ELSEVIER

Blood 142 (2023) 3080–3083

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

624.HODGKIN LYMPHOMAS AND T/NK CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Impact of Therapy Sequence on Survival Outcomes Among Patients with Relapsed or Refractory Mature T and NK Cell Neoplasms: A Global Retrospective Cohort Study

Mark N Sorial, PharmD, RPh[1], Min Jung Koh, MS[2], Leora Boussi, MD[3], Jessy Xinyi Han, BS[4], Luke Peng[5], Ijeoma Julie Eche-Ugwu, PhD[6,7], Rui Duan[8], Matthew M. Lei, PharmD[9], Eliana Miranda, MD PhD[10], Carlos Chiattone, MD PhD[11], Robert Stuver, MD[12], Steven M. Horwitz, MD[13], Maria J. Fernandez Turizo, MD[14], Sean McCabe, BS[15], Mwanasha Hamuza Merrill, MD[16], Eric Jacobsen, MD[17], Jin Seok Kim, MD PhD[18], Yu Ri Kim, MD[19], Jae Yong Cho, MD PhD[20], Hasmukh Jain, MDDM[21], Manju Sengar, MD DM[21], Thomas Eipe, PharmD[22], Tanuja Shet, MBBS, MD DPB, DNB, DTM[23], Shambhavi Singh, MD PhD[24], Uvette Lou[15], Hesham Raghib[15], Judith Gabler, MD[15], Min Ji Koh, BA[24], Carrie Van Der Weyden, MBBS (Hons), FRACP, FRCPA[25], Miles Prince, MBBS (Hons), MD FRACP, FRCPA, AFRCMA, MACD, FAHMS[26], Ramzi Hamouche, MD[27], Tinatin Muradashvili, MD[27], Francine M. Foss, MD[28], Marianna Gentilini, MD[29], Beatrice Casadei, MD PhD[30], Pier Luigi Zinzani, MD PhD[31], Takeshi Okatani, MD[32], Noriaki Yoshida, MD PhD[33], Sang Eun Yoon, MD[34], Won Seog Kim, MD MPH, PhD[35], Girisha Panchoo, MBBS[36], Zainab Mohamed, MBChB, MMed[37], Estelle Verburgh, MBChB, M MDInt, FCPSA, PhD[38], Jackielyn Cuenca Alturas, BA[39], Mubarak Al Mansour, MD[40], Josie Ford, BS[15], Martina Manni, PhD[41], Massimo Federico, MD[42], Owen A. O'Connor, MD PhD[43], Maria Elena Cabrera, MD[44], Enrica Marchi, MDPhD[45], Changyu Shen, PhD[46], Devavrat Shah, PhD[4], Salvia Jain, MD[47]

[1] Department of Pharmacy, Massachusetts General Hospital Cancer Center, Boston, MA
[2] Georgetown University School of Medicine, Arlington, VA
[3] Medical Oncology & Hematology, Memorial Sloan Kettering Cancer Center, New York, NY
[4] Massachusetts Institute of Technology, Cambridge, MA
[5] College of Science, Northeastern University, Boston, MA
[6] Phyllis F. Cantor Center for Research in Nursing and Patient Care Services, Dana-Farber Cancer Institute, Boston, MA
[7] Beth Israel Deaconess Medical Center, Boston, MA
[8] Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA
[9] Department of Pharmacy, Massachusetts General Hospital, Boston, MA
[10] University of Campinas (UNICAMP), Hematology and Hemotherapy Center (Hemocentro), Sao Paulo, Brazil
[11] University of Campinas (UNICAMP), Hematology and Hemotherapy Center (Hemocentro), San Paulo, Brazil
[12] Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
[13] Memorial Sloan Kettering Cancer Center, New York, NY
[14] Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Brookline, MA
[15] Massachusetts General Hospital Cancer Center, Boston, MA
[16] Dana Farber Cancer Institute, Boston, MA
[17] Dana-Farber Cancer Institute, Boston, MA
[18] Division of Hematology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, Republic of (South)
[19] Division of Hematology, Department of Internal Medicine, Hematology, Gangnam Severance Hospital, Seoul, South Korea
[20] Department of Medicine, Gangnam Severance Hospital, Yonsei University School of Medicine, Seoul, Korea, Republic of (South)
[21] Department of Medical Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India
[22] Department of Clinical Pharmacology, Tata Memorial Centre, Mumbai, India
[23] Department of Pathology, Tata Memorial Centre, Mumbai, India
[24] Division of Hematology and Oncology, Department of Medicine, Massachusetts General Hospital Cancer Center, Boston, MA
[25] Department of Hematology, Peter MacCallum Cancer Center, Melbourne, AUS
[26] Peter MacCallum Cancer Inst., East Melbourne, AUS

