Survival analyses in patients with thymidine kinase 2 deficiency aged ≤12 years at symptom onset who received pyrimidine nucleos(t)ide therapy

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Michio Hirano[1*], Caterina Garone[2,3], Richard Haas[4,5], Carmen Paradas[6,7], Fernando Scaglia[8,9,10], Cynthia Beller[11], Carl Chiang[11], Anny-Odile Colson[12], Susan VanMeter[11], Cristina Domínguez-González[13,14,15]

[1]The H. Houston Merritt Center for Neuromuscular and Mitochondrial Disorders, Department of Neurology, Columbia University Irving Medical Center, New York, NY, USA; [2]Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy; [3]Scientific Institute for Research, Hospitalization and Healthcare (IRCCS) Istituto delle Scienze Neurologiche, Unità Operativa Complessa (UOC) Neuropsichiatria dell'età Pediatrica di Bologna, Bologna, Italy; [4]Department of Neurosciences, University of California, San Diego, CA, USA; [5]Rady Children's Hospital, San Diego, CA, USA; [6]Neuromuscular Disorders Unit, Neurology Department, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío, Consejo Superior de Investigaciones Científicas, University of Seville, Seville, Spain; [7]Center for Biomedical Network Research on Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain; [8]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA; [9]Texas Children's Hospital, Houston, TX, USA; [10]Baylor College of Medicine (BCM)–Chinese University of Hong Kong (CUHK) Joint Centre for Medical Genetics, Prince of Wales Hospital, Shatin, Hong Kong SAR, China; [11]UCB, Morrisville, NC, USA; [12]UCB, Colombes, France; [13]Neuromuscular Diseases Unit, Neurology Department, Hospital Universitario 12 de Octubre, Madrid, Spain; [14]Research Institute Hospital 12 de Octubre (i+12), Madrid, Spain; [15]Centre for Biomedical Network Research on Rare Diseases (CIBERER), Instituto de Salud Carlos III, Madrid, Spain

***Presenting author:** Michio Hirano (mh29@cumc.columbia.edu)

Introduction

- Thymidine kinase 2 deficiency (TK2d) is an ultra-rare, autosomal recessive, mitochondrial disease manifesting as progressive, life-threatening myopathy[1,2]
  - Pathogenic variants of the thymidine kinase 2 gene (*TK2*) result in mitochondrial DNA (mtDNA) depletion and/or multiple mtDNA deletions,[3] leading to proximal, bulbar and axial muscle weakness[1,4]
  - TK2d frequently causes premature death, often from respiratory failure[1,2]
- There are no approved treatments for TK2d, with current management across the world focused on supportive care, which does not change the progressive disease trajectory[5]
- Doxecitine and doxribtimine is a pyrimidine nucleoside therapy containing deoxycytidine (dC) and deoxythymidine (dT) currently in development for use in TK2d
  - Doxecitine and doxribtimine targets the underlying disease pathology of TK2d by utilizing residual thymidine kinase 2 activity in the mitochondria, as well as thymidine kinase 1 and dC kinase in the cytosol, to increase mtDNA quantity that supports increased energy metabolism in cells[6–9]
- There is a wide spectrum of age of TK2d symptom onset. Generally, patients with earlier symptom onset have more rapid disease progression[1,2]
  - Using a threshold of ≤12 years versus >12 years for the age of symptom onset is largely considered a clinically meaningful approach to disease categorization[1,2]

Objective

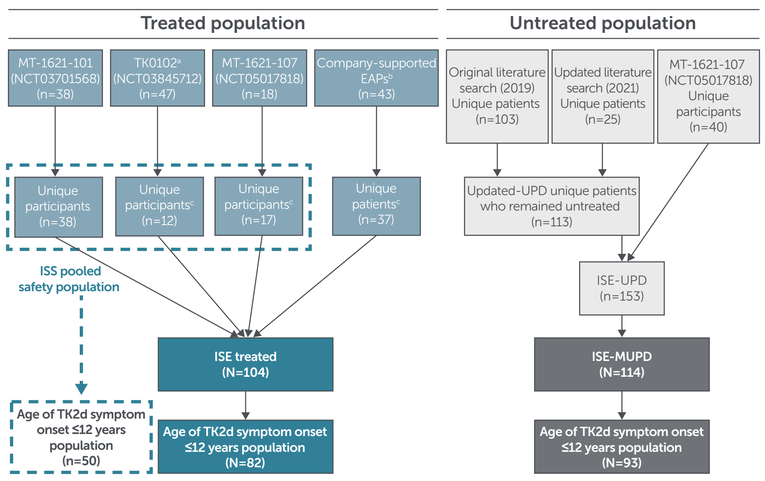
- To assess survival and safety in pediatric and adult participants with an age of TK2d symptom onset ≤12 years who received pyrimidine nucleos(t)ide therapy

