Combining the target trial and estimand frameworks: an application using real-world data to contextualize a single-arm trial

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Industry WG on estimands in oncology
ASA NJ Chapter Webinar
December 2nd, 2022

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Introduction

- Randomized controlled trials (RCT) are the gold standard for providing evidence for regulatory approval of new medicines
- Single-arm trials (SAT) considered for regulatory approval when RCTs are infeasible or unethical to conduct
  - Rare diseases
  - Unmet need in last line of therapy with no effective standard of care
  - Highly promising early data can impact ethics / integrity of a RCT
- Real-world data (RWD) may be used as external control to contextualize the single arm trial results
  - Target trial and estimand frameworks are useful tools for causal inference

Clinical context: Single arm pivotal trial

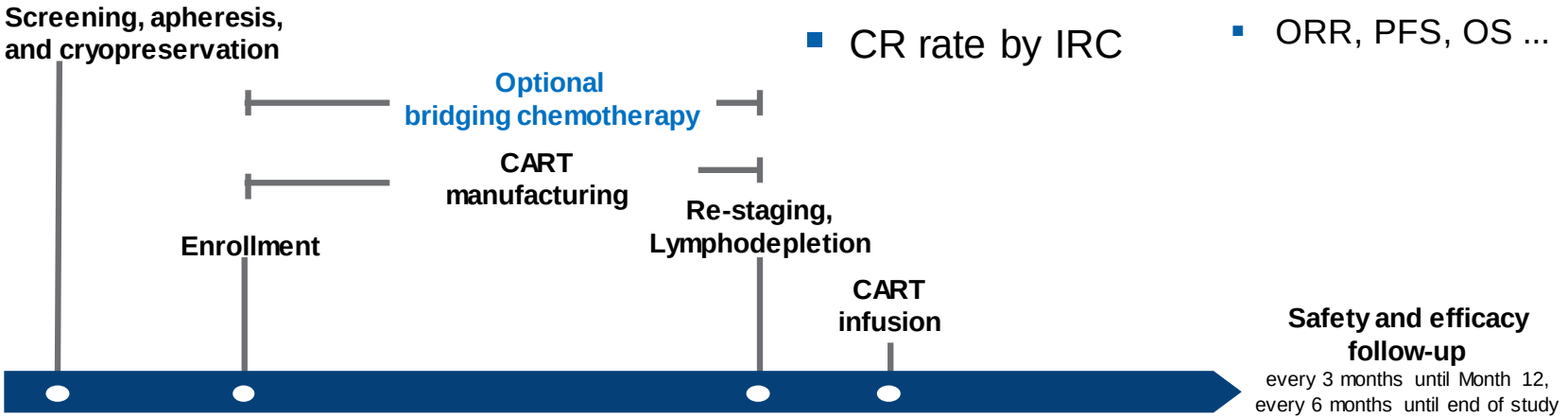
ELARA: A single arm, multi-center, phase II study to determine the efficacy and safety of tisagenlecleucel in adult patients with FL after ≥2 lines of prior therapy

Primary endpoint:

- CR rate by IRC

Secondary endpoints:

- ORR, PFS, OS ...



IRC: independent review committee, CART: chimeric antigen receptor T cell, CR: complete response, ORR: overall response rate, PFS: progression free survival, OS: overall survival

External control requested by HAs

- Need for external control with **patient-level data** highlighted by the Norwegian Health Authority (Tisagenlecleucel rapporteur country) during protocol review:

3 Question #2

Being a single-arm trial, we assume that, prior to any comparative analyses, the external control will be pre-specified and consist of a population (e.g. from registries or historical trials) where there is access to individual patient-level data. Furthermore, the selection criteria of the external control should match with the selection criteria for the patient population proposed in this trial, to make the two populations as similar as possible. If matching on patient characteristics to the

Two sources of real-world data

ReCORD

- a non-interventional retrospective cohort study based on chart review
- Data collection in academic centers in EU and North America by an electronic data collection form (eDCF) via a secure web-based data collection portal

