

5TH World Congress of Cutaneous Lymphomas



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

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.

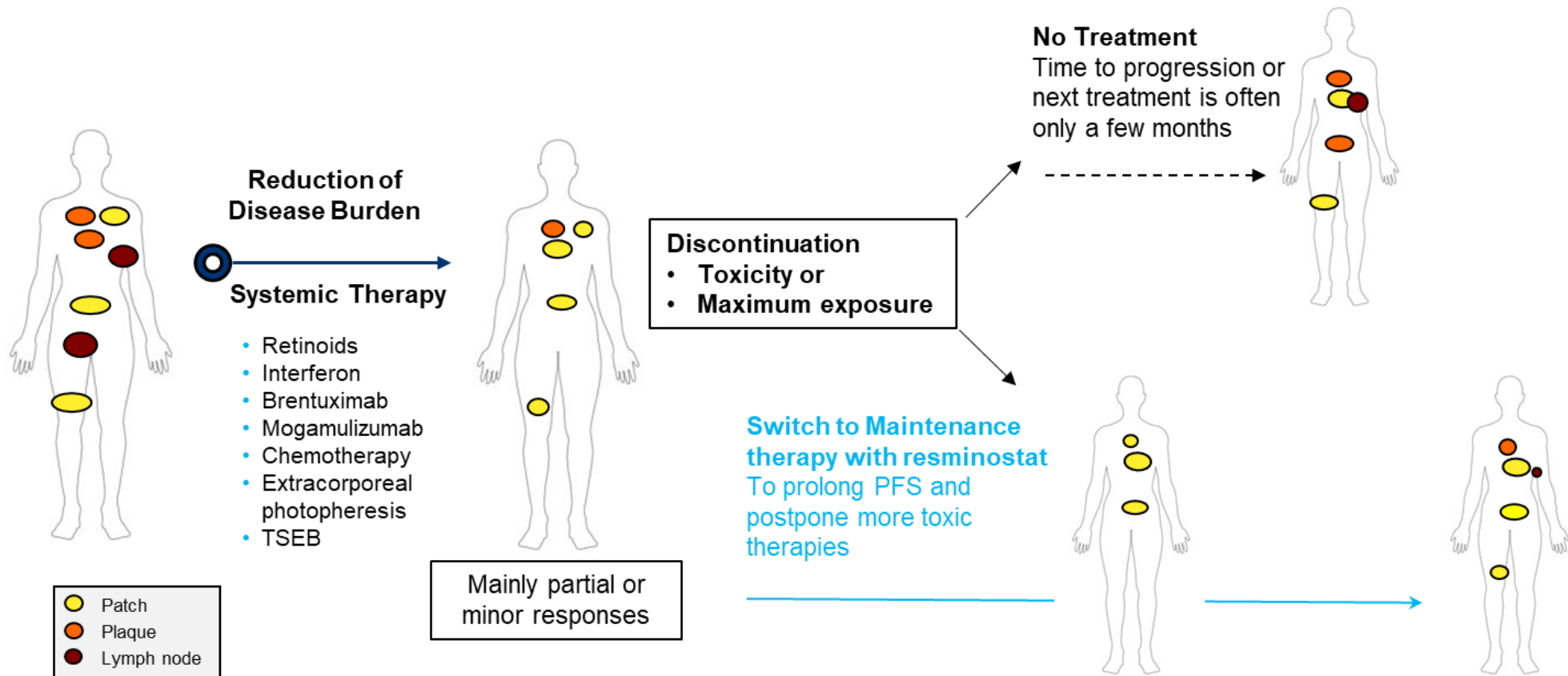
This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

