SARCOMA connect

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MEETING SUMMARY
ESMO 2019, Barcelona, Spain

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SARCOMA UPDATE

DISCLAIMER

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TOP 3 HIGH-IMPACT SARCOMA PRESENTATIONS AT ESMO 2019

INVICTUS: A PHASE 3 STUDY TO ASSESS THE SAFETY & EFFICACY OF RIPRETINIB VS PLACEBO AS ⩾4TH LINE THERAPY IN PATIENTS WITH ADVANCED GIST WHO HAVE RECEIVED TREATMENT WITH PRIOR ANTICANCER THERAPIES

von Mehren M, et al. ESMO 2019 Abstract #LBA87

GIST, gastrointestinal stromal tumour

BACKGROUND

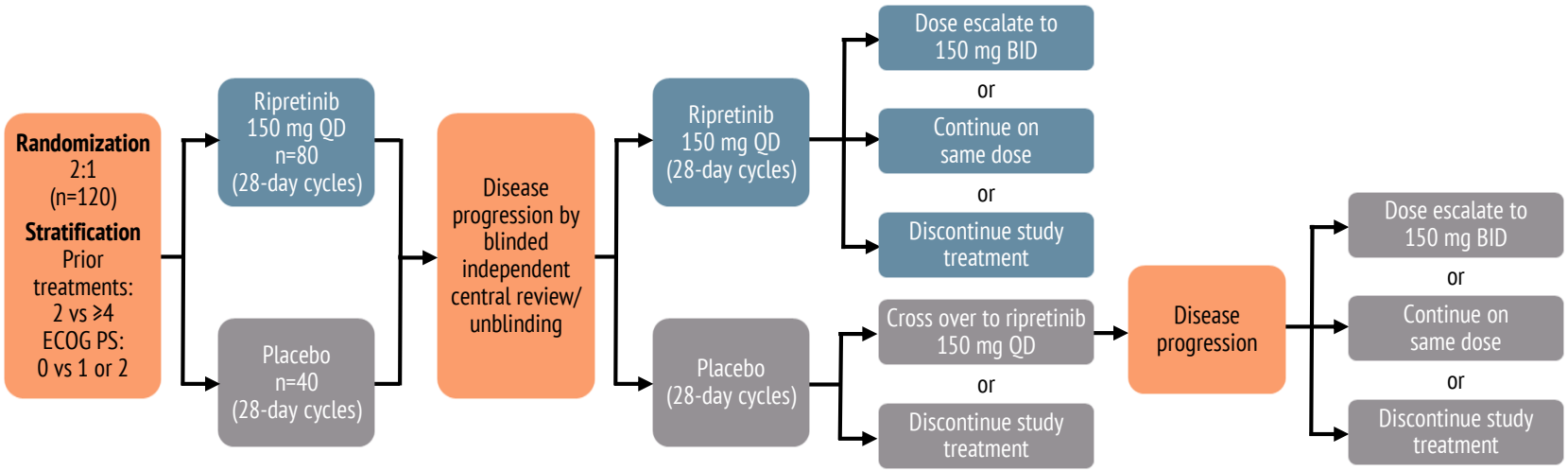
- **GIST** is a rare sarcoma accounting for **1-2% of GI malignancies**[1]
- There are **no 4th line therapies available to treat GIST** patients
- Primary **mutations in KIT or PDGFRA occur in 85-90% of patients with GIST**[2]
- **Ripretinib** is a switch-control kinase inhibitor that broadly **inhibits KIT- and PDGFRA-mutated kinases** by regulating the kinase switch pocket and activation loop[3]
- INVICTUS investigated the effect of ripretinib versus placebo as ⩾4th line therapy in advanced GIST patients[4]

GI, gastrointestinal; GIST, gastrointestinal stromal tumour

1. Parab TM, et al. J Gastrointest Oncol 2019: 10: 144-54; 2. Hsueh YS, et al. PLOS One 2013: e65762; 3. Smith BD, et al. Cancer Cell 2019; 35:738-51; 4. von Mehren M, et al. Presented at ESMO 2019 Abstract #LBA87.

