



Bruno Vincenzi
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Standard versus histotype-tailored CT



Homogeneous group of STS

Grade III, adult type STS
Extremities and trunk wall
Size ≥ 5 cm

EI x 3 → Surg ± RT
R ↖
ht-CT x 3 → Surg ± RT

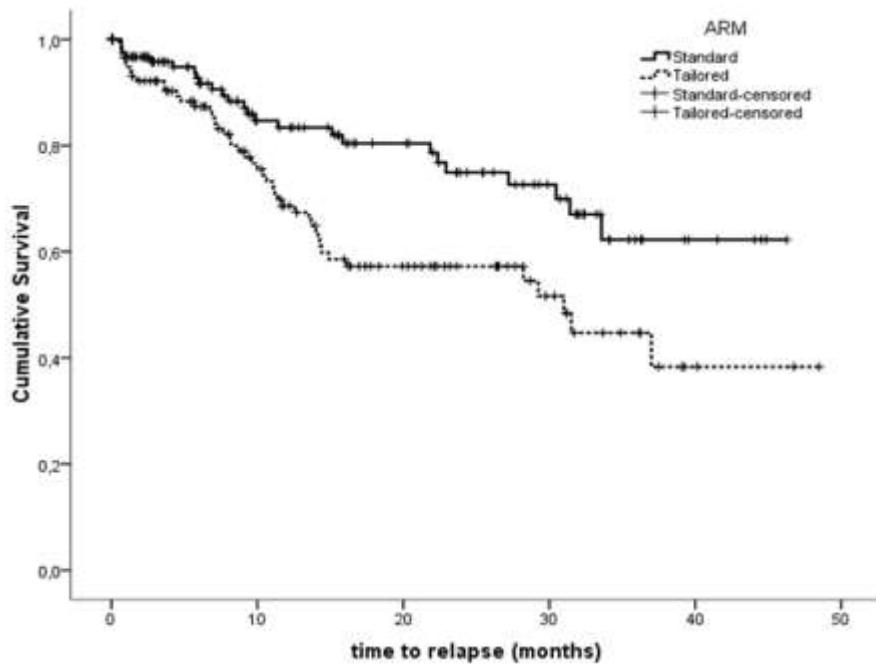
MRC LipoS	→ Trabectedin
Synovial S	→ HD-IFX
LeiomioS	→ GEM - DTIC
UPS	→ GEM – TAX
MPNST	→ IFX + Etoposide

Hypothesis: HT CT reduces by 30% the risk of relapse (**40 to 27%, HR: 0.66**)

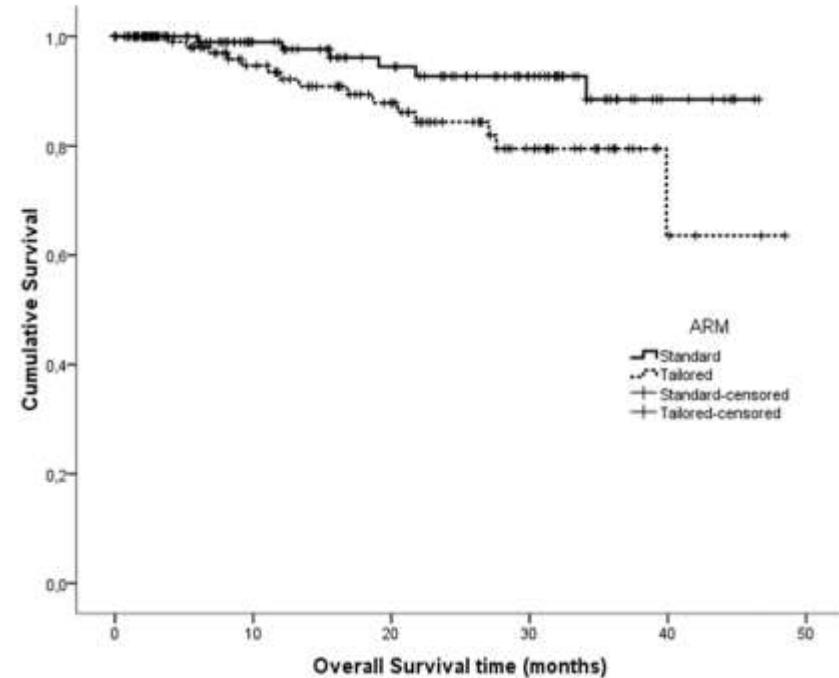
N random = 350, 500 registered

Analysis: 150 events (relapses or deaths) with interim analysis for futility (IDMC)