Methods

Pooled analysis

- The efficacy and safety of pyrimidine nucleos(t)ide therapy were assessed in the Integrated Summary of Efficacy (ISE) and Safety (ISS)
- Data from participants treated with pyrimidine nucleos(t)ides (**ISE treated group**) were pooled from retrospective (MT-1621-101 [NCT03701568], MT-1621-107 [NCT05017818]) and prospective (TK0102 [NCT03845712]) studies and company-supported expanded access programs (**Figure 1**)
- Data from untreated participants (**ISE-modified Untreated Patient Database [MUPD]**) were pooled from literature reviews and a retrospective chart review study (MT-1621-107; **Figure 1**)
- The ISS pooled safety population included participants from MT-1621-101, TK0102 and MT-1621-107
- Subgroups were stratified by age of TK2d symptom onset categories; here, we report data from participants with an age of symptom onset ≤12 years
  - Survival analyses in participants with symptom onset >12 years of age are presented in poster P256

Figure 1. Study analysis populations



Individual participant data described in each publication/source were cross-referenced with the aim of removing duplicates to obtain unique data. The ISE-MUPD is only used in comparative survival analyses.
[a]Data cutoff date: March 15, 2024. [b]Data cutoff date: March 1, 2024. [c]Individuals who participated in multiple studies are only counted once, although their data across studies are included.
EAPs, expanded access programs; ISE, Integrated Summary of Efficacy; ISS, Integrated Summary of Safety; MUPD, modified UPD; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

Patient population

- Inclusion and exclusion criteria were specific to each source study
- The main eligibility criteria for treated participants were confirmed biallelic pathogenic *TK2* variants, absence of other genetic disease or polygenic disease, and treatment with nucleos(t)ides for TK2d (non-good manufacturing practice [GMP]-grade deoxycytidine monophosphate/deoxythymidine monophosphate, non-GMP-grade dC/dT or doxecitine and doxribtimine [GMP-grade dC/dT])
  - Available medical records, or at a minimum information pertaining to survival, were required for retrospective studies
- Untreated patients required individual-level patient data and genetic confirmation of biallelic pathogenic *TK2* variants

Outcomes

- The primary ISE outcome was survival, defined as time to death from TK2d symptom onset and from treatment start
- Functional outcomes were also assessed (poster P255)
- Safety outcomes were assessed in the ISS pooled safety population (**Figure 1**)
  - Some safety outcomes were not collected in MT-1621-107

Statistical analysis

- The primary analysis assessed survival for pair data from the ISE treated and ISE-MUPD groups matched using the 50th-percentile matching algorithm
  - Matched pairs from the same age-of-TK2d-symptom-onset group were selected after sorting untreated patients based on survival time, and treated participants based on treatment time
  - Cox proportional hazard models, with and without age of TK2d symptom onset as covariate, and marginal Cox models, were utilized to assess risk of death
  - Restricted mean survival time (RMST) analyses were used to summarize improvement in survival time with treatment over a prespecified number of years (30 years for RMST analyses after TK2d symptom onset; 6 years for RMST analyses after treatment start)

Results

Patient baseline characteristics and demographics

- In total, 175 participants with age of TK2d symptom onset ≤12 years were included in the ISE analysis (ISE treated, n=82; ISE-MUPD, n=93; **Table 1**)
  - Most participants in the ISE treated group were White (81.7%), 32.9% resided in Europe and 67.1% were from the rest of the world, with more male (56.1%) than female (43.9%) participants
- Most participants had an age of symptom onset ≤2 years (ISE treated, 56/82 [68.3%]; ISE-MUPD, 69/93 [74.2%])
  - Median (quartile [Q]1, Q3) age of symptom onset was 1.50 (1.08, 2.41) years and 1.33 (0.75, 2.49) years in the ISE treated and ISE-MUPD groups, respectively
- In the ISE treated group, median (Q1, Q3) age at first treatment was 4.26 (2.11, 10.49) years and duration of treatment was 54.8 (15.2, 78.4) months

