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Enhancing the Ability to Diagnose, Interpret and Apply Best Treatment Options for Cutaneous Lymphomas

Therapeutics/Preclinical studies | #83

RESMAIN: Results of a multicenter, randomized, double blind, placebo-controlled trial to evaluate RESminostat for MAINtenance treatment in advanced stage Mycosis fungoides or Sézary syndrome

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Disclosures

- Consultant for 4SC, Innate Pharma, Kyowa Kirin, Recordarti Rare Diseases, and Takeda Pharmaceuticals.

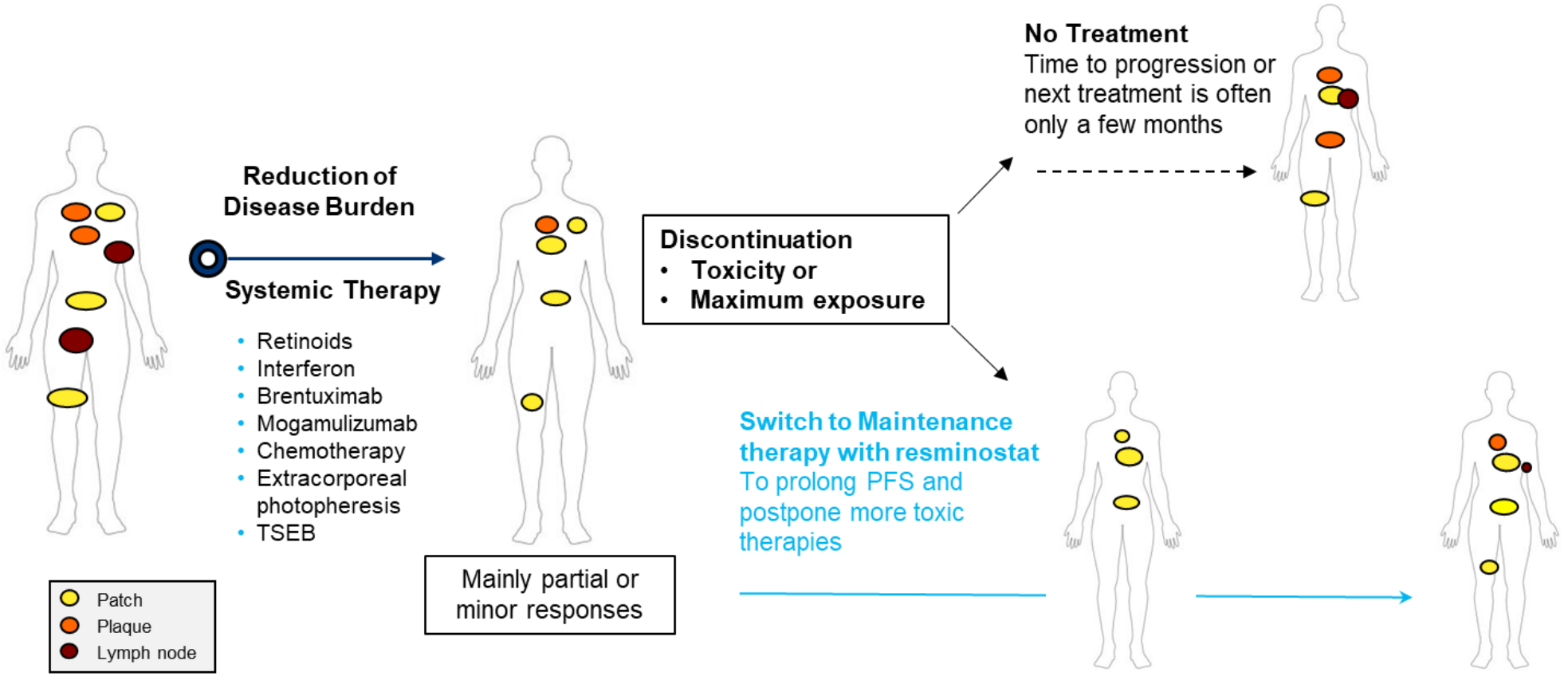
This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Resminostat will be addressed.

