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SAKK 17/16: LURBINECTEDIN AS SECOND OR THIRD LINE PALLIATIVE CHEMOTHERAPY IN MALIGNANT PLEURAL MESOTHELIOMA (MPM): A MULTI-CENTER, SINGLE-ARM PHASE II TRIAL.

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DISCLOSURE SLIDE

Advisory Board / travel grant:

PharmaMar

Pierre Fabre

BMS

MSD

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Merck-Serono

BACKGROUND

- **Incidence** of MPM is expected to **rise** in the next few years[1]
- Platinum-pemetrexed (+/- Bev) tx standard first-line treatment→ pts ultimately progress[2]
- **No standard second-line** therapy exists[3]
    1. Mostly used: vinorelbine and gemcitabine
    2. Median PFS: <2-3mo; median OS<9mo

- Plethora of **trials failed**: "…there has been no relevant improvement in second- and beyond line treatment in mesothelioma from 2005 to 2017…" (Petrelli et al., 2018)[4]

- **High unmet medical need for novel treatments in progressive MPM**

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[1]Robinson et al., Lancet, 2005; [2]Baas et al., Ann Oncol, 2015;
[3]Ceresoli et al., Cancer Treat Rev, 2015; [4]Petrelli et al., Respir Med, 2018

BACKGROUND

- Lurbinectedin is a new molecule with a dual function[1]:
  1. Binds to the DNA in regulatory regions, evicting oncogenic transcription factors and inhibiting their transcriptional program
  2. modulates the transcriptional program of monocytes/ TAMs

- Tested in several Phase I-III clinical trials with promising activity (eg. SCLC)[2]

- Single progressive MPM pts treated in Phase I trial(s)[3]
  1. Acceptable tolerability; PFS ranged from 3 to >8 months

→ **Efficacy and safety of lurbinectedin in progressive MPM in a Phase II trial**

[1]Santamaria et al., Mol Cancer Ther, 2016; [2]Paz-Ares et al., ASCO, 2019;
[3]Metaxas et al., Lung Cancer, 2017

PATIENTS AND DESIGN

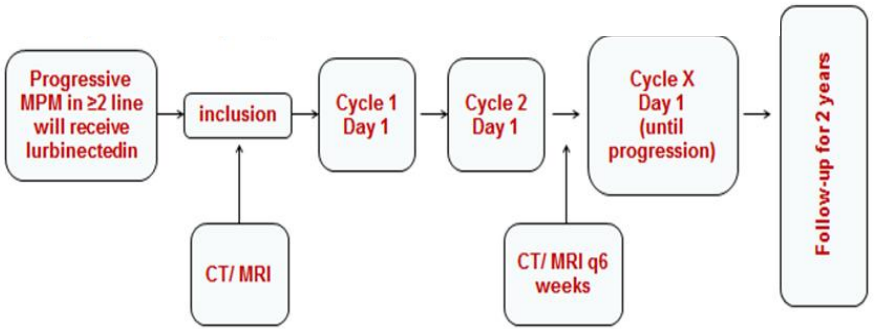
INCLUSION CRITERIA

- Histologically or cytologically confirmed MPM
- Progression on previous platinum-pemetrexed
- One additional line of **immunotherapy** allowed
- ECOG 0-1, adequate bone marrow and chemistry

EXCLUSION CRITERIA

- >1 prior chemotherapy lines
- CNS disease
- Prior malignancy
- Grade ≥2 AEs on prior treatment

- Prospective 2-stage single-arm open-label multicenter phase II trial
- Lurbinectedin 3.2mg/m^2 i.v. q3 weeks (one cycle) until progression, unacceptable toxicity or patient's withdrawal



STATISTICS

Primary endpoint:
Progression-free survival (PFS) at 12 weeks (PFS12wks)

Secondary endpoints:
PFS
Overall survival (OS)
Adverse events (as per CTCAE v4.03).

Sample size calculation:

- Null hypothesis: PFS12wks: p0 ≤ 35% (<21/42 pts reach this time point → equivalent to median PFS: 2.0mo)
- Alternative hypothesis: PFS12wks: p1 ≥ 55% (≥21/42 pts reach this time point → equivalent to median PFS: 3.5mo)
- Simon's two stage design, first stage: 7/21 pts reach PFS12wks
- Total 42 pts needed for a type I error: 0.05, power: 0.8

RESULTS: BASELINE CHARACTERISTICS

Characteristics		N=42 (100%)
Median age (range), years		68 (52,84)
Sex (female/ male)		7 (17%) / 35 (83%)
ECOG perfomance status	0	20 (48%)
	1	22 (52%)
Stage[1], initial diagnosis	I-II	10 (24%)
	III-IV	31 (76%)
Histology	epithelioid	33 (79%)
	biphasic	4 (9%)
	sarcomatoid	5 (12%)