ISG-STS 1001 - Results



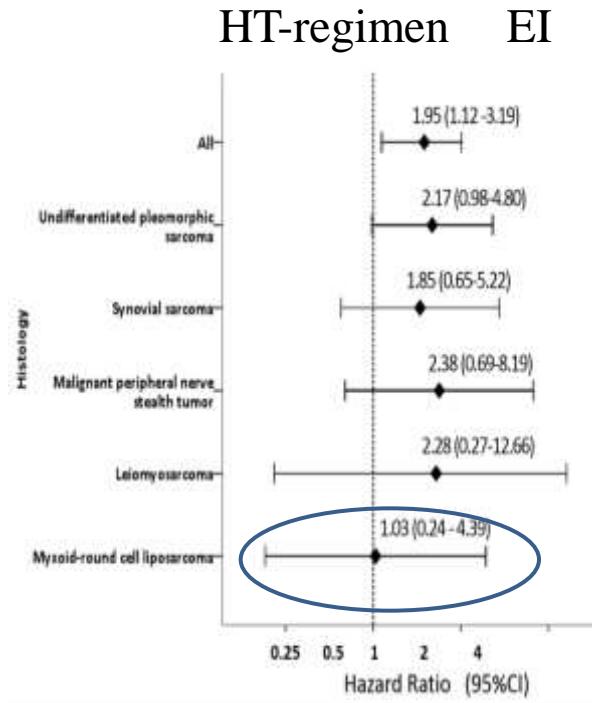
RFS



OS

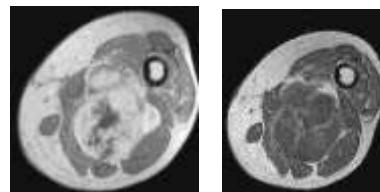
A. Gronchi et al, Lancet Oncol 2017

RFS by histology subtype: Histological response

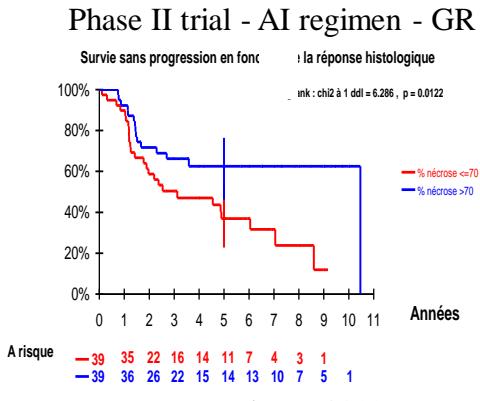


A. Gronchi et al, Lancet Oncol 2017

Phase II trial - trabectedin in resectable MLPS N = 23



4 pCR, 10 pPR, no clinical PD
A. Gronchi et al, Annals of Oncol 2011



R. Ruiz et al, EJC 2011

OLARATUMAB between past, present and future...



Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial

William D Tap, Robin L Jones, Brian A Van Tine, Bartosz Chmielowski, Anthony D Elias, Douglas Adkins, Mark Agulnik, Matthew M Cooney, Michael B Livingston, Gregory Pennock, Meera R Hameed, Gaurav D Shah, Amy Qin, Ashwin Shahir, Damien M Cronier, Robert Ilaria Jr, Ilaria Conti, Jan Cosaert, Gary K Schwartz

Phase 2

- Same entry criteria as Phase 1b
- Stratification:
 - PDGFR α (IHC)
- Lines of prior treatment
- ECOG PS
- Histology (leiomyosarcoma, synovial, other)

R
A
N
D
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M
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E