[27] Department of Hematology, Yale Cancer Center, New Haven, CT
[28] Yale University School of Medicine, New Haven, CT
[29] IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Istituto Di Ematologia "ser, BOLOGNA, ITA
[30] Hematology, Istituto di Ematologia "Seràgnoli", Bologna, Italy
[31] IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli" and Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy
[32] Hiroshima Red Cross & A-Bomb Survivors Hospital, Hiroshima City, JPN
[33] Radiation Effects Research Foundation, Hiroshima-Shi, JPN
[34] Division of Hematology-Oncology, Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Korea, Republic of (South)
[35] Samsung Medical Center, Center for Hematologic Malignancy, Seoul, Korea, Republic of (South)
[36] University of Cape Town and Groote Schuur Hospital, Cape town, South Africa
[37] University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa
[38] Department of Medicine, Division of Clinical Haematology, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa
[39] Department of Medicine, King Abdulaziz Medical City, Jeddah, Saudi Arabia
[40] Department of Medicine, King Abdulaziz Medical City, Jeddah, SAU
[41] Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Modena, ITA
[42] University of Modena and Reggio Emilia, Modena, ITA
[43] University of Virginia, Charlottesville, VA
[44] Hospital Del Salvador, Santiago, CHL
[45] Program for T-Cell Lymphoma Research, University of Virginia, Charlottesville, VA
[46] Biogen, Cambridge, MA
[47] Broad Institute of Harvard and MIT, Boston

Despite evolution of therapeutic strategies, there is no universal standard of care for relapsed or refractory (RR) mature T and NK-cell neoplasms (TNKL). Most patients receive multiple lines of therapy and cycle through many available options. [1-3] There is no data to inform optimal therapy sequence, however emerging data suggest that exposure to epigenetic modifiers (EM) can sensitize tumors to other therapies. [4-6] Here we report results of comparative analyses assessing survival outcomes based on therapy sequence using a global RR TNKL patient cohort with data from 15 centers across 6 continents.

We conducted a retrospective target-trial [7,8] cohort study using an updated global patient cohort. [9] Patients were excluded from analyses if they had anaplastic large cell lymphoma (as EM is infrequently used [10,11]), did not receive first line cytotoxic chemotherapy (CC), or no documented second line (2L) start date. Cohort assignment was based on 2L therapy received: EM (e.g. histone deacetylase or DNA methyltransferase inhibitors), small molecule inhibitors (SI; broad or selective), or CC. Antibody-drug conjugates were included in CC. Outcomes were overall survival (OS; time from 2L start to death) and real-world progression-free-survival-2 (rwPFS2; time from 2L start to fourth line start or death [12] to assess if 2L modifies the effect of third line [3L]). Planned subgroups included histologic subtype and those who received allogeneic hematopoietic transplant (HSCT) after 2L. For sequence analyses, included patients must have received 3L. Outcomes were assessed between all prespecified 2L to 3L sequences using a single comparator, and pairwise. Kaplan Meier curves were used, and adjusted hazard ratios (aHR) were estimated using Cox regression with previously described *a priori* covariates. [9] Maximal, minimal, and no covariate Cox models were compared using likelihood ratio tests and Akaike's information criterion.

Of the 925 RR patients in the global cohort, 472 were included who received EM (n=89), SI (n=46), or CC (n=337) at 2L. The most common SI included immunomodulatory imide drug (26.1%), PI3K inhibitor (21.7%), investigational pathway inhibitor (19.6%) and JAK inhibitor (17.4%). Within EM, SI, and CC, 42.7%, 37%, and 47.2% of patients were primary refractory to first line, respectively. The most common histologies were PTCL-NOS (51.7%, 41.3%, and 57.3%) and AITL (43.8%, 54.3%, and 26.4%) in EM, SI, and CC, respectively. Most patients had a Prognostic Index for T-cell Lymphoma (PIT) score at diagnosis of 1 (27%, 34.8%, and 27%) or 2 (28.1%, 26.1%, and 25.8%) in EM, SI, and CC, respectively. In EM, 34.8% received first-line autologous HSCT, versus 28.2% in SI, and 15.4% in CC. Following 2L, 12.4%, 17.4%, and 9.8% received allogeneic HSCT in EM, SI, and CC, respectively.