Characteristics (cont.)	N=42 (100%)
Prior tumor surgery: Yes / No	20 (47.6%) / 22 (52.4%)
Prior radiotherapy: Yes / No	15 (35.7%) / 27 (64.3%)
Time to progression[2] <6 months / ≥ 6 months	14 (33.3%) / 28 (66.7%)

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[1]: one information was missing; [2:] on prior, platinum-based, chemotherapy

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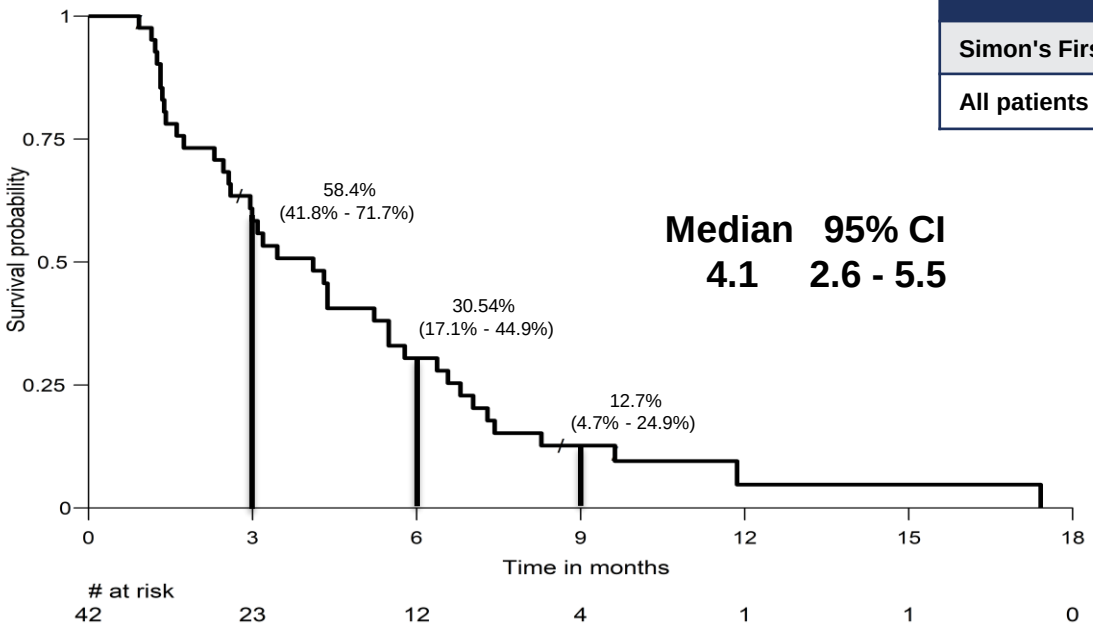
RESULTS: TREATMENT OVERVIEW

N=42	
Data downloaded on	21st August 2019
Follow-up, median (95% CI)	14.9mo (10.6mo - 18.6mo)
Cycles administered, median (range)	5 (1 - 22)
Duration of treatment, median (range)	98 days (22 - 525)
Best overal response	CR: 1 / PR: 1 / SD: 20
Treatment ongoing	1 pt
Treatment discontinued	41 pts
Reason for discontinuation	
Progressive disease	32 pts
Other*	9 pts
Toxicity	0 pts

*patient's decision, physician's decision,

RESULTS: PFS



PFS12wks	N (%)
Simon's First-stage	11/21
All patients	**22/42 (52.4%)** (90%CI: 38.7%-63.5%)

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Duration of disease control (n=22; median)	**6.6mo 95% CI (5.2mo - 7.4mo)**