Olaratumab 15
mg/kg D1,8 + **Dox 75**
mg/m² D1
for 8 cycles*

Dox 75 mg/m² D1
for 8 cycles

Olaratumab monotherapy until progression

Optional olaratumab monotherapy after progression

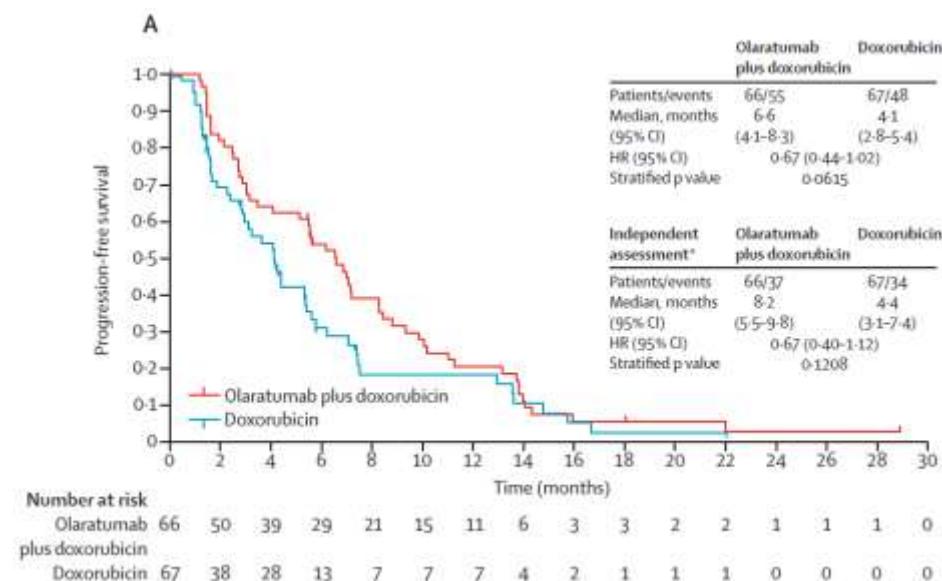
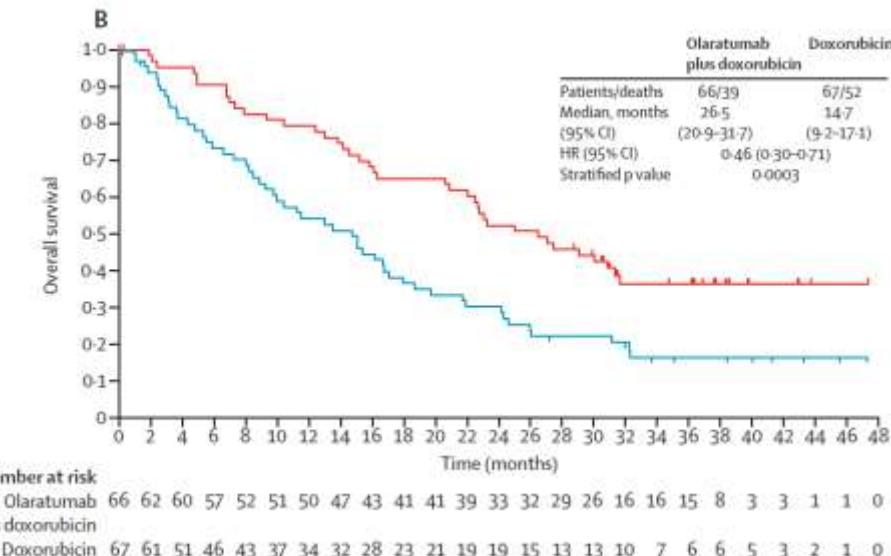
Primary endpoint: Progression-free survival (PFS) : 2-sided alpha = 0.2)
Secondary end points: Overall survival (OS), RR, PFS at 3 months
Biomarkers: PDGFR α (IHC) and its ligands

*During Cycles 5-8, patients receiving Dox could receive dexamethasone at the investigator's discretion.

OLARATUMAB between past, present and future...

► JGDJ Ph 1b/II trial

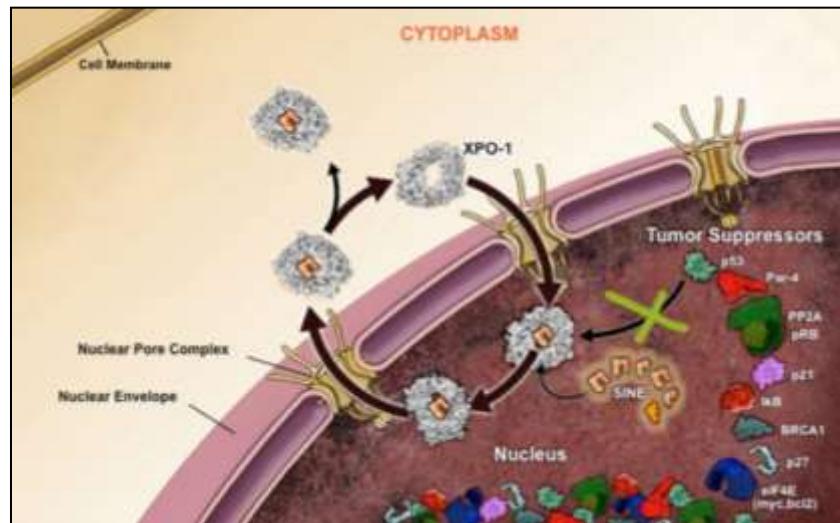
- ❖ Conditional approval



TARGET THERAPIES in STS: SELINEXOR

► SELINEXOR in dedifferentiated LPS (SEAL)

❖ Results (Abs #11512)

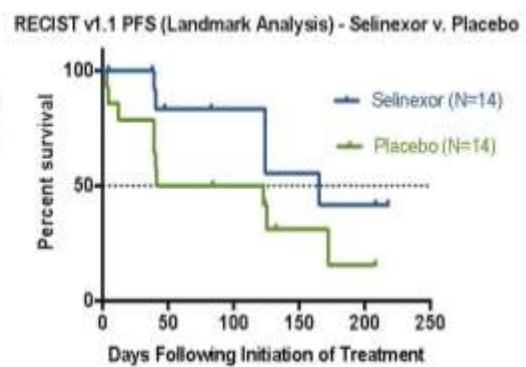
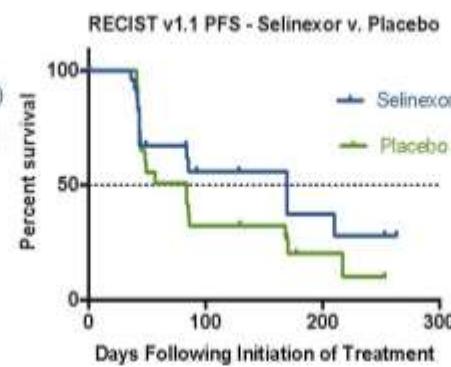
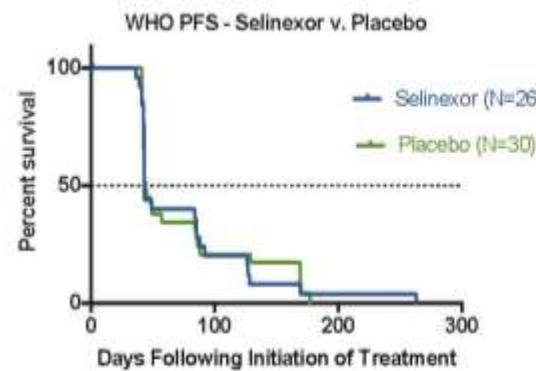