Table 1. Baseline demographics and characteristics of participants with age of TK2d symptom onset ≤12 years

Baseline demographics and characteristics	ISE treated (N=82)	ISE-MUPD (N=93)
Sex, n (%)		
Male	46 (56.1)	49 (52.7)
Female	36 (43.9)	44 (47.3)
Race,[a] n (%)		
White	67 (81.7)	24 (25.8)
Other	11 (13.4)	2 (2.2)
Not reported	4 (4.9)	67 (72.0)
Ethnicity, n (%)		
Hispanic or Latino	30 (36.6)	12 (12.9)
Not Hispanic or Latino	41 (50.0)	14 (15.1)
Not reported	11 (13.4)	67 (72.0)
Geographic region of residence,[a] n (%)		
Europe	27 (32.9)	20 (21.5)
Rest of world	55 (67.1)	47 (50.5)
Not reported	0 (0)	26 (28.0)
Age of TK2d symptom onset, years		
Median (range)	1.50 (0.01–11.67)	1.33 (0.00–11.00)
Q1, Q3	1.08, 2.41	0.75, 2.49
Age at first treatment (any treatment), years		
Median (range)	4.26 (0.69–35.52)	NA
Q1, Q3	2.11, 10.49	

[a]Owing to the ultra-rare nature of TK2d and the small number of participants, some details relating to race and geographic region of residence were grouped for reporting purposes to minimize risk of participant reidentification.
ISE, Integrated Summary of Efficacy; MUPD, modified Untreated Patient Database; NA, not available; Q, quartile; TK2d, thymidine kinase 2 deficiency.

Patient survival

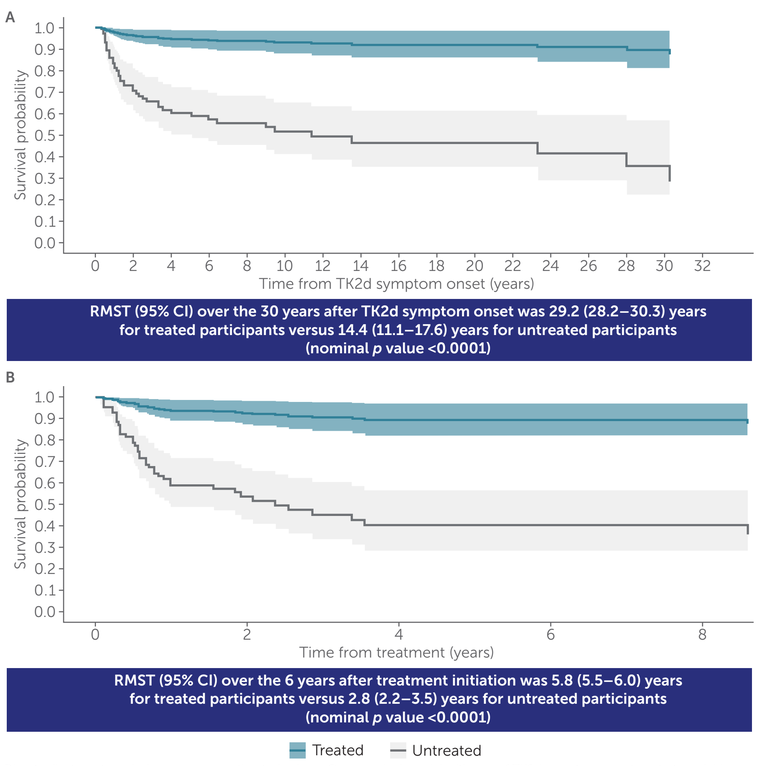
- There were three deaths (3.7%) in the ISE treated group and 53 deaths (57.0%) in the ISE-MUPD group, with median (Q1, Q3) age at death of 1.11 (0.94, 31.77) years and 2.64 (1.58, 4.00) years, respectively.
- The risk of death was reduced with treatment by 92–94% (hazard ratio [HR] = 0.06–0.08; $p<0.0001$) in the time from TK2d symptom onset and by 87–95% (HR = 0.05–0.13; $p<0.0001$) in the time from treatment initiation (HR ranges resulting from proportional hazard and marginal Cox models; **Figure 2**, **Table 2**)
- RMST estimates were increased for treated versus untreated participants (**Figure 2**)