INVICTUS STUDY DESIGN

RIPRETINIB AS ⩾4TH LINE THERAPY IN PATIENTS WITH ADVANCED GIST



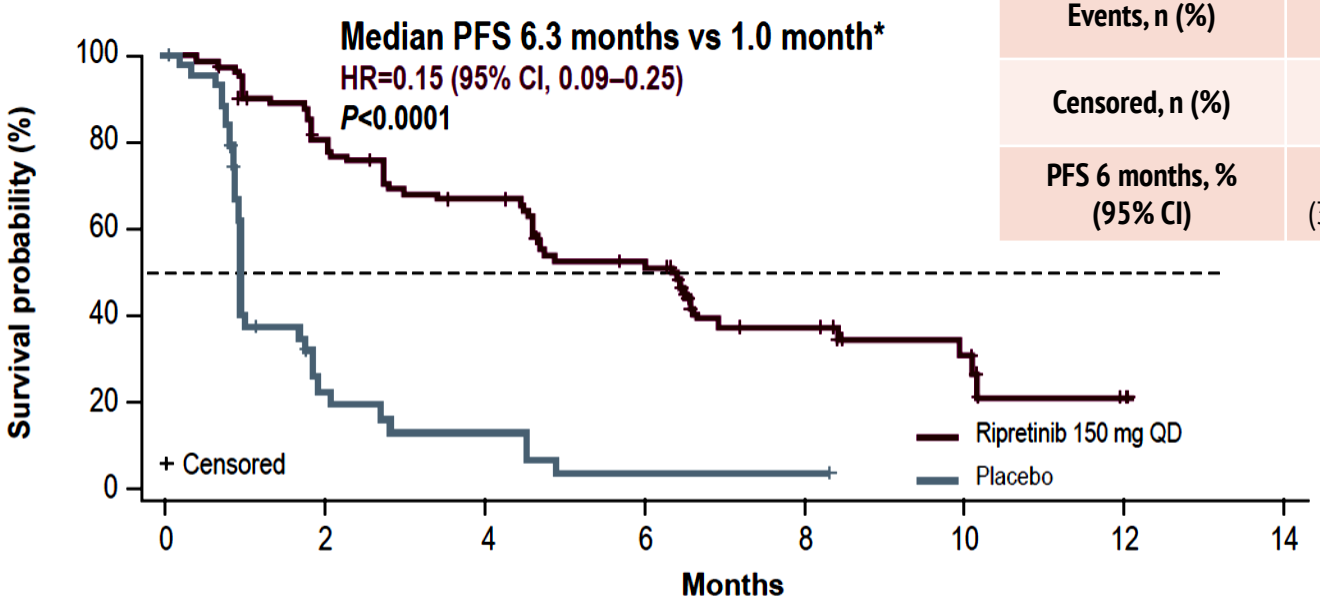
Primary endpoint	Select secondary endpoints
PFS (per modified RECIST based on **Blinded Independent Central Review** [BICR])	• **Objective response rate (ORR)** assessed by BICR (Key endpoint) • **Overall survival (OS)**

BICR, blinded independent central review; ECOG PS, eastern cooperative oncology group performance status; GIST, gastrointestinal stromal tumour; ORR, objective response rate; OS, overall survival; PFS, progression free survival;
von Mehren M, et al. Presented at ESMO 2019 Abstract #LBA87.

