13° CONGRESSO NAZIONALE AIOM GIOVANI

2019 NEWS IN ONCOLOGY

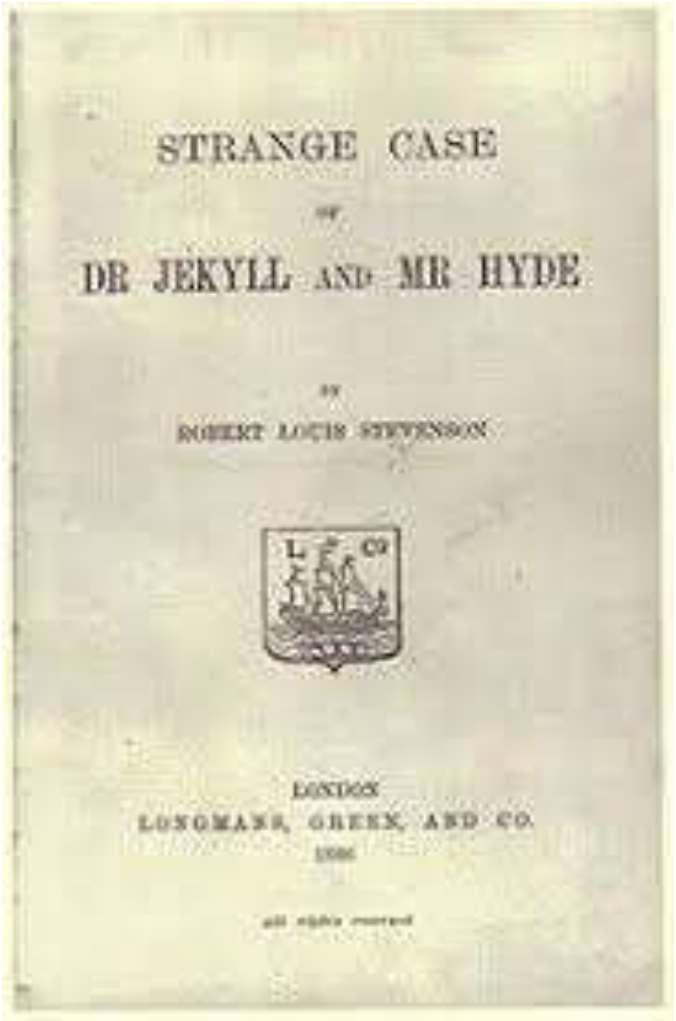
Eccellenze regolatorie e best practices: lo strano caso di Olaratumab

Lorenzo D'Ambrosio MD PhD

SC Oncologia

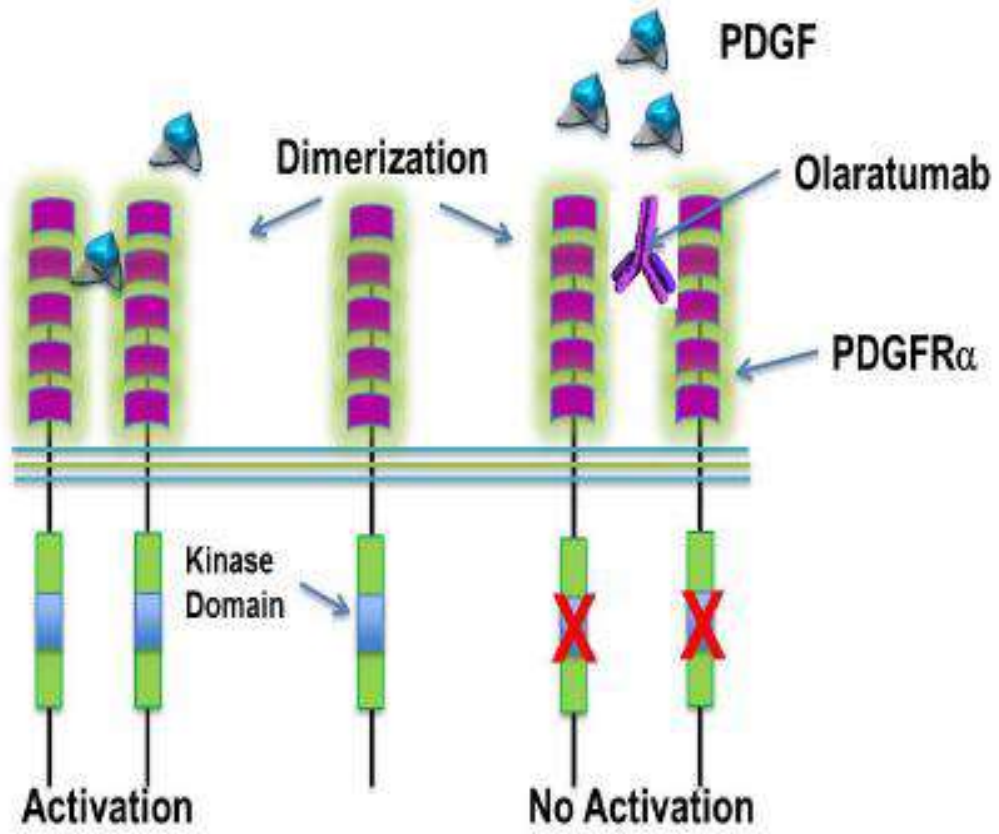
Ospedale Cardinal Massaia - Asti

The strange case of olaratumab



Olaratumab

- Fully human monoclonal antibody (IgG1) that selectively binds PDGFRα1.
- Blocks PDGF binding (PDGF-AA, -BB, -AB and -CC) and PDGF-induced PDGFRα activation.