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



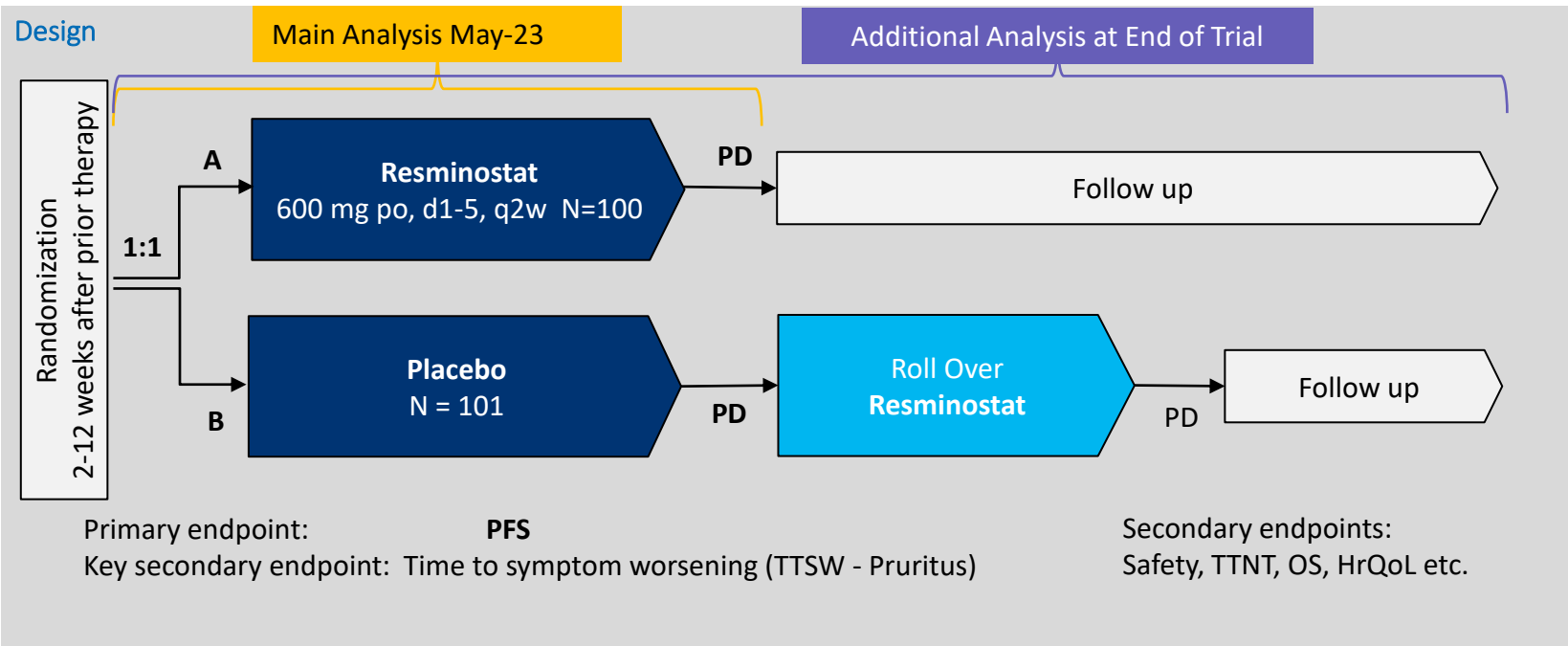
CTCL: Cutaneous T-cell lymphoma, PFS: Progression Free Survival, TSEB: Total Skin Electron Beam Radiation, Images modified according to Stadler & Scarisbrick, Eur J Cancer 2021