Rationale for Maintenance Treatment in CTCL



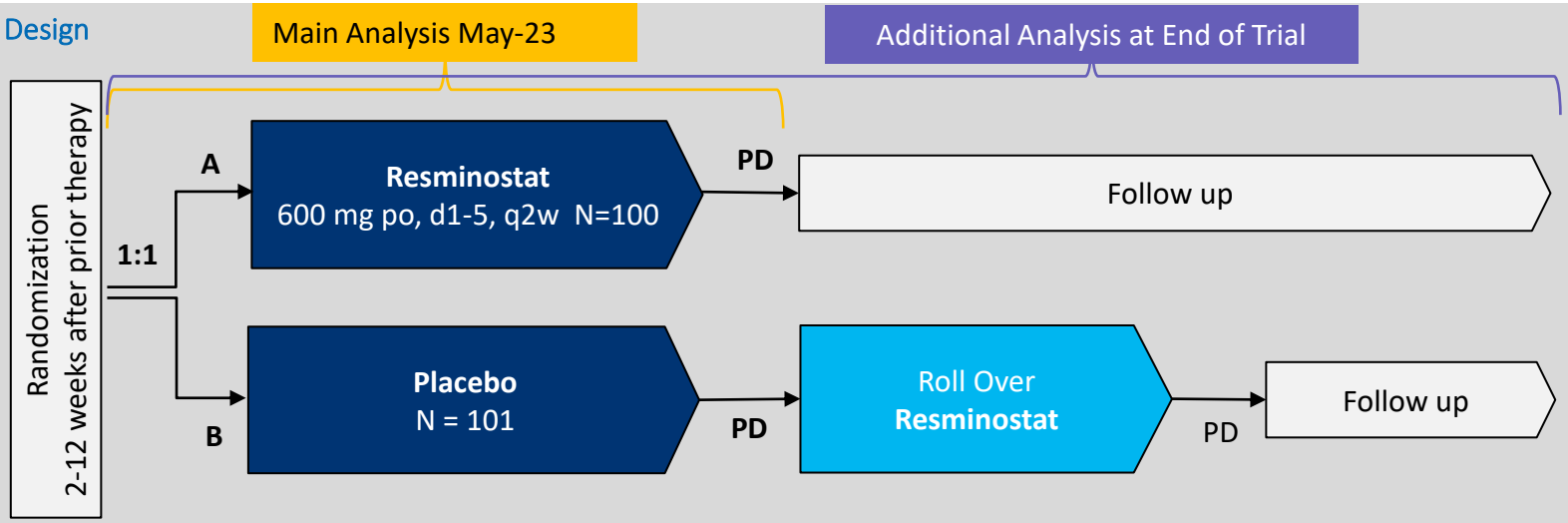
CTCL: Cutaneous T-cell lymphoma, PFS: Progression Free Survival, TSEB: Total Skin Electron Beam Radiation,
Images modified according to Stadler & Scarisbrick, Eur J Cancer 2021

RESMAIN – Trial Design

Patients

- Mycosis fungoides (stage IIB – IVB) or Sézary Syndrome
- In CR, PR or SD after prior systemic therapy or TSEB

