seattle Cancer Care Alliance

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Key Milestones

Milestone	Timing
Steering Committee Organizational Meeting	October 2009
Final protocol	December 2009
Kick-off at ASH	December 2009
First patient enrolled	February 2010
First abstract submitted (Lugano meeting) First data presented	January 2011 June 2011
Enrollment (n=500) completed	February 2014
11th abstract presented	June 2015

Note: accrual was closed between October 2012 and March 2013

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Overview of publications (1 of 2)

First author, title	Abstract
Foss FM, et al. Comprehensive oncology measures for peripheral T-cell lymphoma treatment (COMPLETE), **a new international treatment registry**	11-ICML 2011
Foss F, et al. Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE): First Report of **Supportive Care** Information	TCF 2012
Foss FM, et al. Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE): First **Detailed Report of Primary Treatment**	ASH 2012
Hsi ED, et al., **Biomarker Quality Assurance (QA) Findings** from the Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE) Registry	ASH 2012
Foss FM, et al. Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE): Early Data on **Transplantation**	TCF 2013
Carson KR, et al. Analysis of Peripheral T-Cell Lymphoma (PTCL) **Subtype by Race and Geography** using the Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE) Dataset	ASH 2013

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Overview of publications (2 of 2)

First author, title	Abstract	Manuscript
Hsi ED, et al. Analysis of peripheral T-cell lymphoma (PTCL) **diagnostic work-up** in the United States using the COMPLETE dataset	TCF 2014	Hsi et al., In progress
Foss FM, et al. Management of T-cell lymphoma: **What the registries tell us**	TCF 2014*	
Pinter-Brown LC, et al. **Patient Characteristics and Initial Treatment Patterns** in US for **Most Common Subtypes** of PTCL	ASH 2014	Carson et al., In progress
Shustov AR, et al. Baseline characteristics, treatment and outcomes of patients with **CD30+ PTCL**	TCF 2015	
Nabhan C, et al. Patterns of care and treatment characteristics of **patients >70 years of age with PTCL**	13-ICML 2015	

*Plenary presentation (no abstract)

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This was the introductory presentation (data "light"). Not sure if you want to summarize.

Abstract 1: Key findings

Foss FM, et al. Comprehensive oncology measures for peripheral T-cell lymphoma treatment (COMPLETE), a new international treatment registry

- COMPLETE is designed to complement T-Cell Project

Details	COMPLETE registry	T-Cell Project
Objective	Patterns of care	Prognosis
Detailed data collection	Treatment	Baseline
Diagnosis	Per clinical practice	Tissue, central confirmation
Endpoint	Descriptive	5-year survival

- The first patient was enrolled on 5 February 2010
- 98 patients enrolled, as of May 2011
- 60% of patients received induction chemotherapy alone
- COMPLETE is a new initiative that will further the understanding of the care of PTCL patients

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Foss FM, et al., *Ann Oncol*. 2011;22(4) (Suppl 4): abstract 242.

Abstract 2: Key findings

Foss F, et al. Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE): First Report of Supportive Care Information

- 214 patients enrolled, as of January 2012
- 85% of patients received induction chemotherapy alone
- Grade 3/4 or clinically significant toxicities were common
  - Neutropenia (44% of patients); thrombocytopenia (36%); febrile neutropenia (31%); anemia (25%); and nausea (19%)
- Several supportive care measures administered
  - Antiemetics (69% of patients); G-CSF (63%); steroids (44%); blood transfusions/platelets (38%); and opioid analgesics (27%)
- 47% of patients were hospitalized (23% due to infection)
  - Mean hospitalization: 19 days (range: 2-69 days)
- Broad supportive measures are required to carry out induction therapy for PTCL patients

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Foss F, et al., T-Cell Forum. 2012: abstract TS_2.