RESMAIN – Trial Design

Patients

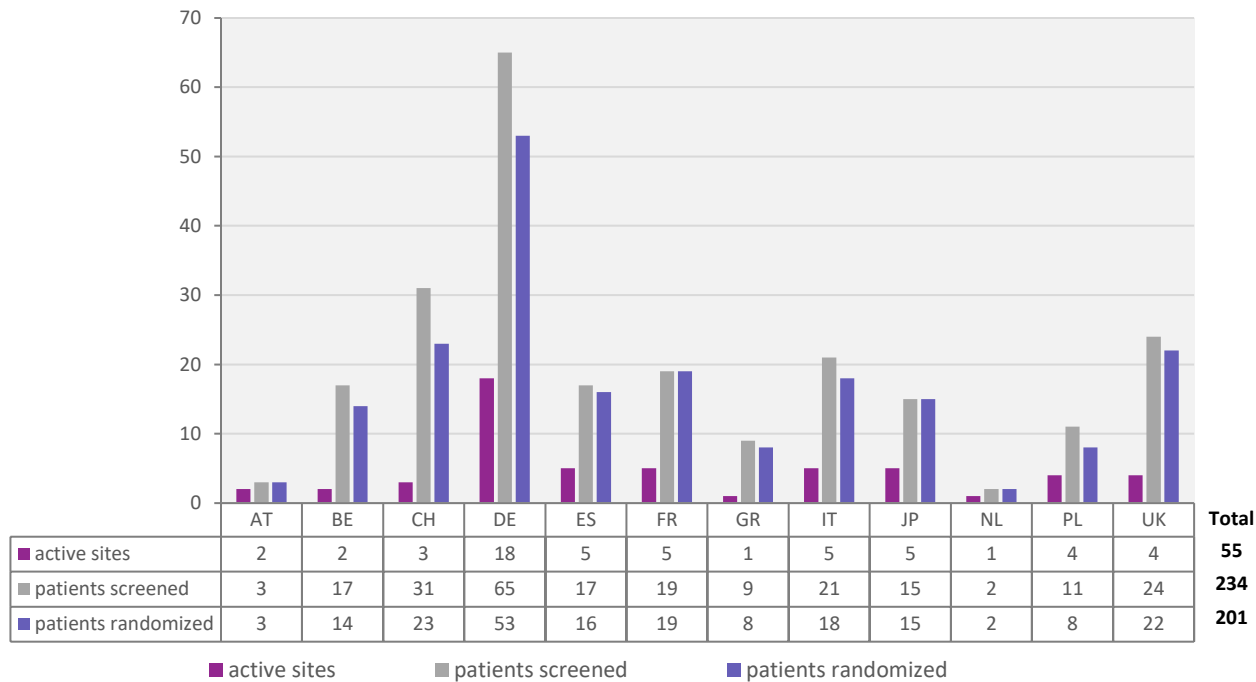
- Mycosis fungoides (stage IIB – IVB) or Sézary Syndrome
- In CR, PR or SD after prior systemic therapy or TSEB

