Available and emerging novel systemic agents in the treatment of metastatic uLMS

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Disclosures

Advisory Committee	Caris Life Sciences, EMD Serono Inc, GlaxoSmithKline, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Lilly, Novartis Pharmaceuticals Corporation
Contracted Research	Eisai Inc, Merck, Pfizer Inc
Paid Research	Eisai Inc, Merck
Speakers Bureau	Caris Life Sciences, GlaxoSmithKline, Novartis Pharmaceuticals Corporation

Case Study 1: Uterine LMS

- 46-year-old white woman presents for a second opinion
- Originally morcellated for her fibroids 4 years ago.
- Pathology was not sent.
- Developed widespread abdominal and lung disease within 6 months
- First treated with gemcitabine and docetaxel.
- At progression was referred to me for participation in a clinical trial.

Phase II: Olaratumab ± Doxorubicin

- **Same entry criteria as phase Ib**
- **Stratification:**
  - **PDGFRα (IHC)**
  - **Lines of prior treatment**
  - **ECOG PS**
  - **Histology (leiomyosarcoma, synovial sarcoma, other)**

RANDOMIZE

Olaratumab 15 mg/kg D 1,8 + Dox 75 mg/m² D1 × 8 cycles (21 days)[a] → **Olaratumab monotherapy until progression**

Dox 75 mg/m² D1 × 8 cycles → **Optional olaratumab monotherapy after progression**

Primary end point: progression-free survival (PFS) (predefined statistical significance: 2-sided alpha = 0.2)

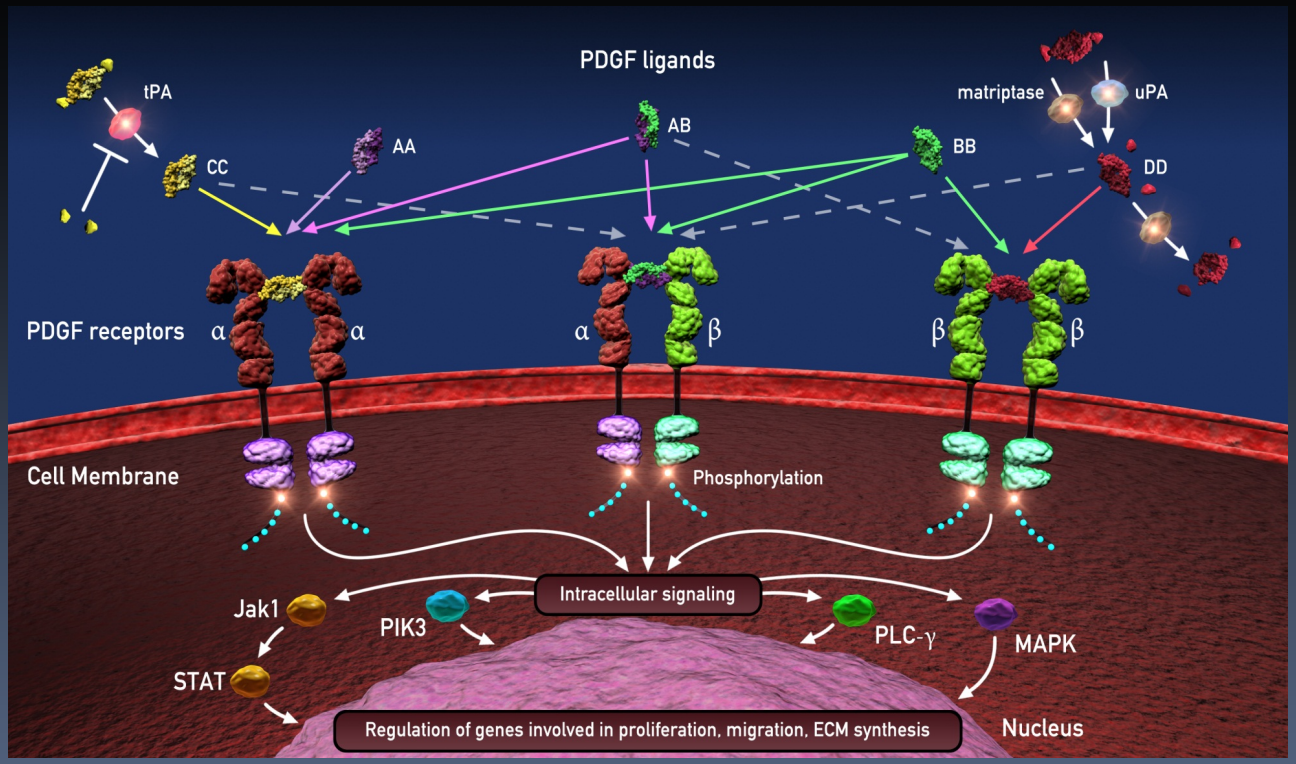
Secondary end points: overall survival (OS), objective response rate, PFS at 3 months

Biomarker: PDGFRα (IHC) and related ligands

[a]During cycles 5 to 8, patients receiving doxorubicin could receive dexrazoxane at the investigator's discretion.