TARGET THERAPIES in STS: SELINEXOR

► SELINEXOR in dedifferentiated LPS (SEAL)

❖ Results (Abs #11512) of phase II → phase III ongoing

Variable	WHO Criteria	RECIST v1.1 Criteria
Measurability at baseline	Bi-dimensional, any size, determine product of longest (LD) and shortest (SD) diameters	Uni-dimensional (LD only) with LD ≥ 1 cm. Non-measurable: All other lesions, including small lesions (LD < 1 cm)
No. of Target Lesions Evaluated	All lesions are considered target lesions, including small (1 cm) lesions	Up to 5 total target lesions (maximum 2 per organ)
Progressive Disease	$\geq 25\%$ increase in product (LD \times SD) of one or more isolated lesions or appearance of new lesions	$\geq 20\%$ increase over smallest SUM of LDs observed (absolute increase of at least 5 mm) or appearance of new lesions



WHO Criteria
Median PFS= 1.4 Months, Selinexor and Placebo
Hazard Ratio (95% CI)= 1.02 (0.59, 1.77)
Progression Events= 25 Selinexor; 28 Placebo

RECIST v1.1 Criteria
Selinexor Median PFS= 5.5 Months
Placebo Median PFS= 2.7 Months
Hazard Ratio (95% CI)= 0.67 (0.33, 1.37)
Progression Events= 13 Selinexor; 19 Placebo

Landmark Analysis* RECIST v1.1 Criteria
Selinexor Median PFS= 5.4 Months
Placebo Median PFS= 2.7 Months
Hazard Ratio (95% CI)= 0.43 (0.15, 1.26)
Progression Events= 5 Selinexor; 10 Placebo (*in patients on study ≥ 45 days)

TARGET THERAPIES in STS: SORAFENIB and PAZOPANIB

► SORAFENIB and PAZOPANIB in desmoid tumors

Abstract 11500

Alliance A091105: A phase III, double blind, randomized, placebo-controlled trial of sorafenib in desmoid tumors or aggressive fibromatosis (DT/DF)

Minal M. Gounder^a, Michelle R. Mahoney^b, Brian Andrew Van Tine^c, Vibud Ravi^d, Steven Arista^e, Hari Agast Deshpande^f, Alka A. Gupta^g, Mohammad M. Milhem^h, Robert Martin Conryⁱ, Sejana Mavor^j, Michael J. Pidleyan^k, Richard F. Kiessl^l, Tarek Sabagh^m, William D. Tapⁿ, Nataly De Souza Horwitz^o, Ethan Basch^p, Lawrence Schwartz^q, Robert G. Maki^r, Narayanan P. Agarwal^s, Robert A. Lefkowitz^t, Yousaf Mazaheri^u, Bikiya Yamasakir^v, John Joseph Wright^w, Amylon C. Durck^x, Gary K. Schwartz^y

^a Memorial Sloan Kettering Cancer Center and Weill Cornell Medical Center, New York, NY; ^b Alliance Statistics and Data Center, Mass General, Boston, MA; ^c Washington University in St. Louis School of Medicine, St. Louis, MO; ^d MD Anderson Cancer Center, University of Texas, Houston, TX; ^e Mayo Clinic in Florida, Jacksonville, FL; ^f Yale University, New Haven, CT; ^g University Health Network Princess Margaret Cancer Center, Toronto, ON; ^h University of Iowa, Holden Comprehensive Cancer Center, Iowa City, IA; ⁱ University of Michigan, Ann Arbor, MI; ^j Fox Chase Cancer Center, Philadelphia, PA; ^k MedStar Georgetown University Hospital, Washington, DC; ^l Duke Cancer Institute, Duke University Medical Center, Durham, NC; ^m Duke NCI Community Oncology Research Program, Durham, NC; ⁿ University of North Carolina, Chapel Hill, North Carolina; ^o Cleveland University, Cleveland College of Physician Assistant Programs and New York Presbyterian Hospital, New York, NY; ^p Maimonides Medical Center, Brooklyn, NY; ^q University of Colorado Anschutz Medical Campus, Aurora, CO; ^r UConn Cancer Center, Farmington, CT; ^s Mayo Clinic, Rochester, MN; ^t Mayo Clinic, Scottsdale, AZ

Abstract 11501

DESMOPAZ Pazopanib versus IV methotrexate/vinblastine in adult patients with progressive desmoid tumors

A randomized phase II study from the French Sarcoma Group.