Abstract 3: Key findings

Foss FM, et al. Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE): First Detailed Report of Primary Treatment

- 392 patients enrolled, as of October 2012
- 66% of patients received induction chemotherapy alone
- CHOP/CHOP-like regimen or EPOCH given to 42% of patients
  - Remaining 58% of patients received a variety of regimens
- Treatment intent was cure in 79% of patients
- 19% of patients were deceased at end of treatment
- PTCL is still largely being treated with regimens derived from B-cell lymphoma; a single standard of care in the US does not exist
- Death rate at the end of initial treatment underscores the need for more effective, disease-specific therapy

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Foss FM, et al., *Blood*. 2012;120(21): abstract 1614.

Abstract 4: Key findings

Hsi ED, et al., Biomarker Quality Assurance (QA) Findings from the Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE) Registry

- Pathology reports can be difficult to interpret, particularly for those who have not received specialized training
- Data for 119 patients from 43 centers comprising a sum of 3570 biomarker entries were reviewed by external hematopathologists
  - Data in database reviewed against de-identified pathology reports
  - Queries issued to sites for clarification/corrections as needed
- 11% of patients had records with no errors; over half (57%) had 1-5 errors
- Most common errors involved: CD8, CD20, CD30, EBV & TCR-γ
- Errors in interpretation or recording of biomarker data from pathology reports are common. For interventional trials, central review should be considered.

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Hsi ED, et al., *Blood*. 2012;120(21): abstract 4263.

Abstract 5: Key findings

Foss FM, et al. Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE): Early Data on Transplantation

- 123 patients had locked treatment records, as of October 2012
- 16 (13%) patients received a transplant
  - Autologous, n=14 (88%)
  - Best response prior to transplant: CR (93%), PR (7%)
  - Primary intent of cure (100%)
- In 17 cases, a transplant was planned but not performed
  - Reasons: progressive disease (47% of cases); patient choice (24%); other (18%) and lack of donor (12%)
- Transplant patients appeared to differ from non-transplant patients principally by age (median 52 vs. 61, respectively)
- As database grows, insights will be generated about types of patients being selected for transplantation

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Foss FM, et al., T-Cell Forum. 2013: abstract TR-1.

Abstract 6: Key findings

Carson KR, et al. Analysis of Peripheral T-Cell Lymphoma (PTCL) Subtype by Race and Geography using the Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE) Dataset

- 269 patients had locked baseline records, as of November 2013
- Univariate analysis indicated significant differences in histologic distribution by region (p=0.0003), with a higher proportion of:
  - AITL patients in the West (30%) vs. South (4%)
  - PTCL-NOS patients in the South (55%) vs. other regions (28-34%)
  - Other PTCL patients in Northeast (30%) vs. other regions (9-20%)
- Multinomial regression model suggests a relatively high likelihood of being diagnosed with PTCL-NOS for both races in the Midwest, South and West. White patients in the West had the highest likelihood of being diagnosed with AITL.
- These results suggest a modest independent influence of race and region in the US on PTCL subtype

Carson KR, et al., *Blood*. 2013;122(21): abstract 4284.

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Abstract 7: Key findings

Hsi ED, et al. Analysis of peripheral T-cell lymphoma (PTCL) diagnostic work-up in the United States using the COMPLETE dataset

- 311 patients had locked baseline records, as of January 2014
- PTCL-NOS diagnosed more frequently than ALCL and AITL
  - PTCL-NOS (33% of patients); ALCL (19%), AITL (16%)
- Most PTCL cases were evaluated for 6-15 markers
- CD30 frequently but not uniformly assessed in non-ALCL cases
- Tfh markers were not uniformly assessed in AITL/PTCL-NOS
  - This may account for fewer cases/under diagnosis of AITL
- No cases were evaluated with a recommended panel
- Gene rearrangement performed in 1/3 of cases
- These results suggest there is an opportunity for education and standardization in the diagnostic work-up of PTCL in the US

Hsi ED, et al., T-Cell Forum. 2014: abstract MPM14_2.