Flatiron

- a non-interventional study utilizing electronic health records from the US Flatiron Health Research Database (FHRD)
- Mostly community-based cancer centers in US

Totality of the data expected to support a comprehensive efficacy assessment of tisagenlecleucel in r/r FL patients

Challenges of using RWD as external control

Bias

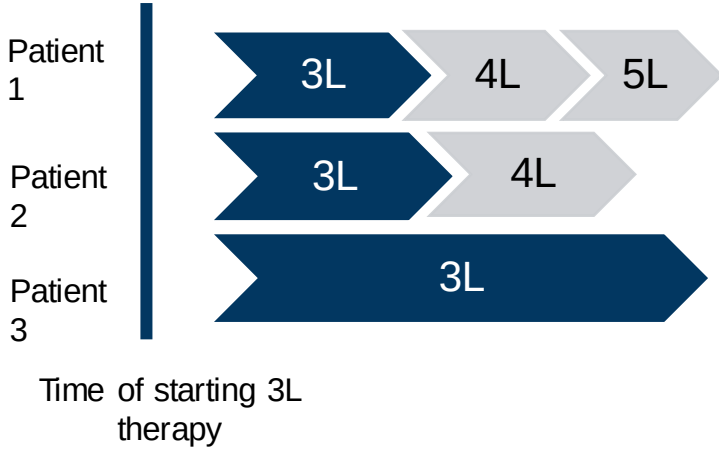
- Baseline confounding
- Selection bias
- Immortal time bias
- Missing data on prognostic factors

Communication

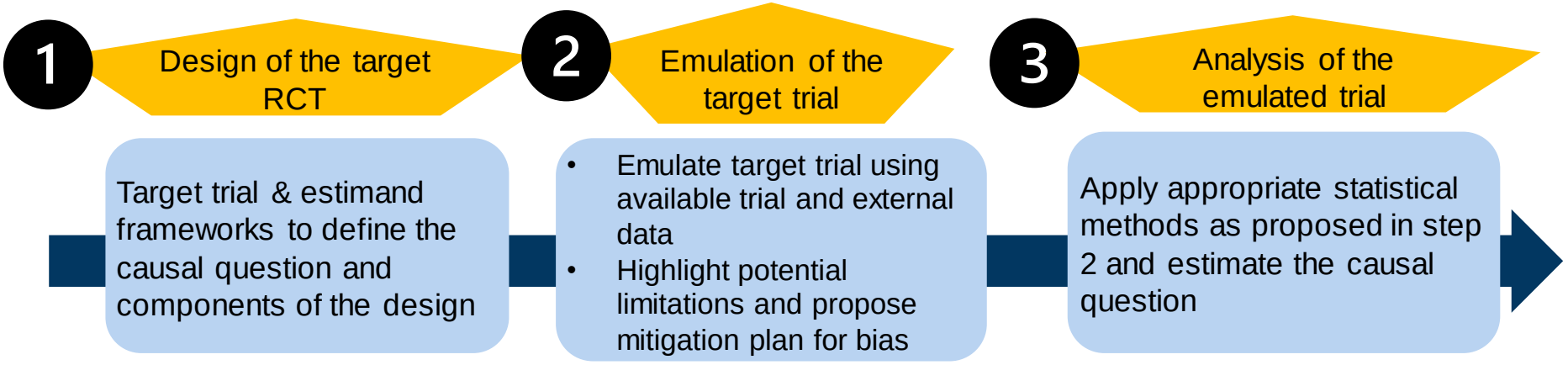
- Transparent discussion from different line functions
- Interpretation of results
- Regulatory agreement and acceptance

Selection of index line

- Patients in external cohort could meet the eligibility of ELARA multiple times



Target trial & Estimand frameworks



- Provides formal frameworks to identify and avoid common methodological pitfalls of study design and statistical analysis
- Facilitates transparent communication about potential limitations

Applying target trial & estimand frameworks

Question: ***What's the treatment effect of prescribing tisagenlecleucel vs SoC in the patient population who participated in the ELARA trial?*** – average treatment effect on treated (ATT)