Design

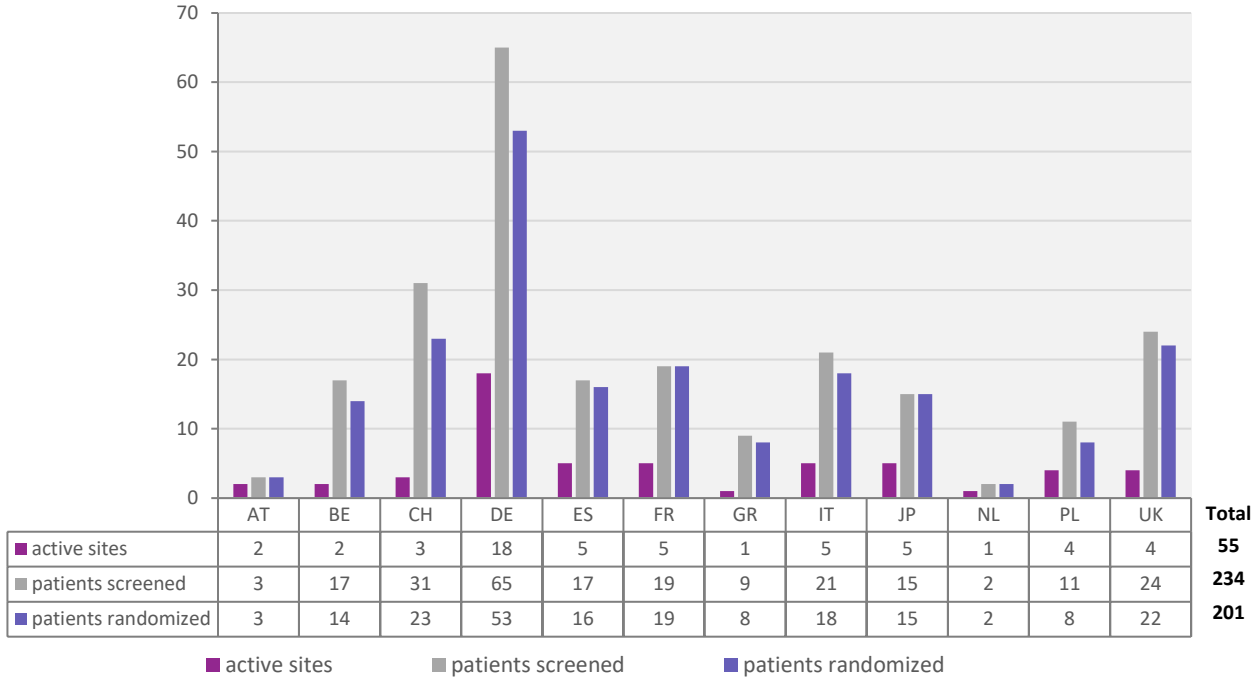


Primary endpoint: **PFS**
Key secondary endpoint: Time to symptom worsening (TTSW - Pruritus)

Secondary endpoints:
Safety, TTNT, OS, HrQoL etc.

CR: Complete Remission; PR: Partial Remission; SD: Stable Disease; TSEB: Total Skin Electron Beam Radiation; PD: Progressive Disease; PFS: Progression Free Survival, TTNT: Time To Next Treatment; OS: Overall Survival; HrQoL: Health-related Quality of Life