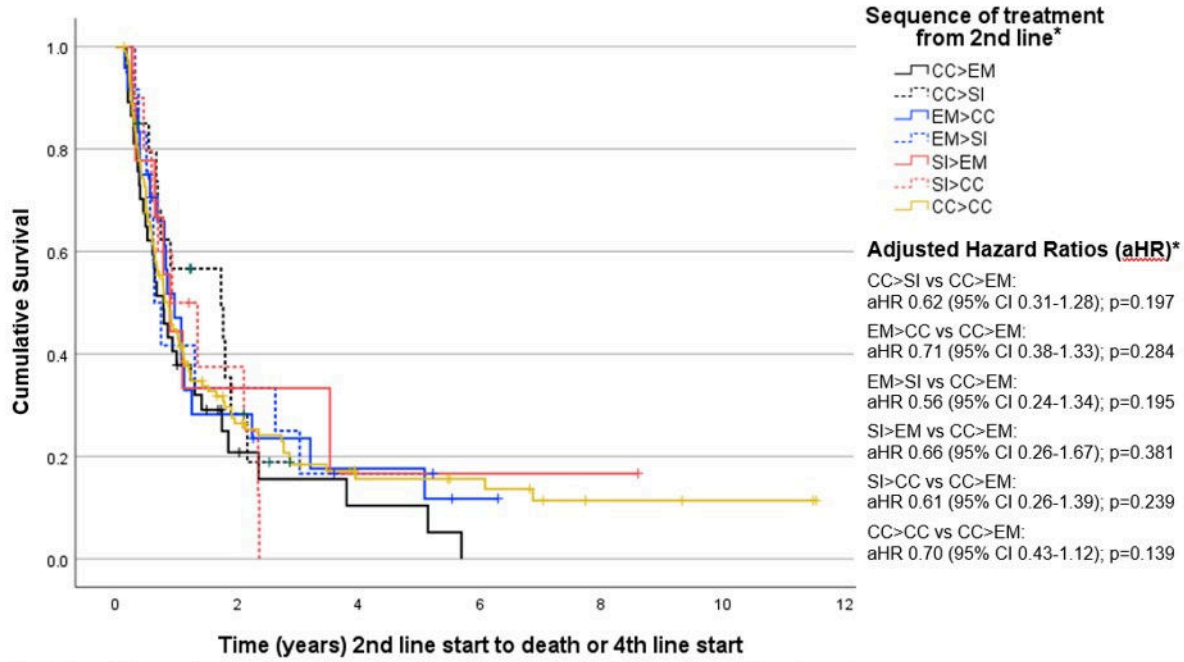
The Cox model containing histology, PIT, and primary refractory status was used as the final model (vs maximal model: p=0.88). Compared to CC at 2L, EM did not affect OS (aHR 0.88, 95% CI 0.63-1.24; p=0.46) or rwPFS2 (aHR 0.84, 95% CI 0.61-1.16; p=0.28), however SI improved OS (aHR 0.61, 95% CI 0.37-0.97; p=0.038) and rwPFS2 (aHR 0.61, 95% CI 0.38-0.90; p=0.038). In the allogeneic HSCT subgroup, there was no difference in OS (EM vs CC: aHR 0.32, 95% CI 0.04-2.40; p=0.27; SI vs CC: aHR 0.51, 95% CI 0.06-4.69; p=0.55) or rwPFS2 (EM vs CC: aHR 0.30, 95% CI 0.05-1.96; p=0.21; SI vs CC: aHR 0.64, 95% CI 0.05-3.90; p=0.46). There were no differences in PTCL-NOS patients in OS (EM vs CC aHR 0.80, 95% CI 0.51-1.25; p=0.33; SI vs CC: aHR 1.00, 95% CI 0.54-1.84; p=0.99) or rwPFS2 (EM vs CC: aHR 0.91, 95% CI 0.61-1.38; p=0.66; SI vs CC: aHR 0.90, 95% CI 0.49-0.97; p=0.16). In AITL, SI improved OS (aHR 0.34, 95% CI 0.16-0.76; p=0.009) and rwPFS2 (aHR 0.36, 95% CI 0.17-0.77; p=0.008) versus CC, but EM showed no difference in OS (aHR 0.80, 95% CI 0.43-1.46; p=0.46) or rwPFS2 (aHR 0.56, 95% CI 0.31-1.02; p=0.059). There was no difference in rwPFS2 or OS across sequences overall (Figure 1) or between pairwise sequence comparisons (Figure 2).