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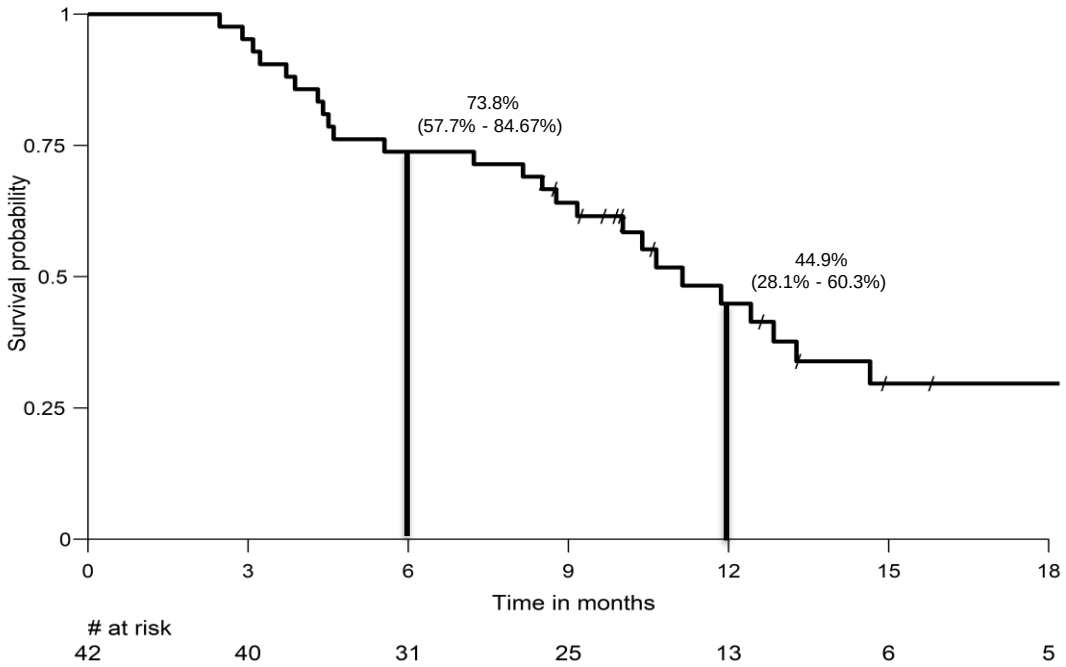
RESULTS: OS

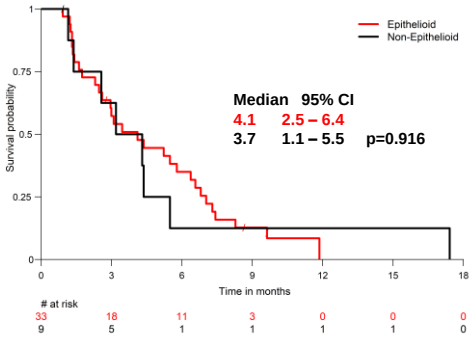


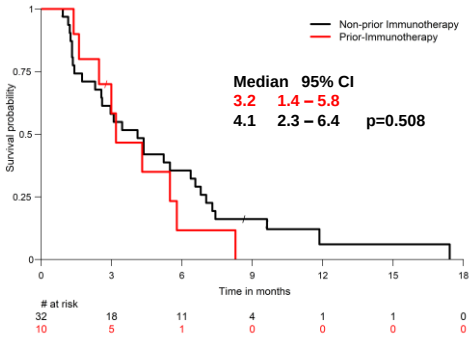
	N=42	
No of events (death)	n	26

Median	95% CI
11.1	8.8 – 14.7

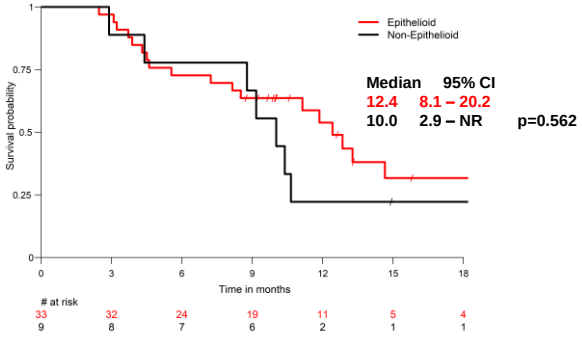
RESULTS: ROLE OF HISTOLOGY AND PRIOR IMMUNOTHERAPY