RESMAIN – The Journey



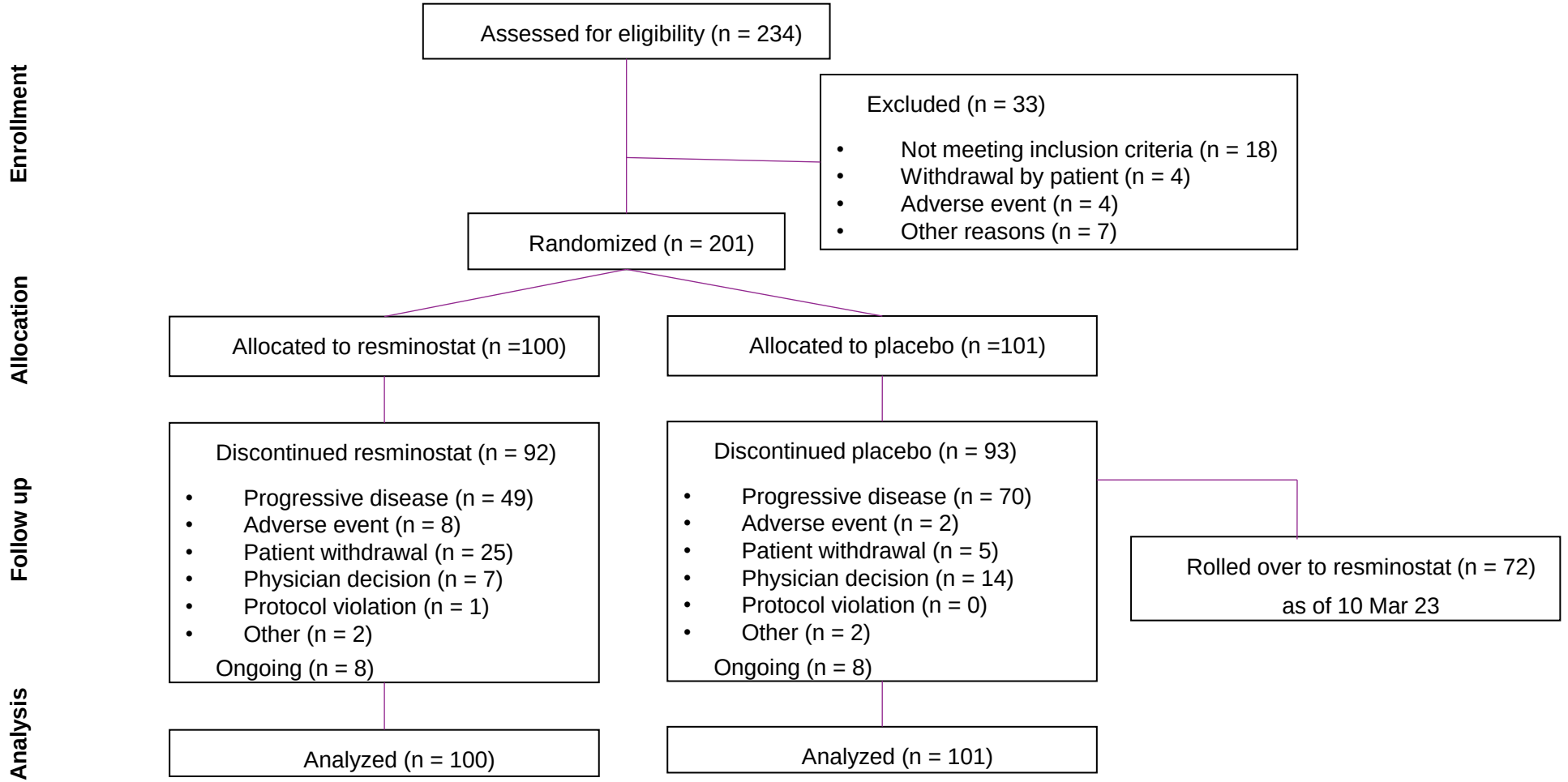
	AT	BE	CH	DE	ES	FR	GR	IT	JP	NL	PL	UK	Total
active sites	2	2	3	18	5	5	1	5	5	1	4	4	55
patients screened	3	17	31	65	17	19	9	21	15	2	11	24	234
patients randomized	3	14	23	53	16	19	8	18	15	2	8	22	201

- First patient randomized: Jan 2017
- Last patient randomized: May 2022
- Main analysis data cut-off: 10 Mar 2023
  - 15 patients ongoing (open label)
- Last patient out – Q3 2024

- 55 active sites
- 12 countries
  - 9 EU member states
  - Switzerland, UK and Japan

RESMAIN is one of the largest randomized controlled clinical trials in advanced stage CTCL

RESMAIN – Patient Flow Chart



RESMAIN – Patient Characteristics I

Characteristic		Resminostat (N=100)	Placebo (N=101)
Age, years Age group, n (%)	Median (Range) > 65 yrs	63.5 (32 – 87) 44 (44.0)	62.2 yrs (30 – 84) 46 (45.5)
Gender, n (%)	Male Female	53 (53.0) 47 (47.0)	70 (69.3) 31 (30.7
Race, n (%)	Caucasian/White Asian African/Black Other	85 (85.0) 11 (11.0) 0 4 (4.0)	88 (87.1) 8 (7.9) 2 (2.0) 3 (3.0)
ECOG performance status, n (%)	0 1 2	82 (82.0) 15 (15.0) 3 (3.0)	81 (80.2) 19 (18.8) 1 (1.0)
CTCL subtype, n (%)	Mycosis fungoides Sézary syndrome	80 (80.0) 20 (20.0)	84 (83.2) 17 (16.8)
Disease stage n (%) (Stratum I)	IIB IIIA IIIB IVA1 IVA2 IVB	59 (59.0) 8 (8.0) 7 (7.0) 10 (10.0) 13 (13.0) 3 (3.0)	58 (57.4) 4 (4.0) 4 (4.0) 16 (15.8) 13 (12.9) 6 (5.9)