Maud TOULMONDE, Isabelle RAY-COQUARD, Marina PULIDO, Thierry ANDRE, Christine CHEVREAU, Nicolas PENEL, Emmanuelle BOMPAS, Antoine THYSS, Fran ois BERTUCCI, Celeste LEBBE, Axel LE CESNE, Patrick SOULIE, Sophie PIPERNO-NEUMANN, Fabiola CECCHI, Todd HEMBROUGH, Florent PETITPREZ, Carine BELLERA, Julien ADAM, Jean-Yves BLAY, Antoine ITALIANO

TARGET THERAPIES in STS: SORAFENIB and PAZOPANIB

► SORAFENIB and PAZOPANIB in desmoid tumors

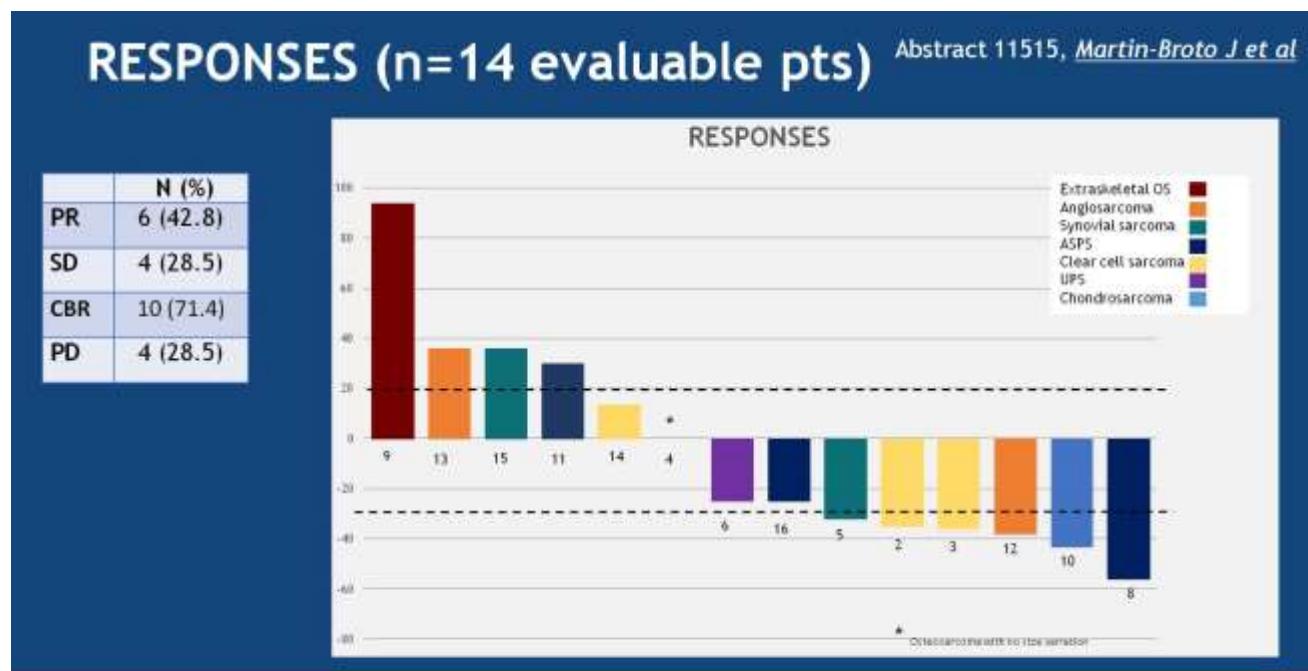
Study Design

	A091105	Desmopaz
Agent	Sorafenib 400 mg daily VEGFR1/2/3, PDGFR-B, KIT A/B/C - RAF and others	Pazopanib 800 mg daily VEGFR1/2/3, PDGFR α /B and KIT
Randomization	2:1, placebo	2:1, Mtx/Vinblastine
Eligibility	RECIST ↑10%/6 mos, surgery unacceptable, Sxs/BPI > 3 (narcotic use)	RECIST PD within 6 months
Primary endpoint	PFS	6 month non-PD rate
Statistics	Median PFS: placebo 6 mo, sorafenib 15 mo. (HR 0.4) 90% power, 1-sided $\alpha=2.5\%$	$P_0=60\%$, $P_1=80\%$, $\alpha=5\%$ and $\beta=20\%$