Table 2. Survival HRs for participants with age of TK2d symptom onset ≤12 years, estimated from Cox models using 50th-percentile matched-pair data from the ISE treated and ISE-MUPD groups

Model	HR (95% CI) for time from TK2d symptom onset to death	HR (95% CI) for time from treatment initiation to death
Cox proportional hazard model, match-pairs as strata variable, age of TK2d symptom onset as continuous covariate, with Firth correction	0.061 (0.006–0.221); $p<0.0001$	0.134 (0.033–0.362); $p<0.0001$
Cox proportional hazard model, match-pairs as strata variable, no covariate, with Firth correction	0.079 (0.016–0.238); $p<0.0001$	0.127 (0.034–0.340); $p<0.0001$
Marginal Cox model with age of TK2d symptom onset as strata variable	0.061 (0.019–0.190); $p<0.0001$	0.052 (0.015–0.179); $p<0.0001$

78 matched pairs were included in the analyses (deaths: ISE treated, n=3; ISE-MUPD, n=40), of which 33 and 30 informative pairs were used to estimate time to death from TK2d symptom onset and from treatment initiation, respectively. Firth correction was used to achieve convergence in Cox proportional hazard model estimates owing to the lack of events in the treated group.
CI, confidence interval; HR, hazard ratio; ISE, Integrated Summary of Efficacy; MUPD, modified Untreated Patient Database; TK2d, thymidine kinase 2 deficiency.

Figure 2. Direct adjustment survival curves and RMST estimates from (A) symptom onset and (B) treatment start for 50th-percentile matched-pairs of participants from the ISE treated and ISE-MUPD groups with age of TK2d symptom onset ≤12 years



Direct adjustment survival curves were estimated using a Cox marginal model with age of TK2d symptom onset as strata variable. RMSTs were estimated from Kaplan–Meier analyses; nominal p values are not multiplicity adjusted.
CI, confidence interval; ISE, Integrated Summary of Efficacy; MUPD, modified Untreated Patient Database; RMST, restricted mean survival time; TK2d, thymidine kinase 2 deficiency.

Conclusions and Outlook

In participants with an age of TK2d symptom onset ≤12 years, pyrimidine nucleos(t)ide therapy substantially decreased the risk of mortality by 87–95% and increased survival time

- Potential bias resulting from the use of an external comparator was addressed by utilizing multiple survival analyses, strict matching methodology, covariate adjustment and stratification

Treatment with pyrimidine nucleos(t)ides was generally well tolerated, with few TEAEs leading to treatment discontinuation in the overall ISS safety population

The observed improvement in survival with pyrimidine nucleos(t)ide therapy may have important implications for addressing the severe unmet need for patients living with TK2d

Safety and tolerability

- In the pooled safety population (MT-1621-101, TK0102, MT-1621-107; n=50 with age of TK2d symptom onset ≤12 years), two participants (4.0%) experienced treatment-emergent adverse events (TEAEs) leading to treatment discontinuation (**Table 3**)
- Among participants with age of TK2d symptom onset ≤12 years and full safety data availability (MT-1621-107 not included; n=39):
  - all participants had at least one TEAE, most commonly diarrhea (33/39 [84.6%])
  - 59.0% of participants (23/39) experienced at least one serious TEAE over the duration of their treatment, most of which were not considered treatment-related
- TEAEs reported in ≥10% of participants are presented in **Supplementary Table 1**

Table 3. Summary of TEAEs in the pooled safety population with age of TK2d symptom onset ≤12 years