84.0%

16.0%

81.2%

18.8%

RESMAIN – Patient Characteristics I

Characteristic		Resminostat (N=100)	Placebo (N=101)
Duration of disease, years	Median (Range)	4.50 (0.2 – 34.1)	5.08 (0.6 – 33.1)
Large Cell Trans-formation n (%)	Yes No	24 (24.0) 76 (76.0)	13 (12.9) 88 (87.1)
Last prior systemic therapy n (%)	Bexarotene / other Retinoids Chemotherapy Brentuximab vedotin Total Skin Electron Beam radiation (TSEB) Extracorporeal Photopheresis (ECP) Other	28 (28.0) 21 (21.0) 10 (10.0) 13 (13.0) 6 (6.0) 22 (22.0)	19 (18.8) 26 (25.7) 20 (19.8) 11 (10.9) 6 (5.9) 19 (18.8)
Remission status n (%) (Stratum II)	Complete remission (CR) Partial remission (PR) Stable disease (SD)	14 (14.0) 49 (49.0) } 63.0% 37 (37.0) 37.0%	11 (10.9) 58 (57.4) } 68.3% 32 (31.7) 31.7%
Number of prior treatment lines	Median (Range)	3 (1 – 20)	3 (1 – 21)
Previous AlloSCT, n (%)		1 (1.0)	2 (2.0)