TARGET THERAPIES in STS: SUNITINIB + NIVOLUMAB

► SUNITINIB + NIVOLUMAB: Phase I/II

❖ Results (Abs #11515) Phase I



TARGET THERAPIES in STS: TRK inhibitors

► LAROTRECTINIB

The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers

Hyman DM,¹ Laetsch TW,² Kummar S,³ DuBois SG,⁴ Farago AF,⁵ Pappo AS,⁶ Demetri GD,⁷ El-Deiry WS,⁸ Lassen UN,⁹ Dowlati A,¹⁰ Brose MS,¹¹ Boni V,¹² Turpin B,¹³ Nagasubramanian R,¹⁴ Cruickshank S,¹⁵ Cox MC,¹⁵ Ku NC,¹⁵ Hawkins DS,¹⁶ Hong DS,¹⁷ Drilon AE¹

PRESENTED AT ASCO ANNUAL MEETING '17

#ASCO17

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Hyman, LBA2501

TARGET THERAPIES in STS: TRK inhibitors

► LAROTRECTINIB

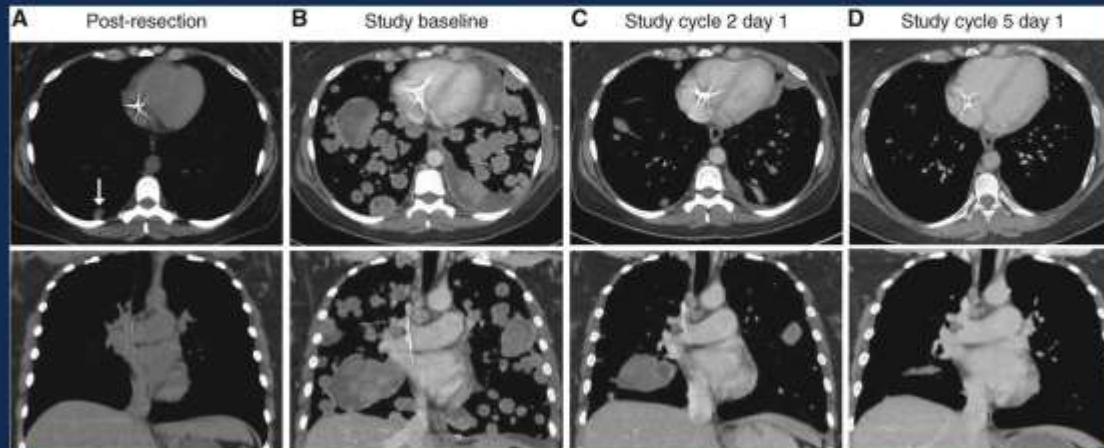
The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and p

60 year old woman with widely metastatic, refractory MPNST

TPM4-NTRK3 fusion

Hyman DM,¹ Laetsch TW,¹ Lassen UN,⁹ Dowlati A,¹ Cox MC,¹⁵ Ku NC,¹⁵ Hav

Enrolled in Phase II trial of larotrectinib – ASCO 2017 Oral Developmental Therapeutics



Robert C. Doebele et al. Cancer Discovery 2015;5:1049-1057

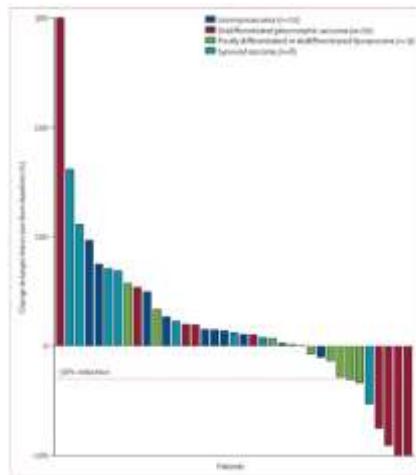
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Presented by: Mrinal Gounder, MSKCC

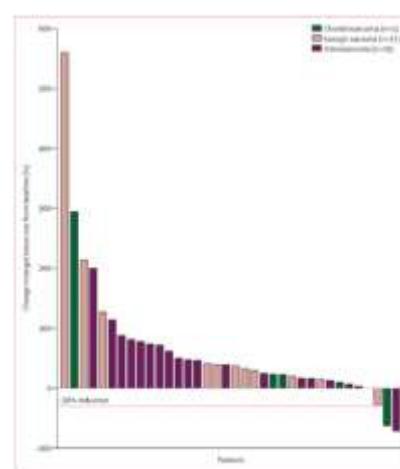
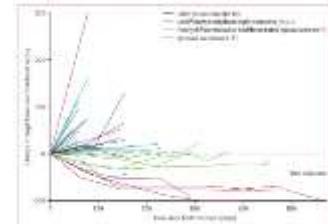
IMMUNOTHERAPIES in STS

Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial

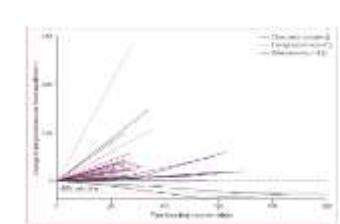
Hussein A Tawbi,¹ Melissa Burgess,¹ Vanessa Bolejack,¹ Brian A Van Tine,² Scott M Schuetze,³ James Hu,⁴ Sandra D'Angelo,⁵ Steven Atkin,⁶ Richard F Biedel,⁷ Dennis A Pilembat,⁸ Sujana Mehta,⁹ Lars E Davis,¹⁰ Scott H Okuno,¹¹ Damon R Reed,¹² John Crowley,¹³ Lisa H Butterfield,¹⁴ Ruth Salazar,¹⁵ Jaime Rodriguez-Canales,¹⁶ Alexander J Lazar,¹⁷ Ignacio I Wistuba,¹⁸ Laurence H Baker,¹⁹ Robert G Maki,²⁰ Denise Reinkes,²¹ Shreyas Kumar Patel²²