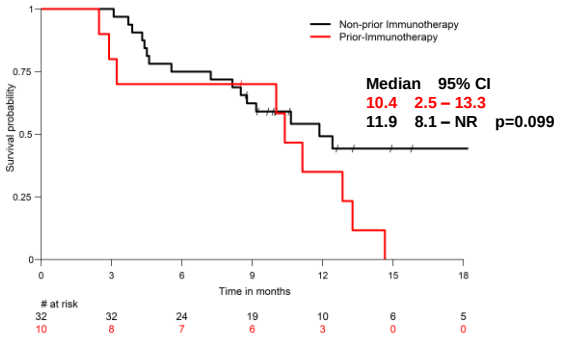
Progression-free survival





Overall survival





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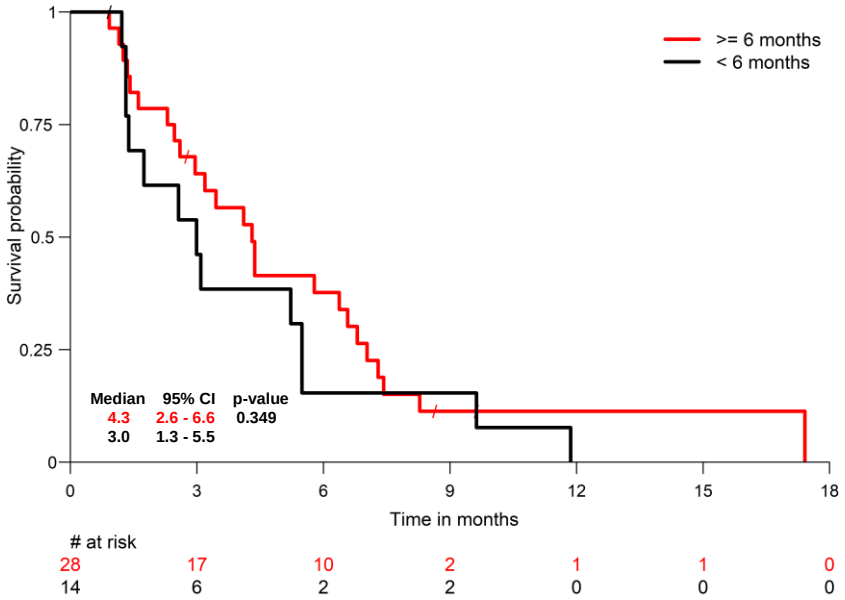
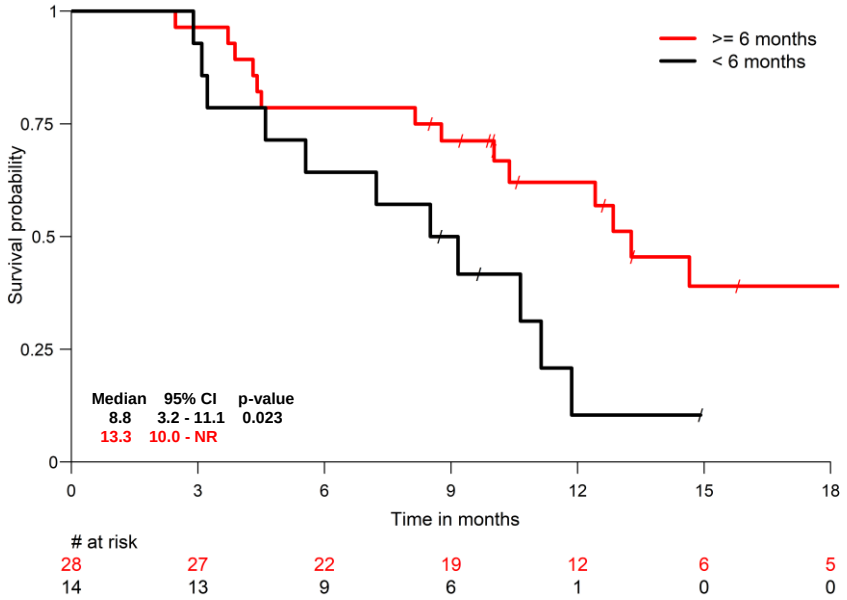
RESULTS: ROLE OF TIME OF PROGRESSION ON PLATINUM-PEMETREXED

Progression-free survival



Overall survival



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RESULTS: TOXICITY

Toxicity, n(%)	All grades	Grade 1-2	Grade 3-4
AEs	42 (100%)	10 (23.8%)	32 (76.2%)
Treatment-related AEs[1, 2]	38 (90.5%)	18 (42.9)	20 (47.6%)
Neutropenia	11 (26.2%)	1 (2.4%)	10 (23.8%)
Febrile neutropenia	4 (9.5%)		4 (9.5%)
Anemia	10 (23.8%)	7 (16.7%)	3 (7.1%)
Thrombopenia	6 (14.4%)	3 (7.2%)	3 (7.2%)
Hepatotoxicity[3]	20 (47.6%)	20 (47.6%)	0 (0%)
Renal toxicity	2 (4.8%)	2 (4.8%)	0 (0%)
Fatigue	25 (59.6%)	18 (42.9%)	7 (16.7%)
Anorexia	9 (21.4%)	7 (16.7%)	2 (4.8%)
Nausea	22 (52.4%)	20 (47.6%)	2 (4.8%)
Vomiting	11 (26.2%)	9 (21.4%)	2 (4.8%)
Diarrhoa	3 (7.1%)	3 (7.1%)	0 (0%)

[1]: 4 pts had no treatment-related AEs; [2]: no grade 5 toxicity
[3]: transaminases, γGT, ALP, bilirubin

CONCLUSIONS

- Trial showed **activity of lurbinectedin in progressive MPM**
- **Toxicity** was **acceptable**
- Lurbinectedin works **independently of histology** or prior **immunotherapy**
- **Both "slow" and "fast" progressive pts** on platinum-pemetrexed benefit respectively from lurbinectedin
- Our data support evaluation of lurbinectedin in a randomized, **Phase III trial**

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