RESMAIN – Primary Endpoint Met

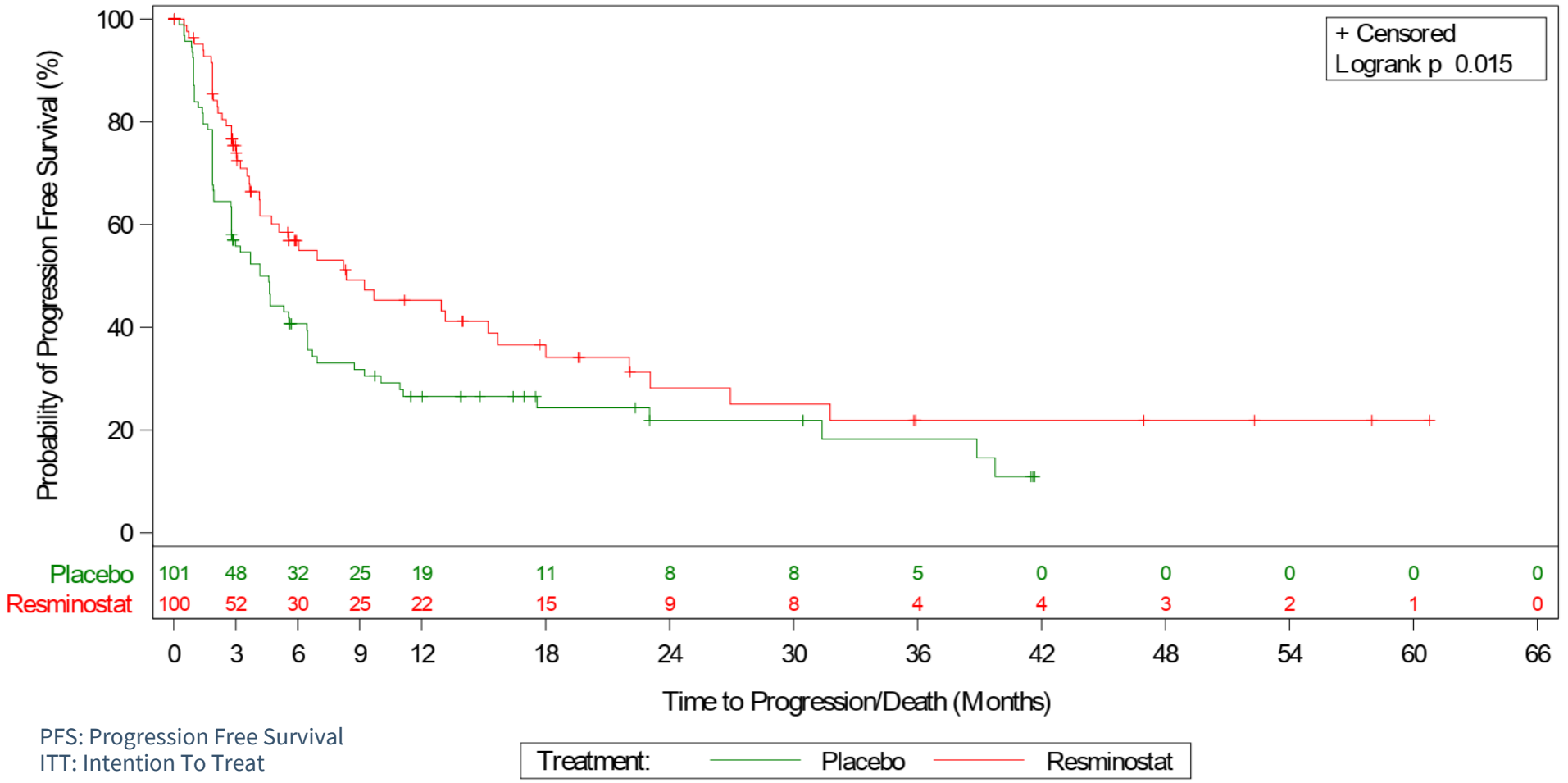
Patient Population	Median PFS, months [95% CI]		p-Value (Stratified log-rank test)	Hazard ratio (Cox proportional hazard model)
	Resminostat	Placebo		
Intention to treat (ITT)	N=100 **8.3** [4.2, 15.7]	N=101 **4.2** [2.8, 6.4]	**0.015**	**0.623** [0.424, 0.916]
Per protocol (PP)	N=90 8.2 [4.2, 15.2]	N=84 3.7 [2.8, 4.7]	0.007	0.585 [0.395, 0.867]

Resminostat significantly improved PFS versus Placebo

- Median PFS: 8.3 vs 4.2 months - nearly a doubling of PFS
- 38% Risk reduction for disease progression

RESMAIN trial proves for the first time that maintenance treatment is beneficial in advanced stage CTCL

Primary Endpoint - PFS (ITT-Population)