	Complete response	Partial response	Stable disease	Progressive disease
Pembrolizumab (n=12)	~75	~15	~15	~15
Pembrolizumab + ipilimumab (n=12)	~50	~35	~15	~15
Anti-PD1/PD-L1 + anti-PD1/PD-L1 + ipilimumab (n=8)	~75	~15	~15	~15
Anti-PD1/PD-L1 (n=8)	~50	~15	~15	~15



	Complete response	Partial response	Stable disease	Progressive disease
Pembrolizumab (n=12)	~75	~15	~15	~15
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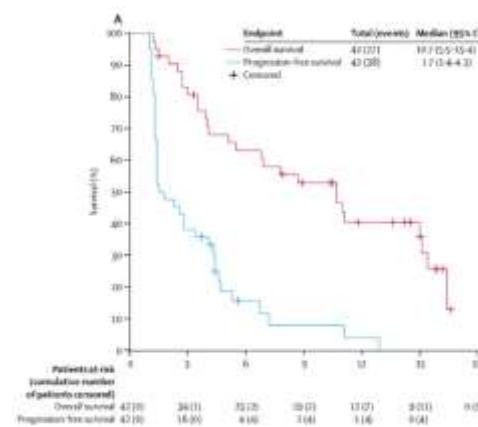
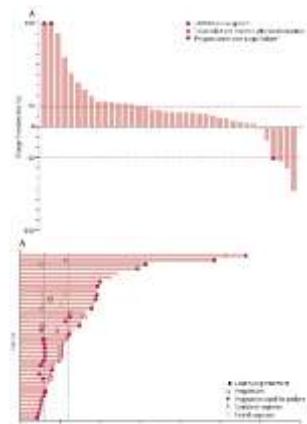
IMMUNOTHERAPIES in STS

Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials

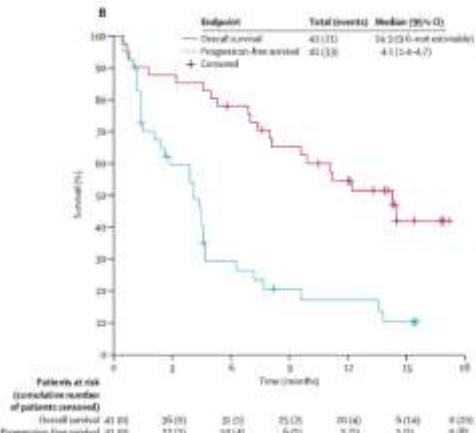
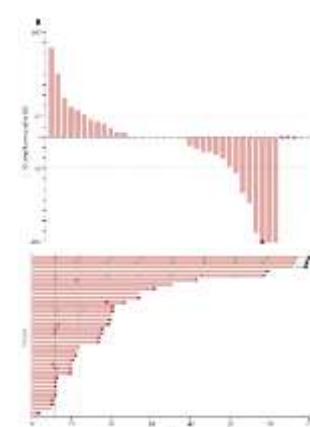
Sandro P D'Angelo, Michelle R Mahoney, Brian A Van Tine, James Atkins, Mohamed M Alifemi, Balkrishna N Juhagirdar, Cristina R Antonescu, Eise Harath, William D Tap, Gary K Schwartz, Howard Strichler



Nivolumab monotherapy



Nivolumab + Ipilimumab



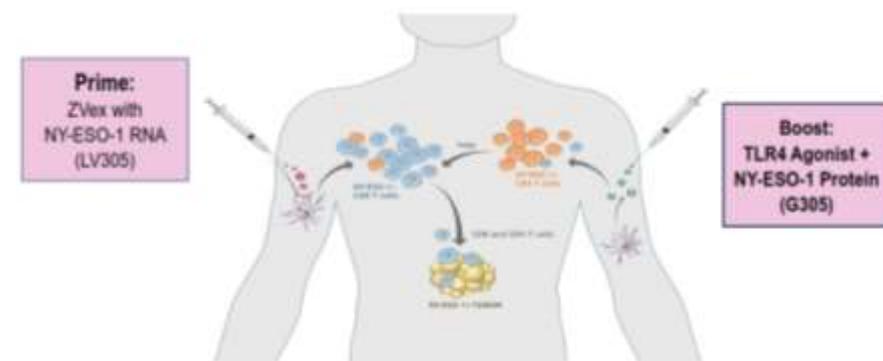
PR: alveolar soft part sarcoma and the non-uterine leiomyosarcoma