Tap et al, 2015.

Platelet-Derived Growth Factor Receptor

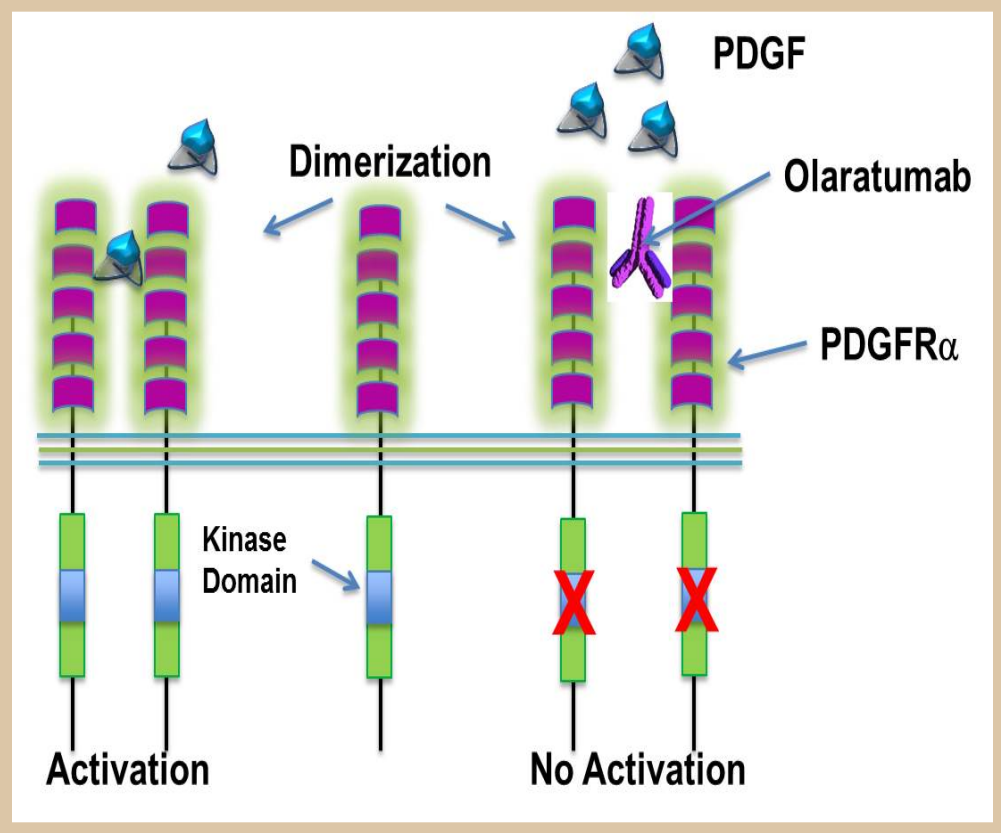


- Cell surface receptor tyrosine kinase (α,β) activated by the platelet-derived growth factor (PDGF A–D) family of ligands
- In normal mesenchymal biology, PDGF/PDGFR signaling has a significant role in mesenchymal stem cell differentiation, growth of mesenchymal cells, and angiogenesis and wound healing

Ng et al, 2008; Li et al, 2014; Andrae et al, 2008.