INVICTUS PRIMARY ENDPOINT RESULTS

PROGRESSION FREE SURVIVAL

	Ripretinib (N=85)	Placebo (N=44)
Events, n (%)	51 (60.0)	37 (84.1)
Censored, n (%)	34 (40.0)	7 (15.9)
PFS 6 months, % (95% CI)	51 (39.4-61.4)	3.2 (0.2-13.8)



Number of patients at risk:

Ripretinib 150 mg QD	85	64	52	37	18	8	1	0
Placebo	44	7	4	1	1	0		

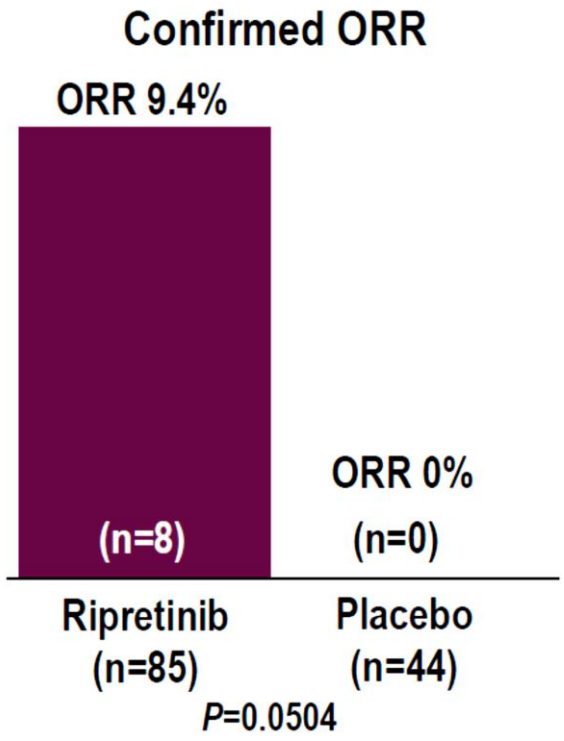
- 85% risk reduction of disease progression or death with ripretinib compared with placebo
- PFS benefit observed in all assessed patient subgroups with ripretinib

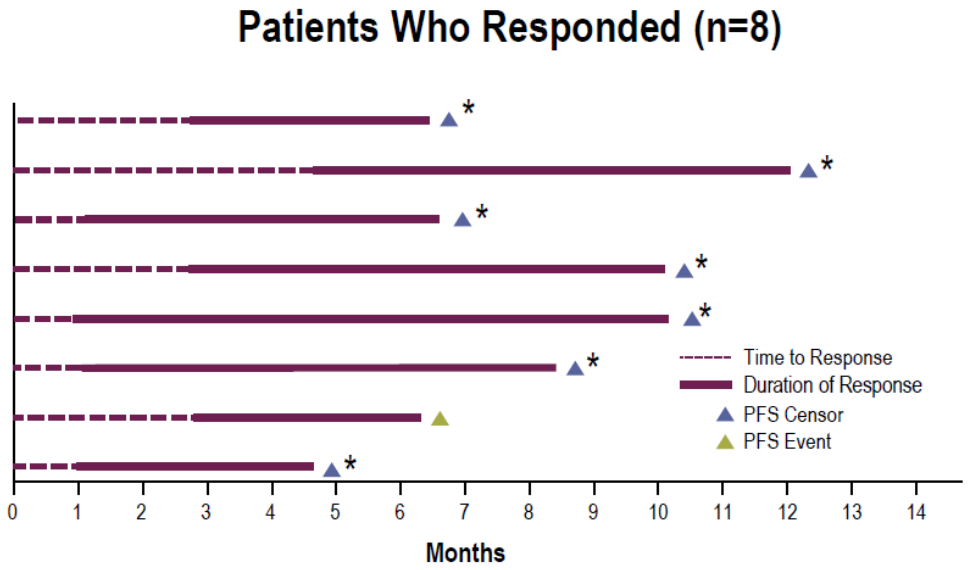
CI, confidence interval; HR, hazard ratio; PFS, progression free survival

von Mehren M, et al. Presented at ESMO 2019 Abstract #LBA87.