PR: uterine leiomyosarcoma, non-uterine leiomyosarcoma, myxofibrosarcoma, angiosarcoma, UPS (n=2)

IMMUNOTHERAPIES in STS: NY-ESO1 vaccine

► NCT02387125: A Phase 1b, Safety Study of CMB305 in Patients With Locally Advanced, Relapsed, or Metastatic Cancer Expressing NY-ESO-1

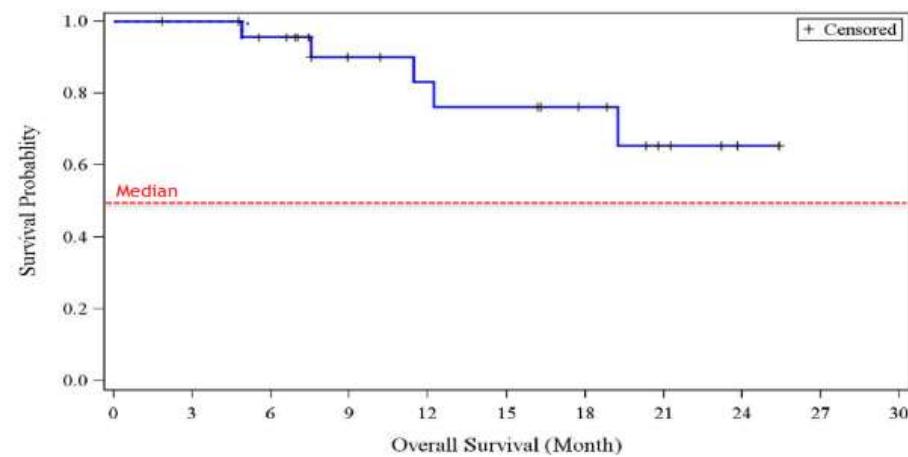
- ❖ **CMB305:** sequentially administered LV305 [lentiviral vector encoding New York esophageal squamous cell carcinoma-1 {NY-ESO-1} gene] and G305 [NY-ESO-1 recombinant protein plus glucopyranosyl lipid A stable emulsion {GLA-SE}]
- ❖ Among STS, SS and MRCL showed high expression of NY-ESO1



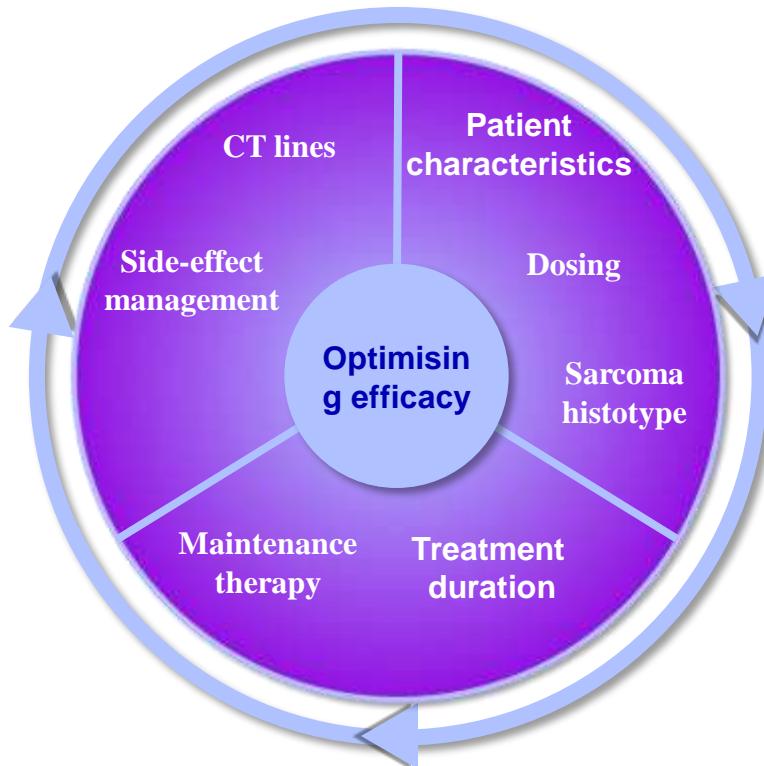
IMMUNOTHERAPIES in STS: NY-ESO1 vaccine

► NCT02387125: A Phase 1b, Safety Study of CMB305 in Patients With Locally Advanced, Relapsed, or Metastatic Cancer Expressing NY-ESO-1

STS patients n=25 (all NY-ESO-1+)	
14 synovial, 9 MRCL, 2 spindle	
recurrent locally advanced, relapsed and/or metastatic with limited tumor burden (<10 cm)	
92% metastatic 92% prior chemotherapy (52% ≥2 prior lines)	
56% disease progression at study start	
Median duration of observation: 11.4 mo	
Median OS [95% CI], mos	NA [12.3, NA]
12-mos OS Rate, %	83.1
18-mos OS Rate, %	76.2



Key factors for successful therapy management in STS with any agent



OPTIMAL USE OF A DRUG

For whom?

For which STS ?

When?

How long?

How?