Compared to CC, SI at 2L improved OS and rwPFS2 in AITL patients. Therapy sequence did not affect OS or rwPFS2. Advanced approaches such as machine learning and dynamic treatment regimes have been initiated to fully elucidate the effect of therapy sequence. Our study highlights several equally effective therapy sequences to treat RR TNKL allowing therapy to be individualized based on patient and disease characteristics, and drug access at a given time.

Disclosures Lei: *Genentech:* Membership on an entity's Board of Directors or advisory committees; *AstraZeneca:* Membership on an entity's Board of Directors or advisory committees; *BTG Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *TScan Therapeutics:* Consultancy; *Genmab US:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Chiattone:** *ROCHE, ABBVIE, JANSSEN, AZ, LYLLI, TAKEDA:* Consultancy; *ROCHE, ABBVIE, JANSSEN, AZ, LYLLI, TAKEDA:* Honoraria. **Horwitz:** *ONO Pharmaceuticals:* Consultancy; *Affimed:* Research Funding; *Cimieo Therapeutics:* Consultancy; *Takeda:* Consultancy, Research Funding; *ADC Therapeutics:* Research Funding; *Tubulis:* Consultancy; *Trillium Therapeutics:* Consultancy, Research Funding; *Shoreline Biosciences, Inc.:* Consultancy; *SecuraBio:* Consultancy; *Abcuro Inc.:* Consultancy; *Auxilius Pharma:* Consultancy; *Daiichi Sankyo:* Consultancy, Research Funding; *Yingli Pharma Limited:* Consultancy; *Kyowa Hakko Kirin:* Consultancy, Research Funding; *Celgene:* Research Funding; *Crispr Therapeutics:* Research Funding; *Millenium:* Research Funding; *Seattle Genetics:* Research Funding; *Verastem/SecuraBio:* Research Funding. **Jacobsen:** *Celgene:* Research Funding; *Merck:* Honoraria, Research Funding; *Pharmacyclics:* Research Funding; *Hoffman-LaRoche:* Research Funding; *Daiichi:* Honoraria; *BMS:* Honoraria; *Bayer:* Honoraria; *UpToDate:* Patents & Royalties. **Jain:** *Intas Pharmaceuticals:* Research Funding; *Zydus Pharmaceuticals:* Research Funding; *ImmunoACT:* Research Funding. **Van Der Weyden:** *Cartherics Pty Ltd:* Ended employment in the past 24 months, Membership on an entity's Board of Directors or advisory committees. **Prince:** *Takeda:* Speakers Bureau; *Merck:* Speakers Bureau; *Mallinkrodt:* Speakers Bureau; *Mundipharma:* Speakers Bureau. **Foss:** *Seagen:* Speakers Bureau; *Astex:* Honoraria; *Conjupro:* Honoraria; *Kyowa:* Honoraria; *Daiichi Sankyo:* Honoraria; *SecuraBio:* Honoraria; *Acrotech:* Speakers Bureau. **Casadei:** *Novartis:* Speakers Bureau; *Lilly:* Speakers Bureau; *Roche:* Speakers Bureau; *Celgene-BMS:* Membership on an entity's Board of Directors or advisory committees; *Beigene:* Membership on an entity's Board of Directors or advisory committees; *Takeda:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Abbvie:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Kite-Gilead:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Zinzani:** *JANSSEN-CILAG:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *SANDOZ:* Membership on an entity's Board of Directors or advisory committees; *ASTRAZENECA:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *CELLTRION:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *MSD:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *GILEAD:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *SERVIER:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *KYOWA KIRIN:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *EUSAPHARMA:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *ROCHE:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *TAKEDA:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *BMS:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *SECURA BIO:* Membership on an entity's Board of Directors or advisory committees; *NOVARTIS:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *ADC THERAPEUTICS:* Membership on an entity's Board of Directors or advisory committees; *INCYTE:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *BEIGENE:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Kim:** *Beigene:* Research Funding; *Donga:* Research Funding; *Sanofi:* Research Funding; *Boryung:* Research Funding; *Kyowa-Kirin:* Research Funding; *Roche:* Research Funding. **Verburgh:** *MSD:* Research Funding. **Marchi:** *Everest Clinical Research:* Other: Data Safety Monitoring Committee; *Astex Pharmaceutical/Myeloid Pharmaceuticals:* Research Funding; *Dren Bio:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Celgene/BMS:* Research Funding; *Merck:* Research Funding. **Shen:** *Biogen Digital Health:* Current Employment. **Jain:** *Myeloid Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Acrotech LLC:* Research Funding; *Crispr Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Daiichi Sankyo:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Mersana Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *SIRPant Immunotherapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Abcuro, Inc:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *SecuraBio:* Membership on an entity's Board of Directors or advisory committees.