INVICTUS SECONDARY ENDPOINT RESULTS

OBJECTIVE RESPONSE RATE





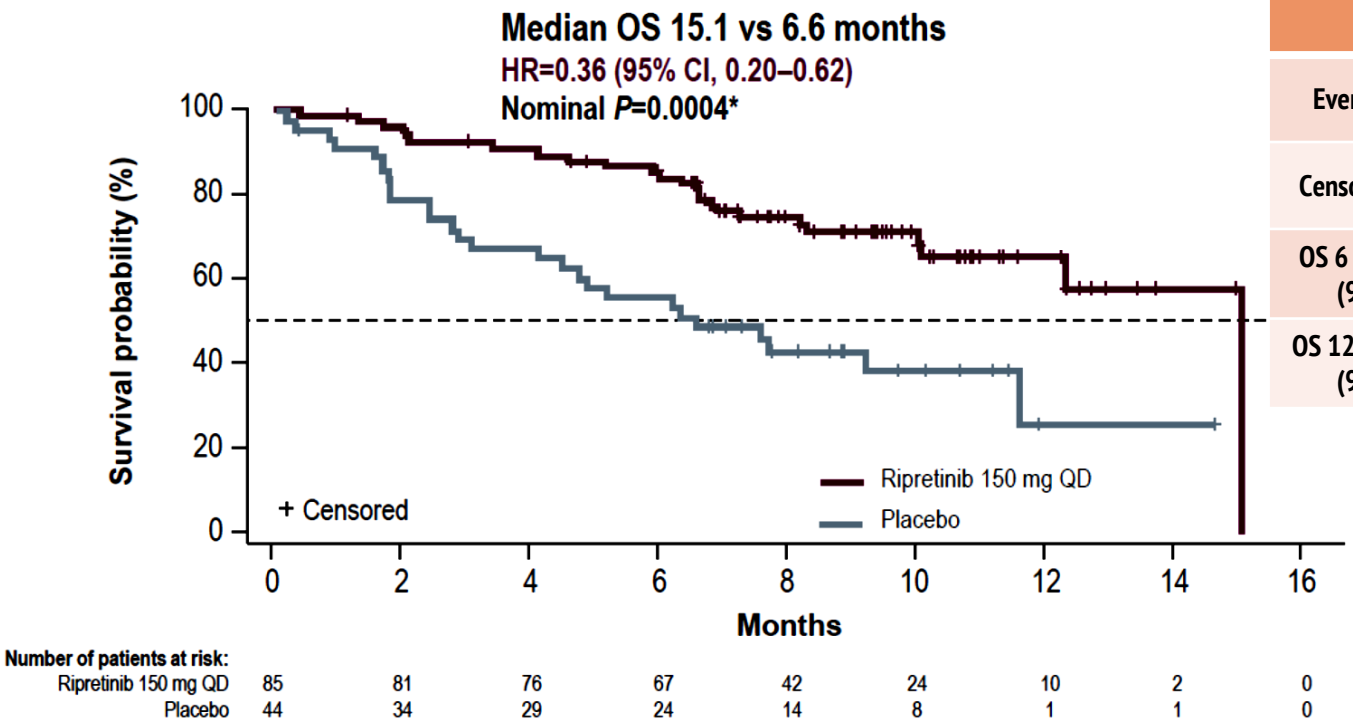
- Durable response was achieved with ripretinib
  - Median duration of response not yet reached
  - *7/8 ripretinib responders were still responding as of data cut-off
  - All responders had partial responses

ORR, objective response rate; PFS, progression free survival

von Mehren M, et al. Presented at ESMO 2019 Abstract #LBA87.