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Abstract 8: Key findings

Pinter-Brown LC, et al. Patient Characteristics and Initial Treatment Patterns in US for Most Common Subtypes of PTCL

- 190 patients had locked treatment records, as of July 2014, for 3 most common PTCL subtypes
  - PTCL-NOS, ALCL and AITL
- Anthracyclines given frequently (64% of patients) but many other different regimens administered
  - CHOP/CHOP-like (41%); CHOP/CHOP-like + etoposide (23%)
  - Platinum-based regimen (3%)
  - Gemcitabine-based regimen (2%)
  - Ifosfamide-based regimen (1%)
  - Other (30%)
- Beyond CHOP-based therapy, this is little consensus on the initial management of PTCL patients

Pinter-Brown LC, et al., *Blood*. 2014;124(21): abstract 4434.

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Abstract 9: Key findings

Shustov AR, et al. Baseline characteristics, treatment and outcomes of patients with CD30+ PTCL

- Locked baseline and treatment records were available for 230, and 187 patients, respectively, as of January 2015
- Patients with CD30 expression tended to be younger, have less extranodal and advanced disease, and have a lower IPI score vs. CD30-negative patients
- Trend toward greater use of induction CT alone (p=0.12) and less use of consolidation or maintenance CT for CD30+ patients
- Anthracyclines were used in most patients (58%)
  - Brentuximab use was rare (n=7)
- CD30 positivity and transplant were associated with improved survival in multivariable regression model
- CD30 expression does not drive initial treatment decisions

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Shustov AR, et al., T-Cell Forum. 2015: abstract TS15_10.

Abstract 10: Key findings

Nabhan C, et al. Patterns of care and treatment characteristics of patients >70 years of age with PTCL

- Data on disease/clinical characteristics were available for 395 patients (≤60: n=207, >60-<70: n=88, ≥70: n=100), while treatment data were available on 363 patients
- Patients ≥70 years were more likely to have underlying liver and cardiac disease, ALK- ALCL and skin involvement
- Patients ≥70 years were less likely to receive curative-intent therapy ($p<0.0001$) and more likely to receive best supportive care alone ($p=0.02$) compared to younger patients
- Younger patients were more likely to undergo high-dose therapy as consolidation ($p<0.0001$)
- PTCL patients ≥70 years in the US are more likely to receive non-curative intent therapy

Nabhan C, et al., 13-ICML: abstract 232.

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Study Status

- Enrollment closed in February 2014
- Number of active sites remaining: 41
- Enrolling sites by type of setting: 27% community / 73% academic
- Median patient follow-up: 30 months
- In planning stage for extension of the registry (in US) in collaboration with T Cell PROJECT to merge datasets
- Joint publications efforts are underway from both registries

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Conclusions

- Distribution of subtypes in US is similar to T cell Project
- Initial pathologic evaluation still not optimal for many patients (AITL may be underdiagnosed)
- A significant number of patients (37%) did not receive anthracycline regimens
- Significant number of patients (47%) hospitalized
- Patients over 70 are largely being treated without curative intent
- Only a small proportion of patients undergo transplant in first remission (PD in 47%, other reasons unclear)

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What we learned

- It took a year to get sites fully engaged, most of enrollment was at academic centers
- Patients have to be enrolled within 30 days of starting treatment, we missed patients who received one cycle of treatment before referral
- Data locks at different stages of treatment and follow up have been useful for ongoing analysis of the data
- Data requirements for entry of initial chemotherapy were too cumbersome and will be streamlined
- Required labs will be streamlined as they did not reflect the patterns of care of the community
- High enrolling sites (centers of excellence) need additional data entry support

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Take Home Messages

- Registry data is important to define the real world patients as distinct from those enrolled in prospective trials
- It is important to identify what factors are important in treatment decisions in diseases like PTCL where there are no clear cut treatment recommendations as per NCCN
- Registries may identify groups of patients whose outcomes could be improved by adaptive treatment strategies
- Ideally, central path review and tissue for genomic studies would enhance the scope of COMPLETE but funding for registries is inadequate at present
- Government agencies and healthcare providers need to be engaged in efforts to expand registries in rare diseases

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Comprehensive **O**ncology **M**easures for **P**eripher**a**l T-C**e**ll Lymphoma **T**r**e**atment (COMPLETE)

Treatment Registry for Patients with Newly Diagnosed Peripheral T-Cell Lymphoma (PTCL)

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