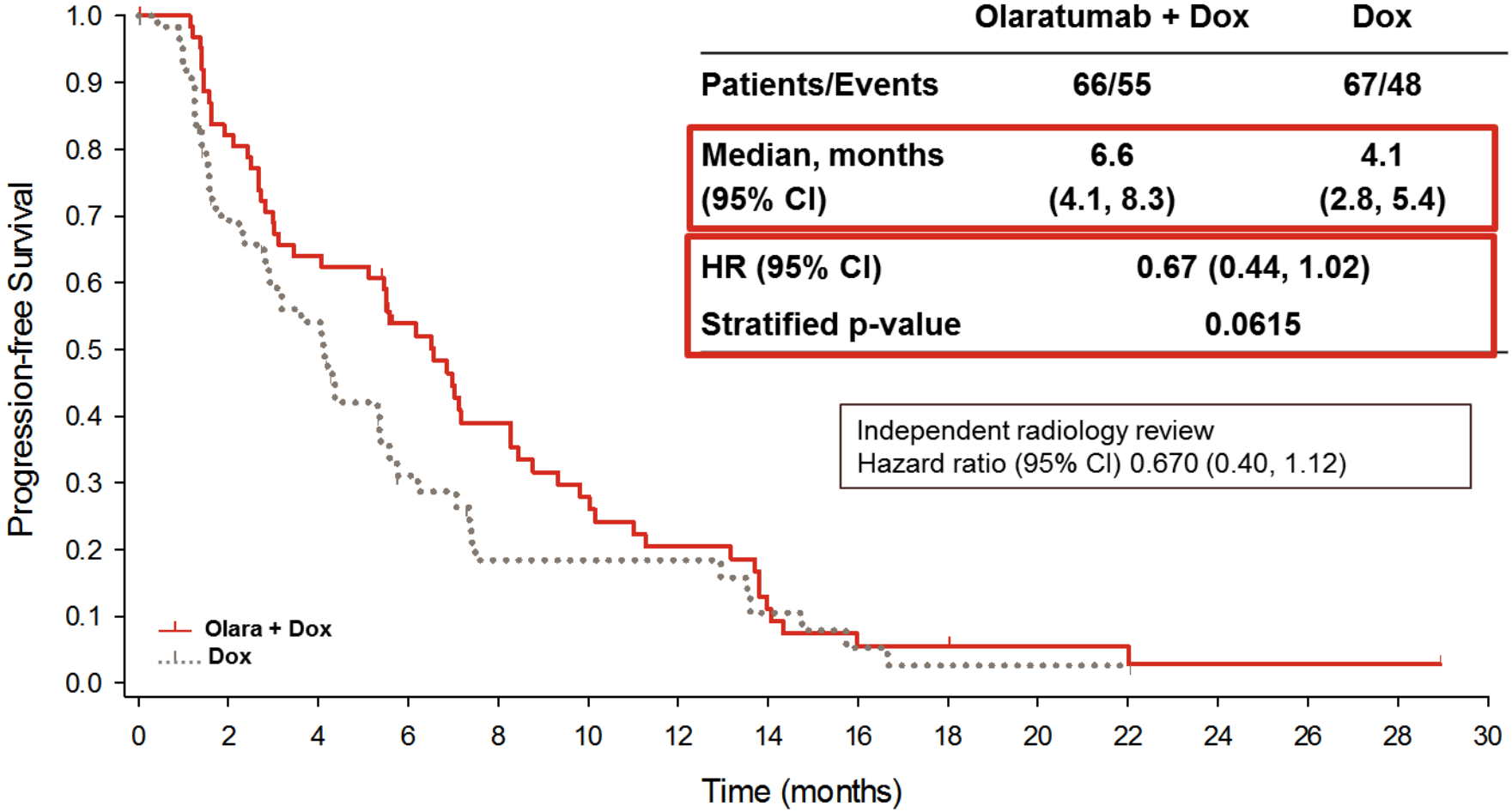
Olaratumab

- Fully human monoclonal antibody of immunoglobulin G class 1 (IgG1) that selectively binds PDGFRα
- Blocks PDGF binding and PDGF-induced PDGFRα activation
- Demonstrated activity in both in vitro and in vivo cancer models known to be driven by a PDGF-PDGFRα autocrine loop
- Demonstrated antitumor activity alone or in combination with Dox in human sarcoma xenograft models



Loizos et al, 2005; Gerber et al, 2012.