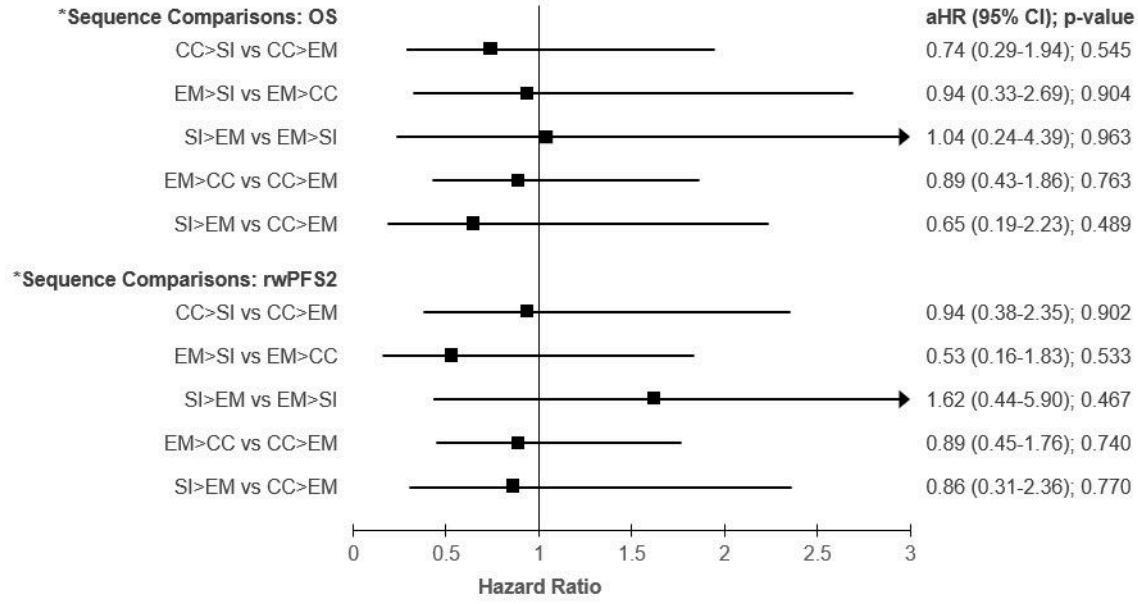
OffLabel Disclosure: There is no established standard of care in relapsed or refractory mature T and NK cell neoplasms. Agents reported in this observational study may have been used off-label as part of clinical practice.

Figure 1: Real-world progression-free-survival-2 based on treatment sequence starting from 2nd line therapy



Abbreviations: CC; cytotoxic chemotherapy, EM; epigenetic modifiers, SI; signaling inhibitors, CI; confidence interval, vs; versus.
*A treatment sequence is defined as treatment in second line followed by treatment in third line, represented with the ">" symbol (e.g., CC>EM refers to the treatment sequence of receiving cytotoxic chemotherapy in the second line followed by epigenetic modifiers in the third line).

Figure 2: Pairwise treatment sequence comparisons of overall survival and real-world progression-free-survival 2



Abbreviations: OS; overall survival, aHR; adjusted hazard ratio, CI; confidence interval, CC; cytotoxic chemotherapy, SI; signaling inhibitors, EM; epigenetic modifiers, rwPFS2; real-world progression-free-survival 2.
* A treatment sequence is defined as treatment in second line followed by treatment in third line, represented with the ">" symbol (e.g. CC>SI refers to the treatment sequence of receiving cytotoxic chemotherapy in the second line followed by signaling inhibitors in the third line)

Figure 1

https://doi.org/10.1182/blood-2023-182341