Participants with TEAEs, n (%)	MT-1621-101 and TK0102 (n=39)	MT-1621-101, TK0102 and MT-1621-107 (n=50)
Participants with ≥1 TEAE	39 (100)	NC[a]
TEAE related to study drug	32 (82.1)	NC[a]
TEAE leading to study drug discontinuation	0 (0)	2 (4.0)
TEAE leading to dose reduction	9 (23.1)	10 (20.0)
Participants with ≥1 serious TEAE	23 (59.0)	NC[a]
Serious TEAE related to study drug	4 (10.3)	NC[a]
TEAEs reported in ≥20% of participants, by preferred term		
Diarrhea	33 (84.6)	NC[a]
Pyrexia	18 (46.2)	
COVID-19	17 (43.6)	
Upper respiratory tract infection	16 (41.0)	
Rhinorrhea	15 (38.5)	
Vomiting	13 (33.3)	
Cough	11 (28.2)	
Headache	11 (28.2)	
Alanine aminotransferase increased	11 (28.2)	
Abdominal pain	10 (25.6)	
Gastroenteritis	9 (23.1)	
Aspartate aminotransferase increased	9 (23.1)	
Respiratory tract infection	8 (20.5)	
Blood creatine phosphokinase increased	8 (20.5)	
Serious TEAEs reported in ≥10% of participants, by preferred term		
Acute respiratory failure	5 (12.8)	NC[a]
Pneumonia	5 (12.8)	
Femur fracture	4 (10.3)	

[a]Some safety outcomes were not collected in MT-1621-107.
NC, not calculable; TEAE, treatment-emergent adverse event; TK2d, thymidine kinase 2 deficiency.

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References: 1. Berardo A, *et al. J Neuromuscul Dis* 2022;9:225–35. 2. Garone C, *et al. J Med Genet* 2018;55:515–21. 3. Lopez-Gomez C, *et al. EBioMedicine* 2019;46:356–67. 4. Dominguez-Gonzalez C, *et al. Orphanet J Rare Dis* 2019;14:100. 5. de Barcelos IP, *et al. Curr Opin Neurol* 2019;32:715–21. 6. Lopez-Gomez C, *et al. Ann Neurol* 2017;81:641–52. 7. Tsurada L, *et al. Neuromuscul Disord* 2020;30:S139. 8. Lopez-Gomez C, *et al. EBioMedicine* 2019;46:356–67. 9. Ramon J, *et al. Int J Mol Sci* 2021;22:6447.

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Please use this QR code to access the supplementary data and download a PDF of this poster.

Poster number: P257 (supplementary data)

Survival analyses in patients with thymidine kinase 2 deficiency aged ≤12 years at symptom onset who received pyrimidine nucleos(t)ide therapy

Supplementary Table 1. Summary of TEAEs reported in ≥10% of participants in the pooled safety population[a] with age of TK2d symptom onset ≤12 years

Preferred term, n (%)	MT-1621-101 and TK0102 (n=39)
Diarrhea	33 (84.6)
Pyrexia	18 (46.2)
COVID-19	17 (43.6)
Upper respiratory tract infection	16 (41.0)
Rhinorrhea	15 (38.5)
Vomiting	13 (33.3)
Cough	11 (28.2)
Headache	11 (28.2)
Alanine aminotransferase increased	11 (28.2)
Abdominal pain	10 (25.6)
Gastroenteritis	9 (23.1)
Aspartate aminotransferase increased	9 (23.1)
Respiratory tract infection	8 (20.5)
Blood creatine phosphokinase increased	8 (20.5)
Ear infection	7 (17.9)
Pneumonia	7 (17.9)
Influenza	7 (17.9)
Oropharyngeal pain	7 (17.9)
Rash	7 (17.9)
Anion gap increased	7 (17.9)
Blood lactic acid increased	7 (17.9)
Femur fracture	5 (12.8)
Acute respiratory failure	5 (12.8)
Influenza-like illness	5 (12.8)
Dyspnea	5 (12.8)
Basophil count increased	5 (12.8)
Dysphagia	5 (12.8)
Platelet count increased	5 (12.8)
Pain in extremity	4 (10.3)
Urinary tract infection	4 (10.3)
Abdominal pain upper	4 (10.3)
Depression	4 (10.3)
Muscular weakness	4 (10.3)
Carbon dioxide decreased	4 (10.3)
Gastroesophageal reflux disease	4 (10.3)
Nasopharyngitis	4 (10.3)
Scoliosis	4 (10.3)
Tachycardia	4 (10.3)

[a]Data were not collected in MT-1621-107.
TEAE, treatment-emergent adverse event; TK2d, thymidine kinase 2 deficiency.