INVICTUS SECONDARY ENDPOINT RESULTS

OVERALL SURVIVAL



	Ripretinib (N=85)	Placebo (N=44)
Events, n (%)	26 (30.6)	26 (59.1)
Censored, n (%)	59 (69.4)	18 (40.9)
OS 6 months, % (95% CI)	84.3 (74.5-90.6)	55.9 (39.9-69.2)
OS 12 months, % (95% CI)	65.4 (51.6-76.1)	25.9 (7.2-49.9)

* Due to hierarchal testing procedures of the end points, the OS end point could be formally tested because the ORR was no statistically significant

- 64% risk reduction of death with ripretinib treatment compared to placebo

CI, confidence interval; HR, hazard ratio; OS, overall survival

von Mehren M, et al. Presented at ESMO 2019 Abstract #LBA87.

INVICTUS ADDITIONAL RESULTS

CROSSOVER PROVIDED OS BENEFIT*

- Placebo patients who crossed over to ripretinib treatment during the study had a median OS of 11.6 months (95% CI: 6.3-NE) compared to a median OS of 1.8 (95% CI: 0.9-4.9) for placebo patients who did not cross over treatment

SAFETY

- Ripretinib was generally well tolerated:-
  - Dose reductions were in 7 pts (8.2%) in ripretinib arm v 1 (2.3%) in placebo arm; interruptions were in 18 pts (21.2%) in ripretinib v 8 (18.6%) in placebo arm

*Presented during oral presentation

CI, confidence interval; NE, not estimable; OS, overall survival

von Mehren M, et al. Presented at ESMO 2019 Abstract #LBA87.

SUMMARY

- **INVICTUS is the first strikingly positive trial in ⩾4th line GIST** and is likely to lead to a new registration for ripretinib
- **Median PFS was significantly improved with ripretinib** compared to placebo
- The **median OS result** whilst not statistically significant is **clinically very meaningful**
- **Ripretinib had a favourable tolerability profile**
- Patients who crossed over to ripretinib from placebo during the trial experienced OS benefit
  - This will affect the clinical trial landscape for GIST going forward as placebo-controlled trials could be considered unethical as a result

GIST, gastrointestinal stromal tumour; OS, overall survival; PFS, progression free survival

von Mehren M, et al. Presented at ESMO 2019 Abstract #LBA87.