Component	Target RCT	Emulated trial		Our strategy
		ELARA	ReCORD	
Population /Eligibility criteria	ELARA inclusion/exclusion (I/E) criteria	**Same as target RCT**	ELARA I/E criteria that are feasible to apply retrospectively	Be transparent and summarize all criteria that were not feasible to apply in ReCORD
Treatment/ Treatment strategy	**CAR-T treatment strategy** vs **Current SoC**	**CAR-T treatment strategy as target RCT**	Current SoC	
Treatment assignment	Block randomized to either CAR-T arm or SoC arm	**Emulate simple randomization**		Propensity score weighting method to mitigate confounding bias Worst-case scenario as sensitivity analysis
Variables	OS is time to death from any cause	**Same as in target RCT**		
	CR best overall response of complete remission per Lugano criteria	**Same as target RCT**	CR and progression based on real-world response criteria	Subgroup analysis ≥ 2014 was conducted as year of introduction of Lugano response criteria
	PFS is time to first progression or death from any cause	**Same as target RCT**	Progression dates unavailable for many patients	**To consider new anticancer therapy as PFS event** and pre-specify in SAP

Applying target trial & estimand frameworks

Component	Target RCT	Emulated trial		Our strategy
		ELARA	ReCORD	
Start of follow-up	Start: date of randomization	Start: enrollment, regarded as prescription date	Start: start date of SoC treatment • Multiple line of therapy	One eligible LoT per patient in ReCORD is systematically selected based on the highest propensity score to be in ELARA
Intercurrent event(s)	**IE: new anti-cancer therapy** OS: Treatment policy strategy CR: ICE reflected in Variable PFS: Hypothetical strategy	Same as target RCT for OS and CR PFS: Composite strategy		✓
Causal effect	**ATT:** Effect of prescribing tisagenlecleucel vs SoC in patients meeting ELARA inclusion/exclusion criteria	Same as in target RCT		✓
Summary measure	Binary endpoints: Difference in marginal response probabilities on CAR-T vs SoC Time-to-event (TTE) endpoints: Marginal HR	Same as in target RCT		✓
Analysis	Binary: Difference in response rates TTE: Cox regression	Binary: Difference in weighted proportions of responders TTE: HR obtained from a weighted Cox regression		✓

Utilize Propensity Score to Select LoT

Step1. Estimation of propensity scores per patient per LoT
(as each patient has new set of 'baseline' covariates at start of each LOT)

Step 2. Selection of one eligible LOT per patient in external cohort
- The **highest** propensity score per patient is chosen, i.e. LoT where the patient is mostly closely aligned with that ELARA population.

External Cohort

Real-world patient ID	LoT where SOC is given	Propensity score
1	3	0.67
1	4	0.49
1	5	0.68
2	4	0.56
2	5	0.75
3	3	0.77
....	....	....

External Cohort

Real-world patient ID	LoT where SOC is given	Propensity score
1	3	0.67
1	4	0.49
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2	4	0.56
2	5	0.75
3	3	0.77
....	....	....

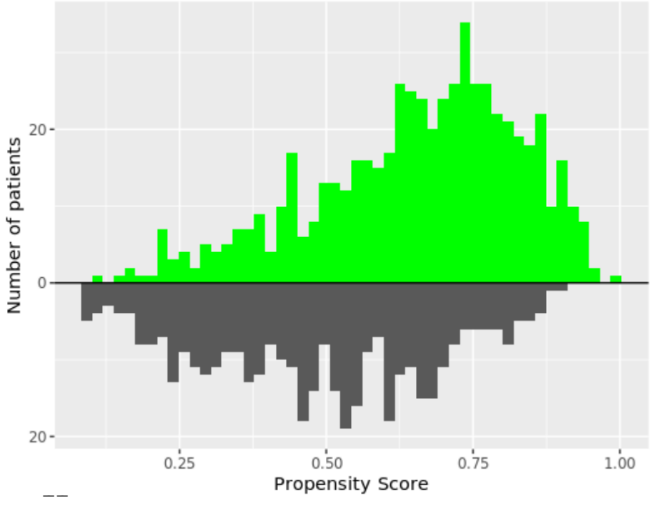
Hampson LV et al. https://arxiv.org/abs/2202.11968