Design



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

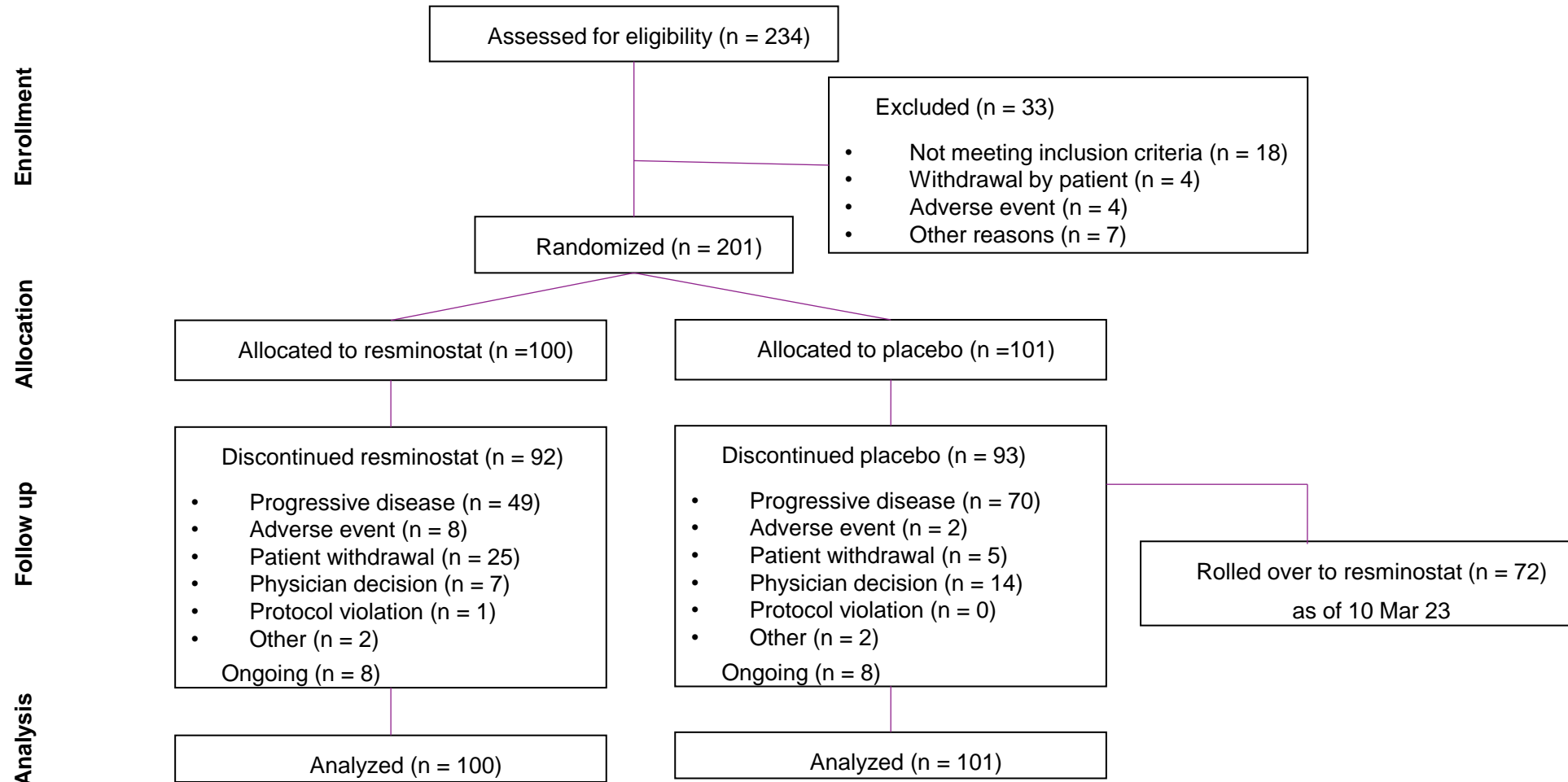


- First patient randomized: Jan 2017
- Last patient randomized: May 2022
- Main analysis data cut-off: 10 Mar 2023
 - 15 patients ongoing (open label)
- Last patient out – Q3 2024

- 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	Median (Range)	63.5 (32 – 87)	62.2 yrs (30 – 84)
Age group, n (%)	> 65 yrs	44 (44.0)	46 (45.5)
Gender, n (%)	Male	53 (53.0)	70 (69.3)
	Female	47 (47.0)	31 (30.7)
Race, n (%)	Caucasian/White	85 (85.0)	88 (87.1)
	Asian	11 (11.0)	8 (7.9)
	African/Black	0	2 (2.0)
	Other	4 (4.0)	3 (3.0)
ECOG performance status, n (%)	0	82 (82.0)	81 (80.2)
	1	15 (15.0)	19 (18.8)
	2	3 (3.0)	1 (1.0)
CTCL subtype, n (%)	Mycosis fungoides	80 (80.0)	84 (83.2)
	Sézary syndrome	20 (20.0)	17 (16.8)
Disease stage n (%)	IIB	59 (59.0)	58 (57.4)
(Stratum I)	IIIA	8 (8.0)	4 (4.0)
	IIIB	7 (7.0)	4 (4.0)
	IVA1	10 (10.0)	16 (15.8)
	IVA2	13 (13.0)	13 (12.9)
	IVB	3 (3.0)	6 (5.9)
		84.0%	81.2%
		16.0%	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	24 (24.0)	13 (12.9)
	No	76 (76.0)	88 (87.1)
Last prior systemic therapy n (%)	Bexarotene / other Retinoids	28 (28.0)	19 (18.8)
	Chemotherapy	21 (21.0)	26 (25.7)
	Brentuximab vedotin	10 (10.0)	20 (19.8)
	Total Skin Electron Beam radiation (TSEB)	13 (13.0)	11 (10.9)
	Extracorporeal Photopheresis (ECP)	6 (6.0)	6 (5.9)
	Other	22 (22.0)	19 (18.8)
Remission status n (%) (Stratum II)	Complete remission (CR)	14 (14.0)	11 (10.9)
	Partial remission (PR)	49 (49.0)	58 (57.4)
	Stable disease (SD)	37 (37.0)	32 (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