Investigator Assessed Progression-Free Survival (ITT)

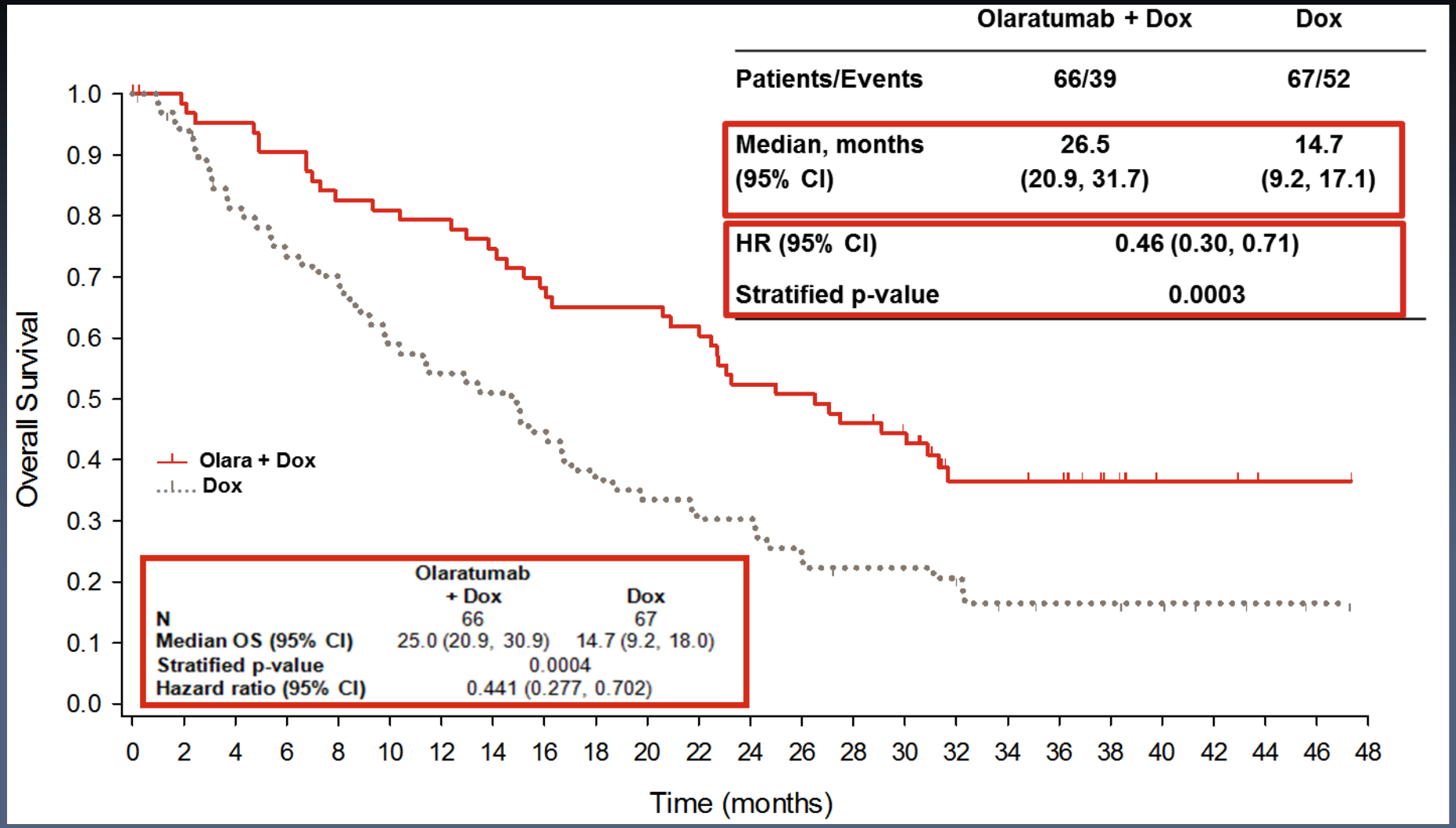


	Olaratumab + Dox	Dox
Patients/Events	66/55	67/48
Median, months (95% CI)	6.6 (4.1, 8.3)	4.1 (2.8, 5.4)
HR (95% CI)	0.67 (0.44, 1.02)	
Stratified p-value	0.0615	

Independent radiology review
Hazard ratio (95% CI) 0.670 (0.40, 1.12)

Tap et al, 2015.

Overall Survival: ITT



Tap et al, 2015.