ADP-A2M4 (MAGE-A4): A PHASE 1 T-CELL DOSE ESCALATION STUDY IN PATIENTS WITH SYNOVIAL SARCOMA

van Tine B, et al. ESMO 2019 Abstract #16700

BACKGROUND

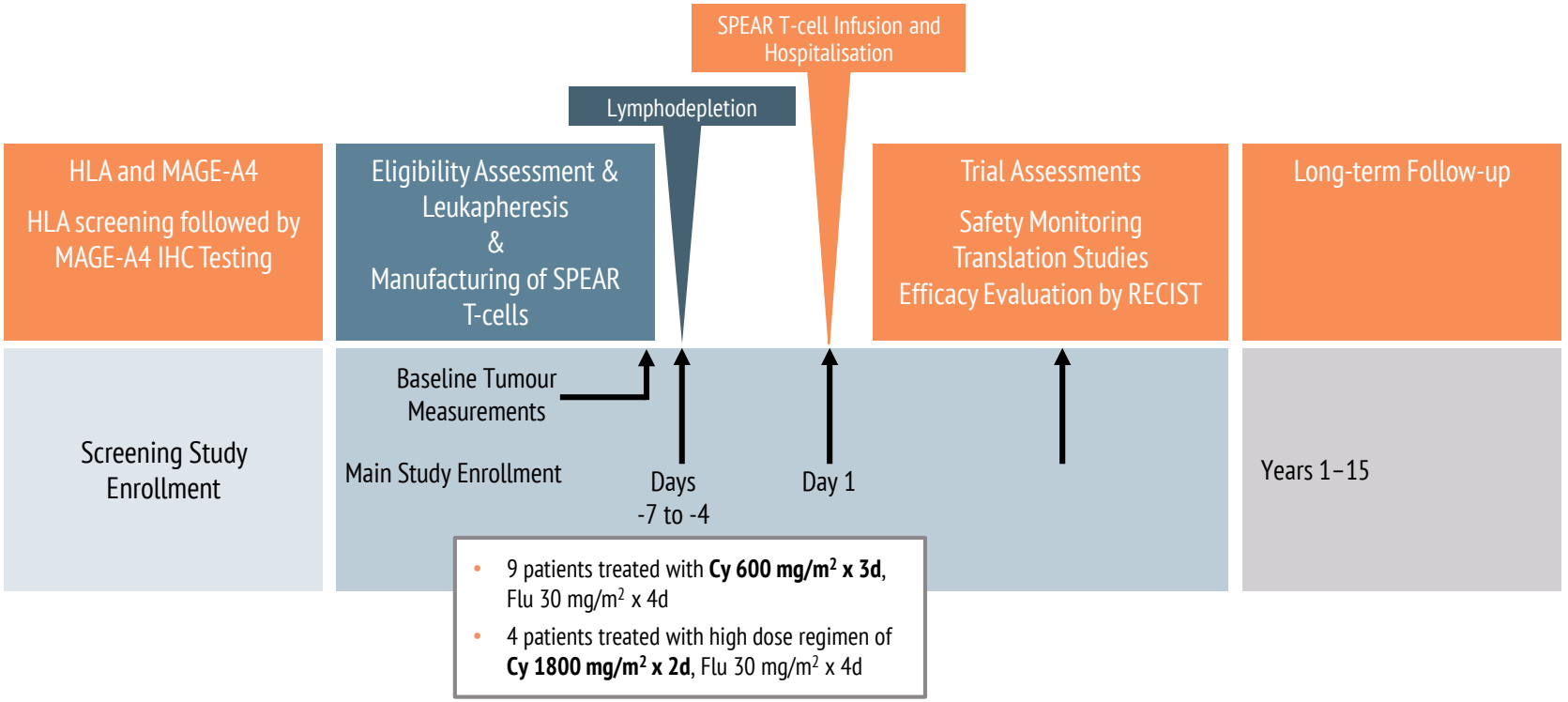
- Synovial sarcoma represents approx. 10% of all soft tissue sarcomas[1]
- Metastatic disease has a poor prognosis
- MAGE-A4 is highly expressed in synovial sarcoma patients
- This study evaluates safety, tolerability and antitumour activity of ADP-A2M4, genetically engineered autologous SPEAR T cells directed towards a MAGE-A4 peptide expressed in the context of HLA-A*02

HLA, human leukocyte antigen; PEAR, specific peptide enhanced affinity receptor

1. Reimann JDR, et al. The Molecular Basis of Cancer (Fourth Edition), 2015
van Tine B, et al. Presented at ESMO 2019 Abstract #16700.

STUDY DESIGN

SYNOVIAL SARCOMA



- Primary objective: evaluate safety & tolerability of ADP-A2M4 T-cell therapy

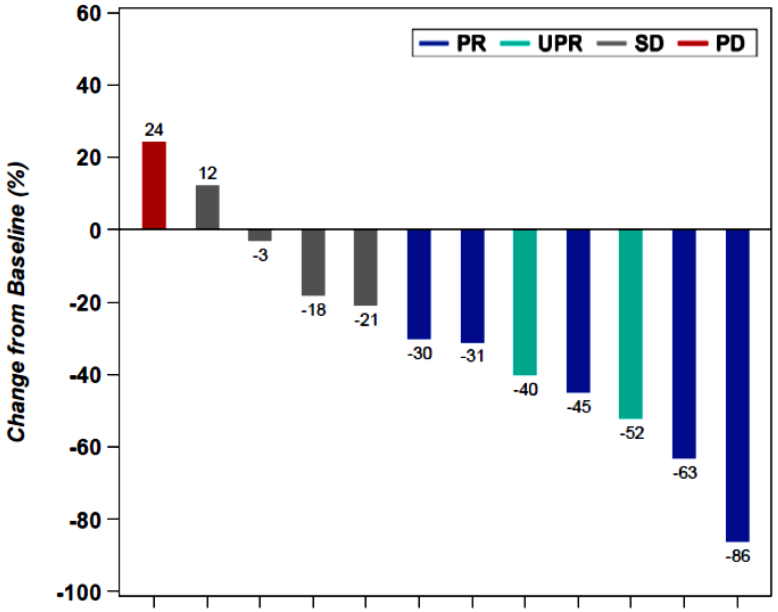
HLA, human leukocyte antigen; IHC, immunohistochemistry; RECIST, response evaluation criteria in solid tumors; SPEAR, specific peptide enhanced affinity receptor