PFS: Progression Free Survival
ITT: Intention To Treat

Resminostat – Broadly Superior to Placebo Across Pre-Defined Subgroups

	Sample Size (Events)		Median (months)		Log-rank test	in favor of	in favor of	
	Resminostat	Placebo	Resminostat	Placebo	p-value	Resminostat	Placebo	Hazard Ratio (95% CI)
Overall	100 (47)	101 (70)	8.3	4.2	0.015			0.623 (0.424, 0.916)
Age								
<= 65 years	56 (26)	55 (36)	9.2	4.6	0.213			0.714 (0.423, 1.206)
> 65 years	44 (21)	46 (34)	8.2	4.2	0.108			0.613 (0.335, 1.122)
Sex								
Male	53 (29)	70 (46)	5.1	4.2	0.818			0.944 (0.587, 1.518)
Female	47 (18)	31 (24)	18.0	4.6	0.003			0.367 (0.184, 0.734)
Remission Status								
CR/PR	63 (31)	69 (49)	8.3	4.6	0.182			0.737 (0.467, 1.164)
SD	37 (16)	32 (21)	15.7	2.8	0.016			0.428 (0.213, 0.863)
Disease Type								
Mycosis Fungoides	80 (35)	84 (58)	9.2	4.2	0.022			0.599 (0.386, 0.929)
Sezary Syndrome	20 (12)	17 (12)	5.6	4.2	0.835			0.858 (0.294, 2.507)
Disease Stage								
IIB	59 (26)	58 (39)	9.2	4.6	0.030			0.572 (0.347, 0.943)
III or IV	41 (21)	43 (31)	8.3	3.0	0.128			0.626 (0.336, 1.165)
Disease Stage (as stratified)								
IIB or IIIA/B or IVA1	84 (36)	82 (54)	9.7	4.6	0.081			0.682 (0.446, 1.042)
IVA2/B	16 (11)	19 (16)	5.6	2.8	0.050			0.417 (0.165, 1.056)
Race								
Caucasian/White	85 (40)	88 (58)	8.2	4.7	0.178			0.748 (0.488, 1.144)
Asian	11 (5)	8 (8)	15.7	2.3	0.007			0.136 (0.027, 0.678)
Other	4 (2)	5 (4)	18.0	1.9	0.222			0.263 (0.027, 2.601)
Last Systemic Therapy prior to Study Entry								
Chemotherapy	21 (10)	26 (22)	6.2	3.0	0.106			0.510 (0.223, 1.166)
Bexarotene and other retinoids	28 (12)	19 (13)	12.9	4.2	0.011			0.327 (0.133, 0.805)
Brentuximab	10 (6)	20 (14)	15.7	5.3	0.662			0.758 (0.227, 2.527)
TSEB	13 (7)	11 (5)	9.7	39.8	0.738			1.255 (0.331, 4.749)
Extracorporal Photopheresis	6 (4)	6 (2)	1.9		0.763			1.319 (0.217, 8.009)
Other Medication	22 (8)	19 (14)	8.3	3.2	0.113			0.457 (0.170, 1.223)
Large-cell Transformation								
Yes	24 (14)	13 (10)	8.2	2.8	0.029			0.333 (0.119, 0.929)
No	76 (33)	88 (60)	9.7	4.6	0.022			0.596 (0.382, 0.930)

Log-rank test and Cox proportional Hazard model were stratified for disease stage and remission status.

RESMAIN - Resminostat Extended Time to Next Treatment

Patient Population	Median TTNT, months [95% CI]		p-Value (stratified log-rank test)	Hazard ratio (Cox proportional hazard model)
	Resminostat N=100	Placebo N=101		
Intention to treat (ITT)	**8.8** [7.4, 13.8]	**4.2**[#] [3.0, 6.9]	**0.002**	**0.594** [0.424, 0.916]

[#] Roll over to open-label resminostat was reported as next treatment for patients in the placebo group

TTNT = time to next tretament ;CI =. confidence interval; N = number of patients

Resminostat significantly extended TTNT versus Placebo

- Median TTNT: 8.8 vs 4.2 months

RESMAIN – Further Secondary Endpoints

- Overall Survival
  - No significant difference demonstrated nor expected
- Time to symptom worsening (TTSW pruritus)
  - Not evaluable due to the low number of pruritus events
- Health-related Quality of Life
  - No significant effect of resminostat on VAS itching or Skindex-29 compared to placebo
  - Resminostat had no negative effect on the emotional and social well being subscale of FACT-G.
  - The physical well being subscale of FACT-G was impacted by gastrointestinal side effects (mainly nausea)

RESMAIN – Post-Hoc Analyses

... demonstrated that resminostat

- **Had a positive effect on skin lesions (mSWAT) in a linear mixed model for repeat measures**
  - Estimate of treatment effect (95% CI): -5.392 (-9.925,-0.859); p-value 0.0199
- **Was able to significantly delay the development or worsening of skin tumors compared to placebo**
  - 17 of 100 patients on resminostat vs 42 of 101 on placebo developed skin tumors* or had worsening* of skin tumors
  - Time to tumor event was median 44.2 (23.1 – NE) vs 6.5 (3.7 – NE) months; HR 0.333 [0.186; 0.597], p=0.0001
- **Was able to improve „Total“ PFS** (defined from start of last systemic therapy to first progressive disease)
  - Median (95% CI): **24.2** (15.5 – 33.6) months for resminostat vs 14.9 (12.6 – 19.2) months for placebo; HR 0.745 [0.59 – 1.09]