Utilize PS to mitigate confounding bias

- **ATT: "What is the effect of prescribing tisagenlecleucel (vs SoC) on efficacy in the population who participated in ELARA?"**

→ **Weight each patient in the external cohort based on their odds of being in ELARA**

- Assign all ELARA patients a weight of 1, as they are in the trial
- Assign external cohort patient i a weight of $ps_i/(1-ps_i)$



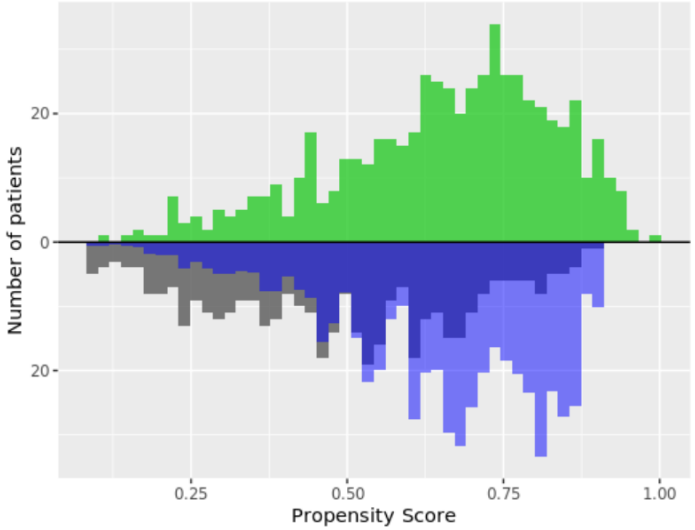


Illustration purpose only
not from real data

Treatment arm (original)

Control arm (original)

Control arm (weighted)

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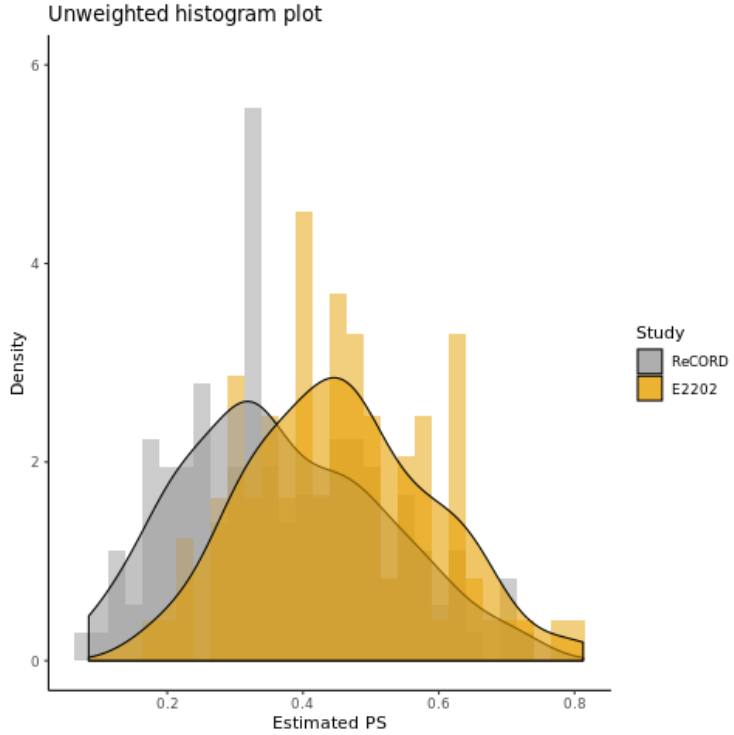
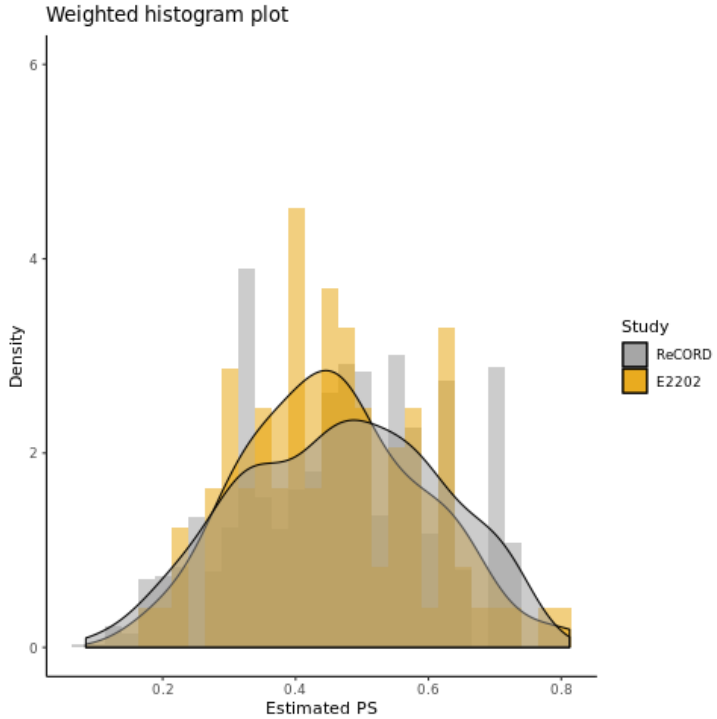
Baseline covariates balance check