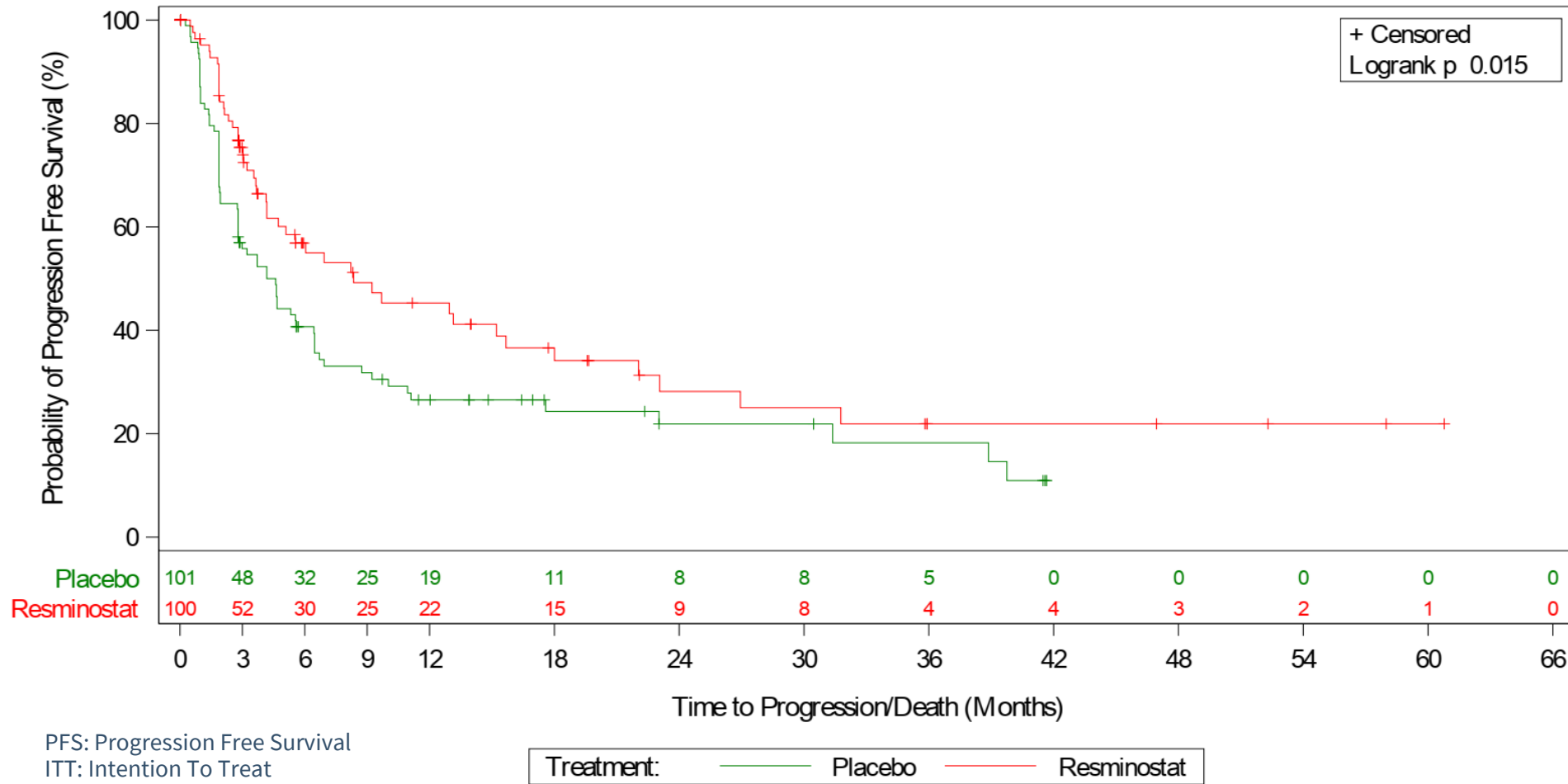
Patient Population	Median PFS, months [95% CI]		p-Value (Stratified log-rank test)	Hazard ratio (Cox proportional hazard model)
	Resminostat	Placebo		
Intention to treat (ITT)	N=100 8.3 [4.2, 15.7]	N=101 4.2 [2.8, 6.4]	0.015	0.623 [0.424, 0.916]
Per protocol (PP)	N=90 8.2 [4.2, 15.2]	N=84 3.7 [2.8, 4.7]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