* Development of skin tumors was defined as any increase of mSWAT „tumor“ in patients with no „tumor“ in mSWAT at baseline; Worsening of skin tumors was defined as any increase of mSWAT „tumor“ in patients with „tumor“ in mSWAT at baseline

RESMAIN – Summary of Adverse Events

Adverse Event Category	Resminosat (N=100) n (%)	Placebo (N=101) n (%)
Adverse Events (AE)	96 (96.0)	83 (82.0)
Treatment-related AE (TRAE) • NCI CTC grade 3 • NCI CTC grade 4	88 (88.0) 24 (24.0) 2 (2.0)	42 (41.6) 3 (3.0) 1 (1.0)
Treatment-related Serious AE (SAE)	11 (11.0)	1 (1.0)
TRAE leading to changes* in study drug treatment	51 (51.0)	12 (11.9)
TRAE leading to study drug withdrawal	8 (8.0)	3 (3.0)
TRAE leading to death	0	0

* Defined as dose reduction, interruption, withdrawal or dose delayed.
N = number of patients, n = number of patients with event; AE = adverse event, TRAE = treatment-related AE, SAE = serious AE

Most Frequent Treatment-Related Adverse Events

Adverse Event	**Resminosat** (N=100) n (%)	**Placebo** (N=101) n (%)
Nausea*	68 (68.0)	6 (5.9)
Diarrhoea	44 (44.0)	9 (8.9)
Vomiting*	32 (32.0)	1 (1.0)
Fatigue	29 (29.0)	14 (13.9)
Dysgeusia	24 (24.0)	2 (2.0)
Decreased appetite	21 (21.0)	2 (2.0)
Muscle spasm	16 (16.0)	4 (4.0)
Headache	16 (16.0)	2 (2.0)
Insomnia	14 (14.0)	1 (1.0)
Abdominal pain upper	13 (13.0)	0 (0.0)
Abdominal pain	11 (11.0)	1 (1.0)
Asthenia	11 (11.0)	3 (3.0)

- The RESMAIN trial confirmed the known safety profile of resminostat
- Side effects were mainly mild to moderate, reversible and manageable*
- **Extensive ECG monitoring** with **central evaluation** did **not indicate an increased risk of QTc prolongation** for resminostat

* Treatment with effective anti-emetics was severely limited in the RESMAIN trial due to their known risk of QTc prolongation

This is expected to change in the future

N = number of patients, n = number of patients with event

Summary

- RESMAIN is the largest randomized controlled maintenance clinical trial in advanced stage CTCL
- Resminostat significantly improved PFS and TTNT vs Placebo (8.3 vs 4.2 and 8.8 vs 4.2 months, respectively)
- Resminostat had no significant effect on VAS itching or Skindex-29
- FACT-G physical well-being subscale was impacted by side effects of resminostat (predominantly nausea)
  - Of note: Treatment with effective anti-emetics was severely limited due to their known risk of QTc prolongation
- Most frequent side effects were nausea, diarrhoea, vomiting, fatigue, dysgeusia and decreased appetite
  - Side effects were mainly mild to moderate, reversible and manageable
  - Extensive ECG monitoring with central evaluation did not indicate an increased risk of QTc prolongation
- Post-Hoc analyses demonstrated that resminostat had a positive effect on skin lesions (mSWAT), was able to significantly delay the development or worsening of skin tumors and showed a remarkable „Total“ PFS of 24.2 months for resminostat

Resminostat is the first drug that showed statistically proven PFS improvement as maintenance treatment in advanced stage CTCL

Thank you very much!

- To all patients and their families
- To all investigators and their site staff
- To the sponsor of the RESMAIN study
  - 4SC AG and their license partner Yakult Honsha Ltd. in Japan
- And to all service providers, who contributed

... to the success of the RESMAIN study!

Thank you!

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