		Before Weighting		After Weighting	
	ELARA (N=97)	ReCORD (N=143)	|SMD|	ReCORD (N=99)	|SMD|
Age, median(range) ≥65y	58 (29-73) 25%	60 (25-86) 38%	0.325 0.284	56 (25-86) 23%	0.038 0.034
Male	66%	57%	0.178	69%	0.063
Region Europe	**45%**	**63%**	**0.358**	**42%**	**0.072**
Prior transplant	**37%**	**37%**	**0.001**	**37%**	**0.013**
>4 prior lines median (range)	**29% 4 (2-13)**	**23% 3 (2-10)**	**0.132 0.117**	**29% 4 (2-10)**	**0.011 0.104**
Stage at diagnosis: III/IV	22% / 59%	18% / 66%	0.087/0.144	26% / 60%	0.095/0.026
Months from diagnosis, median (range)	**66 (6-355)**	**62 (3-255)**	**0.099**	**70 (3-255)**	**0.005**
>4 nodal involvement	**60%**	**48%**	**0.233**	**62%**	**0.035**
Double refractory	68%	68%	0.004	69%	0.01
POD24	63%	60%	0.056	63%	0.009

Propensity score estimates before/after weighting





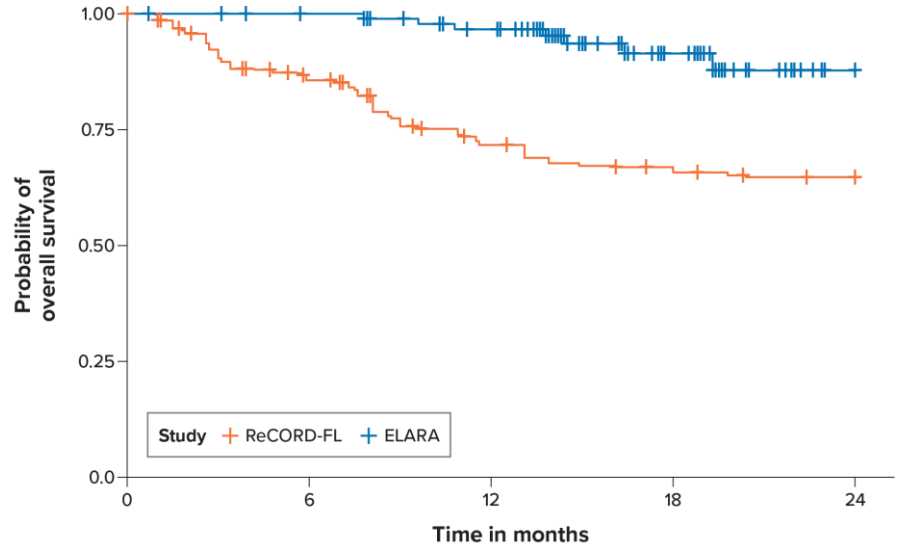
Results: using the ReCORD data as the external control