Resminostat significantly improved PFS versus Placebo

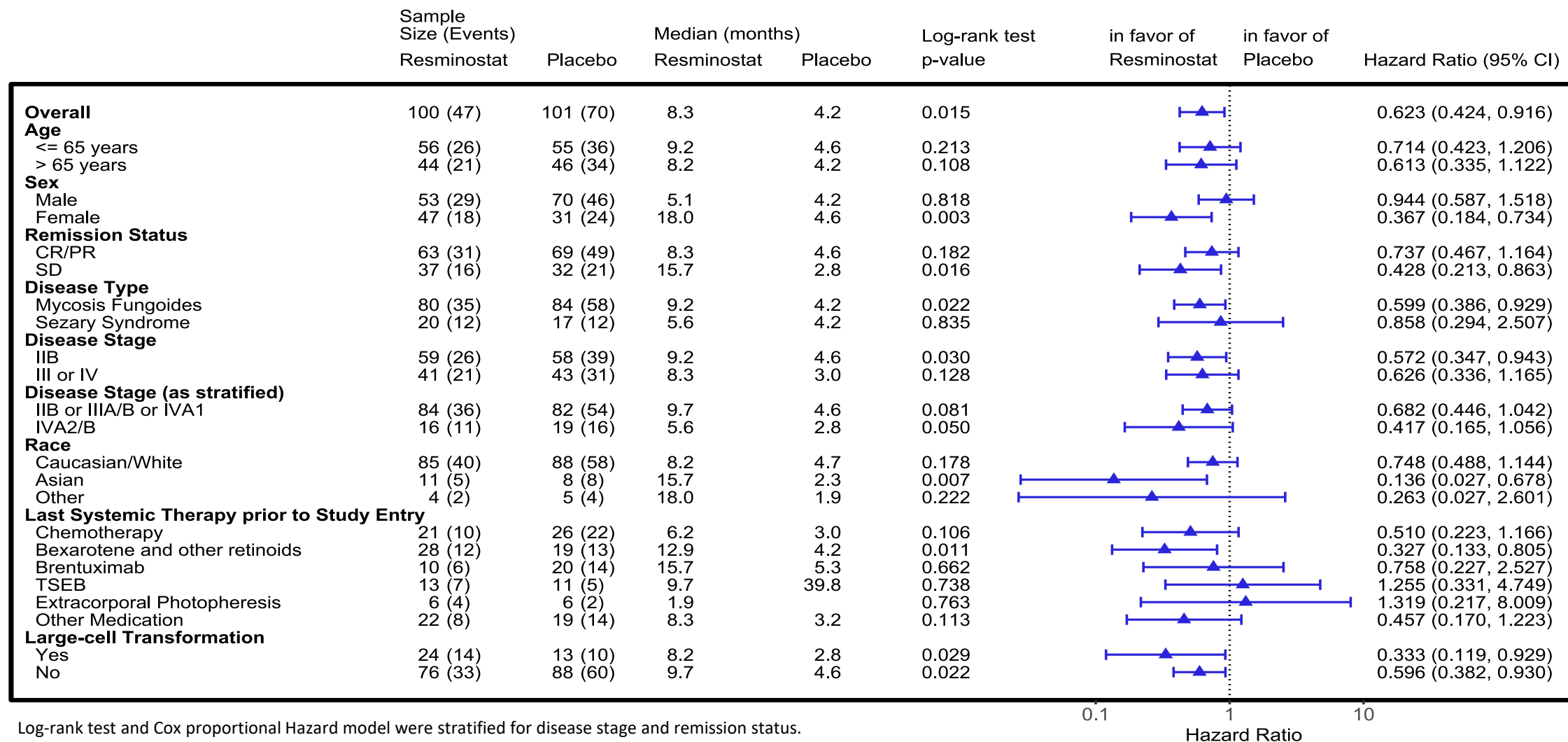
- Median PFS: 8.3 vs 4.2 months - nearly a doubling of PFS
- 38% Risk reduction for disease progression

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

Primary Endpoint - PFS (ITT-Population)



Resminostat – Broadly Superior to Placebo Across Pre-Defined Subgroups



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 treatment ; 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) <ul style="list-style-type: none"> • 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	Resminostat (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

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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!