Grade ≥3 Adverse Events

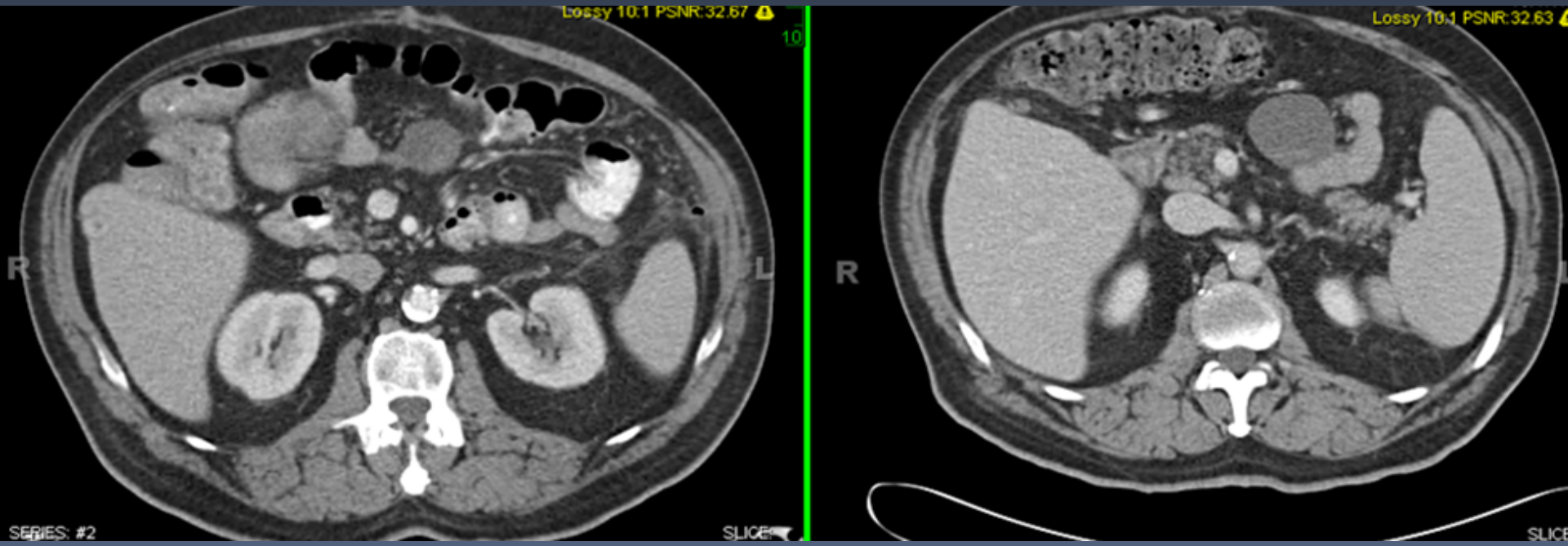
Adverse event	Olaratumab + Doxorubicin (n = 64)	Doxorubicin (n = 65)
Neutropenia	51.5%	33.8%
Anemia	12.5%	7.7%
Febrile neutropenia	12.5%	13.8%
Fatigue	9.4%	3.1%
Thrombocytopenia	9.4%	7.7%
Infections	6.3%	10.8%
Cardiac AE	14.1%	9.2%
Decrease in ejection fraction	4.7%	6.2%
LVEF <50%	11.8%	9.4%
Treatment-related AE	64%	54%
Treatment-related serious AE	22%	25%
AE leading to discontinuation	13%	22%

- Neutropenia did not translate into higher rates of febrile events or infections

Tap W et al. *Proc ASCO* 2015;Abstract 10501.

Case 1 Continued

- Patient went on to receive 8 cycles of doxorubicin and olaratumab
- She then went on to 16 cycles of olaratumab maintenance prior to progression of the nodules she already had.
- Best response on trial was a PR
- No new nodules were seen at the time of progression.



ANNOUNCE

- Olaratumab, in combination with doxorubicin, is the first FDA-approved front-line therapy for soft tissue sarcoma in four decades

  -- The approval was based on results from the positive Phase 2 JGDG trial
  -- Olaratumab received the FDA's Breakthrough Therapy Designation and was approved under the Agency's Accelerated Approval program

- Ongoing Phase III ANNOUNCE trial of doxorubicin versus doxorubicin/olaratumab in patients with advanced or metastatic STS is accrued and awaiting the needed events for analysis.

- This is a randomized placebo controlled Phase III clinical trial of 1:1 randomization of doxorubicin + olaratumab vs. doxorubicin + placebo.

Case 1 becomes Case 2

- Olaratumab important considerations include increased rate of nausea and anaphylaxis.
- A the time of progression, the same patient was still ECOG PS0. She agreed to participate in a second clinical trial.
- At that time the open clinical trial was a randomized clinical trial of dacarbazine versus trabectedin.

Figure 1: Ecteinascidia turbinata, the sea squirt, growing in its natural habitat.

This agent derived from a Caribbean tunicate Ecteinascidia turbinata is a tetrahydroisoquinolone alkaloid. Alkylating drugs bind to DNA and disrupt its function.