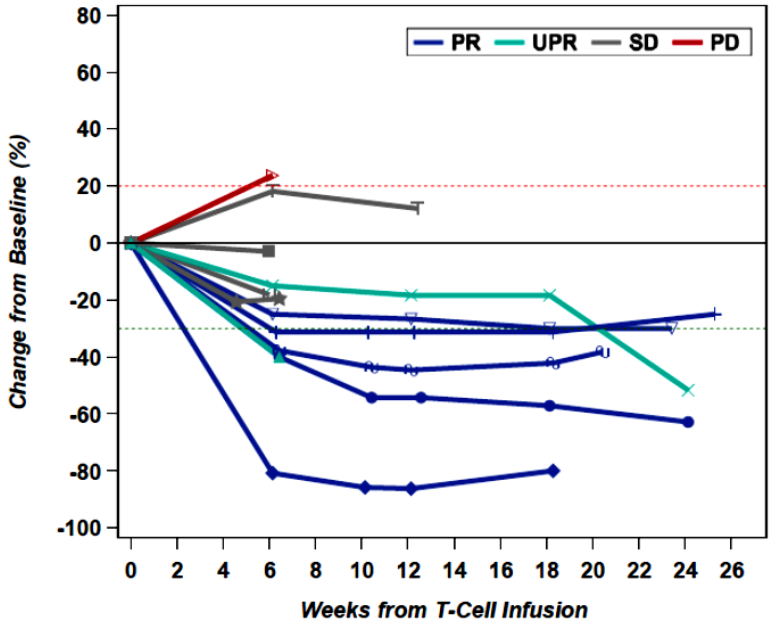
van Tine B, et al. Presented at ESMO 2019 Abstract #16700.

RESULTS

BEST OVERALL RESPONSE IN 12* PATIENTS WITH POST-BASELINE ASSESSMENTS

- ADP-A2M4 SPEAR T-cells induce clinical responses





*13th treated patient did not have post-baseline assessment at time of data cut-off. Data cut-off 03-Sep-19
Updated data taken from oral presentation slides to reflect later cut-off data

SPEAR, specific peptide enhanced affinity receptor

van Tine B, et al. Presented at ESMO 2019 Abstract #16700.

SUMMARY

- The majority of patients who received T cell transfer had tumour shrinkage

- Durability of tumour response appears impressive and ongoing at 6 months
  - Further follow up required to confirm the durability of responses

CRYODESMO-01: A FRENCH NATIONWIDE STUDY ON CRYOABLATION IN PROGRESSING DESMOID TUMOUR PATIENTS

Kurtz J, et al. ESMO 2019 Abstract #16680

BACKGROUND

- Desmoid tumours are rare tumours arising from musculoaponeurotic tissues
- Although benign, they may be locally aggressive, leading to pain and disability and in exceptional cases death
- ESMO guidelines recommend a watch and wait approach
- Medical treatment includes: NSAIDs, anti-oestrogens, chemotherapy, antiangiogenics or radiation therapy
- Cryoablation is an interventional radiology technique under general anaesthetic
  - Several freeze/thaw cycles lead to cell death

ESMO, European society for medical oncology; NSAIDs, nonsteroidal anti-inflammatory drugs;
Kurtz J, et al. Presented at ESMO 2019 Abstract #16680.