	ELARA N = 97	Before Weighting ReCORD N = 143	After Weighting ReCORD N = 99*
Complete response (CR)			
CR rate (95% CI)	69.1 (59.8-78.3)	37.3 (26.4-48.3)	30.5 (13.1-47.8)
Difference in CR (95% CI)		31.8 (18.1-45.3)	38.6 (19.3-57.9)
PFS considering new anticancer therapy as event			
HR (from Cox regression) 95% CI		0.69 (0.41,0.97)	0.60 (0.34, 0.86)
Overall survival			
HR (from Cox regression) 95% CI		0.25 (0.03, 0.46)	0.20 (0.02, 0.38)

* The effective sample size was 95.

Kaplan-Meier plots for ELARA vs ReCORD after weighting

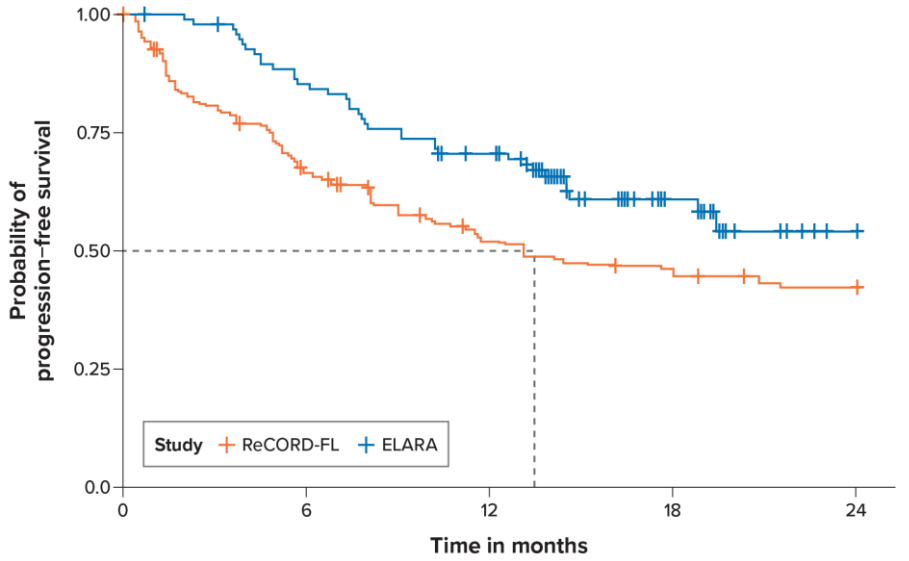
Overall survival



Number at risk

ReCORD-FL	99	79	60	54	50
ELARA	97	93	83	34	2

PFS considering new anticancer therapy as event



Number at risk

ReCORD-FL	99	64	46	40	35
ELARA	97	81	64	23	1

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Regulatory interactions and outcome

HA	Interactions/ Outcome
EMA	• EMA Rapporteur asked for external comparator during the protocol review in 2018 • Scientific Advice received on proposed analysis plan and target • Positive CHMP opinion in March 2022, RWE contributed to contextualization of results • Tisageneleucel approved in r/r Follicular Lymphoma in April 2022 – RWE data not accepted for inclusion in the EU label – RWE data is reflected in EPAR after approval • Target trial and estimand frameworks facilitated the transparent and constructed discussions
FDA	• Tisageneleucel approved in r/r Follicular Lymphoma based on ELARA trial • Considered SAT alone sufficient for benefit-risk assessment in this setting and did not indicate any potential value of RWE submission
HTA	• HTA submissions using RWE ongoing

EPAR: European Public Assessment report, HTA: Health Technology Assessment

Acknowledgements

- Lisa Hampson
- Evgeny Degtyarev
- Aiesha Zia
- Yanni Hao
- Jie Zhang
- Miriam Fuchs
- Ladislas, Mireille
- Masood, Aisha
- Bharani Bharani-Dharan
- Antonella Maniero

Thank you

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