Case 2 Continued

- Patient went on to receive 12 cycles of trabectedin before progression.
- This is given as a 24 hour infusion once every three weeks.
- Important considerations include heart failure, rhabdomyolysis and hepatitis
- Overall between clinical trials and multidiciplinary management the patient lived 4.7 years on active therapy from the time of metastatic disease.

NCCN

- All patients should be managed (not necessarily treated) by a multidisciplinary team with expertise in sarcoma
- Clinical trial is still the best option for a patient with metastatic LMS

Case 3:

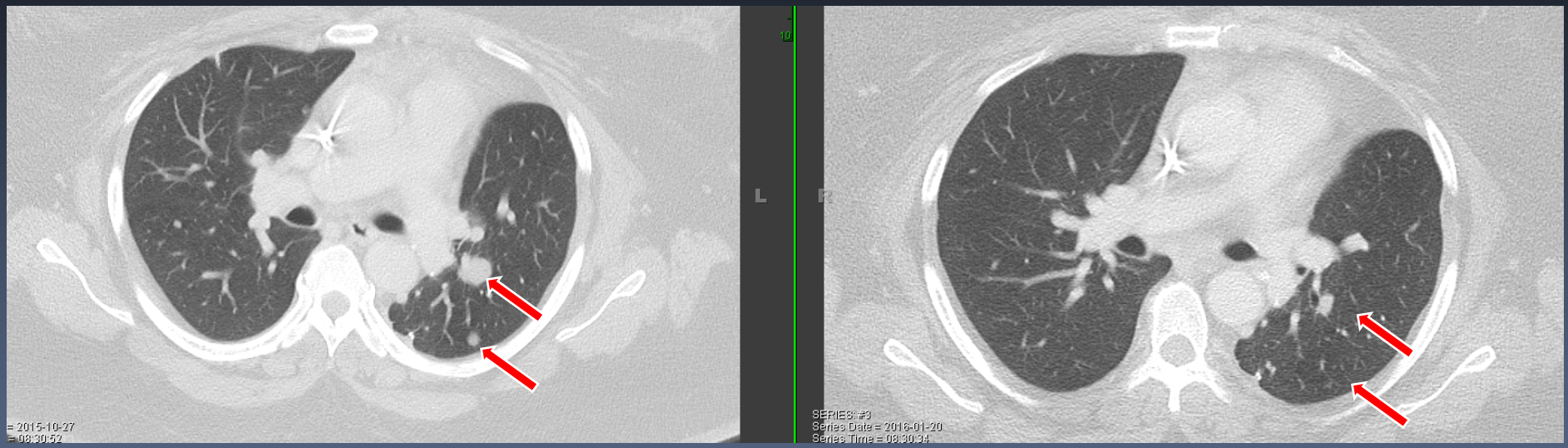
- 49YO AAF originally diagnosed with uLMS in 2013 underwent TAH-BSO.
- In 2014 relapsed with lung disease and underwent treatment with gemcitabine and docetaxel in combination with a TEM1 antibody that was on trial.
- The TEM1 antibody trial was negative.
- By the time she progressed the Alliance trial of ipilimumab and nivolumab was accrued (It took just three weeks).
- She begged to try this.
- Combination administered on compassionate use program.
- This case is interesting in light of the recent beautiful immunity paper suggesting that PD1 does not work well in uLMS

http://dx.doi.org/10.1016/j.immuni.2017.02.001

Patient has a durable CR that is ongoing

Before Immunotherapy

18 Months Later



- At this time I cannot advocate for off label use.

Other trials: Phase II Alliance A091401

- Nivolumab with or without ipilimumab in treating patients with metastatic or unresectable sarcoma
- Confirmed response rate estimated as the number of patients having a best objective tumor status of complete response or partial response lasting at least 4 weeks, divided by the number of evaluable patients
- This will be reported at ASCO this year

Clinicaltrials.gov. NLM Identifier: NCT02500797.

Other Important Pathways and Trials:

- Alisertib – a phase II trial by GOG against Aurora Kinase was negative
- Durvalumab/atezolizumab - PD-L1 inhibitors and other check point inhibitors need to be better explored in this sarcoma subset.
- Anlotinib is another TKI being developed from China to be reported at ASCO 2017
- Pazopanib combinations with topotecan MWSTP or gemcitabine are being tested for efficacy
- The use of hormonal therapies such as onapristone need to be approached from a molecular perspective.