CRYODESMO-01 STUDY DESIGN

STUDY DESIGN

- **Prospective, open label, non-randomised, multicentric phase 2 study**
  - Non-abdominopelvic progressive DT patients were included
  - 50 patients enrolled, 78% female
- **Primary endpoint:** non-progression rate at 12 months
- **Secondary endpoints** included:-
  - Safety
  - QOL
  - Assessment of pain and functional status

PATIENT CHARACTERISTICS

- Tumour locations were limbs (36%), trunk (60%) and cervical area (4%)
- Median tumour volume was 111 cm^3 (range: 0.6-1068)

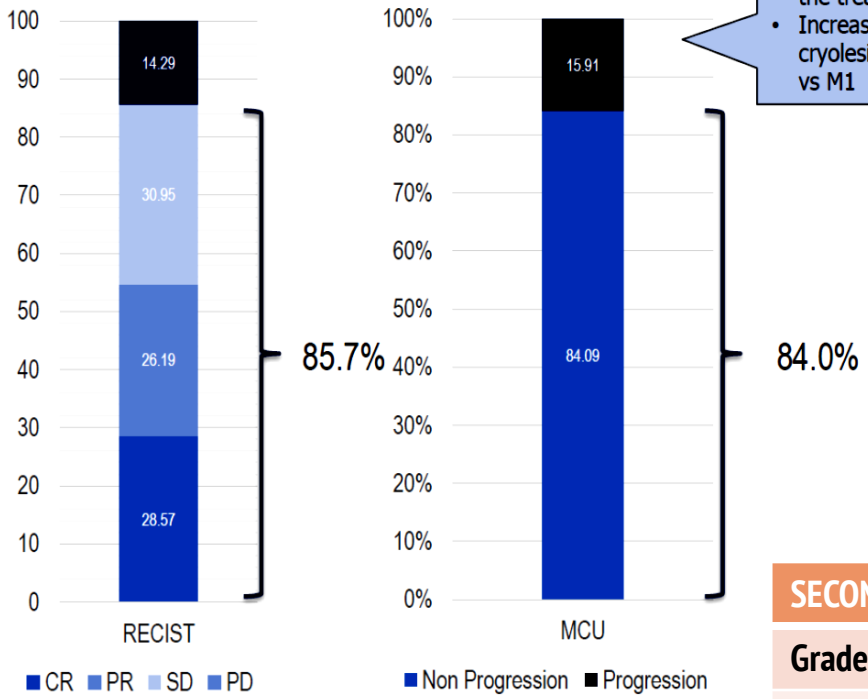
DT, desmoid tumour; QOL, quality of life

Kurtz J, et al. Presented at ESMO 2019 Abstract #16680.

CRYODESMO-01: RESULTS

NON-PROGRESSION RATE AT 12 MONTHS

- **Similar results at M12 by either RECIST or MCU criteria**
- Different informations making MCU more accurate in defining success vs failure of cryoablation



- < 90% necrosis in the selected zone
- Tumor recurrence in the treated zone
- Increase in the cryolesion size at M12 vs M1

SECONDARY ENDPOINTS	
Grade 1 toxicity, %	32.8
Grade 1 toxicity, %	44.5
Grade 3-4 AEs, n (%)	11 (22)
Improved functional status, %	63
Improved pain scores, %	83

- The rate of non-progressing disease at 12 months was 86% (95% CI: 73-94%)

AEs, adverse events; CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease

Kurtz J, et al. Presented at ESMO 2019 Abstract #16680.

SUMMARY

- CRYODESMO-01 is the largest and first prospective trial of cryoablation in desmoid tumours
- Cryoablation is a new technology for the Sarcoma field
- Interesting to see the additional data from CRYODESMO-01 when available

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