PDGFR-α

Direct tumor effect

- **Genetically altered**

  and/or overexpressed in multiple tumor types including certain sarcomas

- Expression associated with **increased metastatic potential**

- **growth of tumor cells**

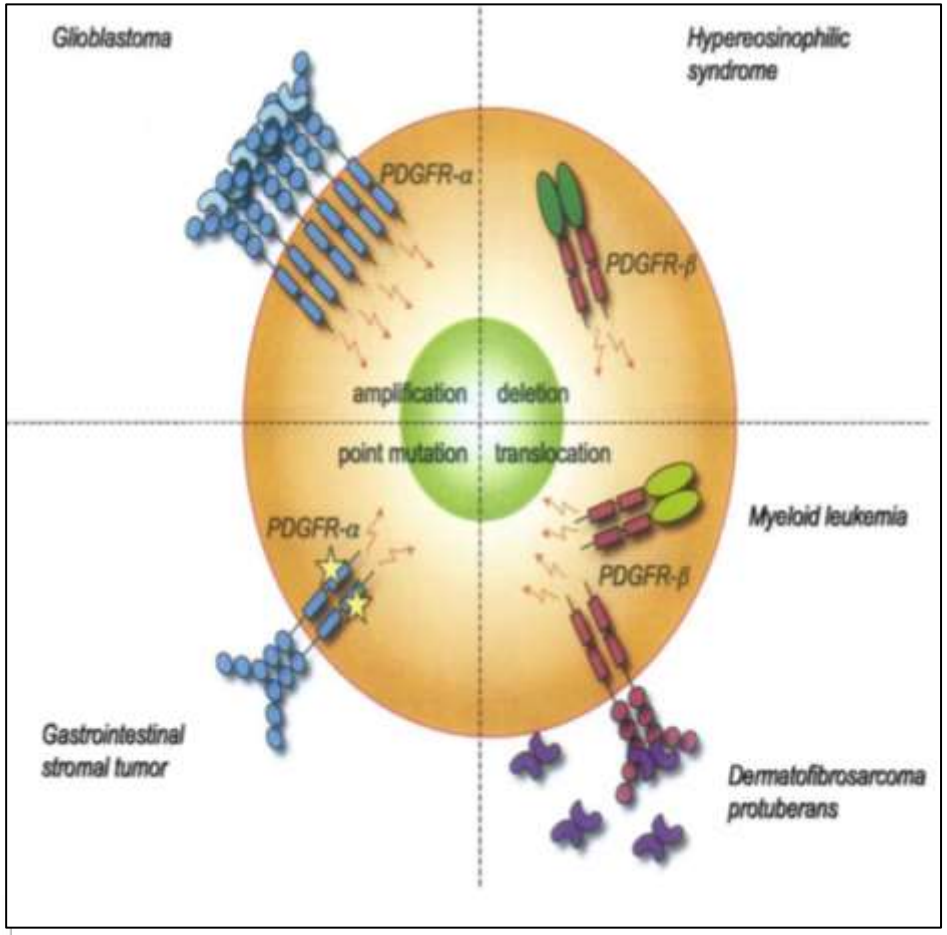
  via autocrine and paracrine functions

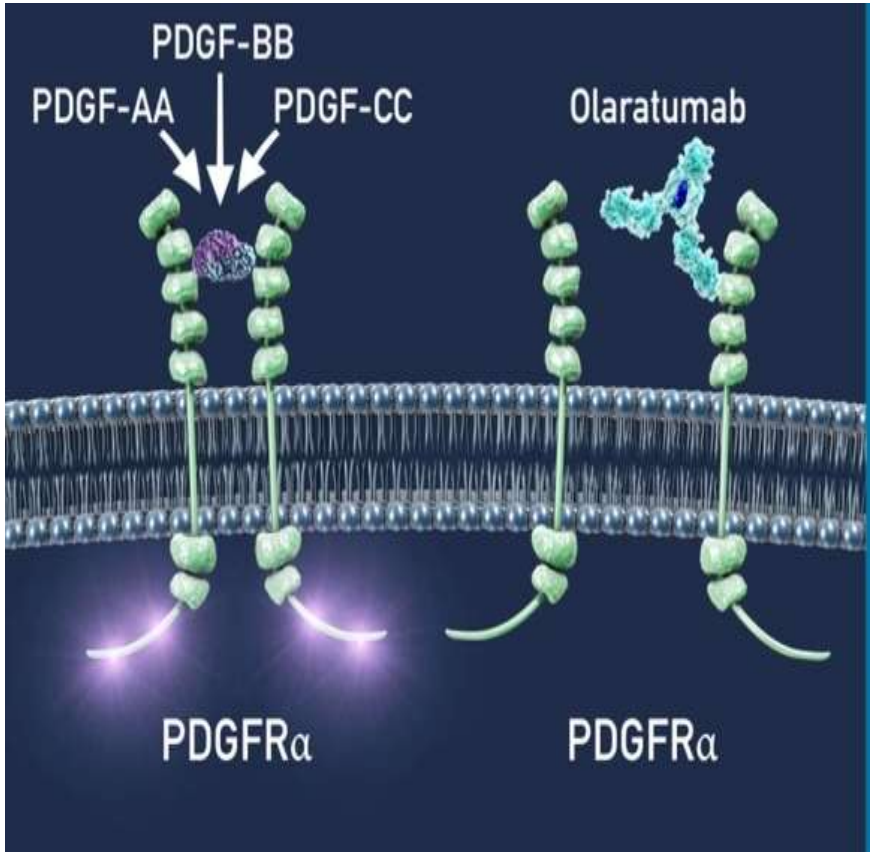
Direct stromal effect

- PDGF stimulation of PDGFRα-positive stromal cells **enhances tumor growth**

- **Angiogenesis**

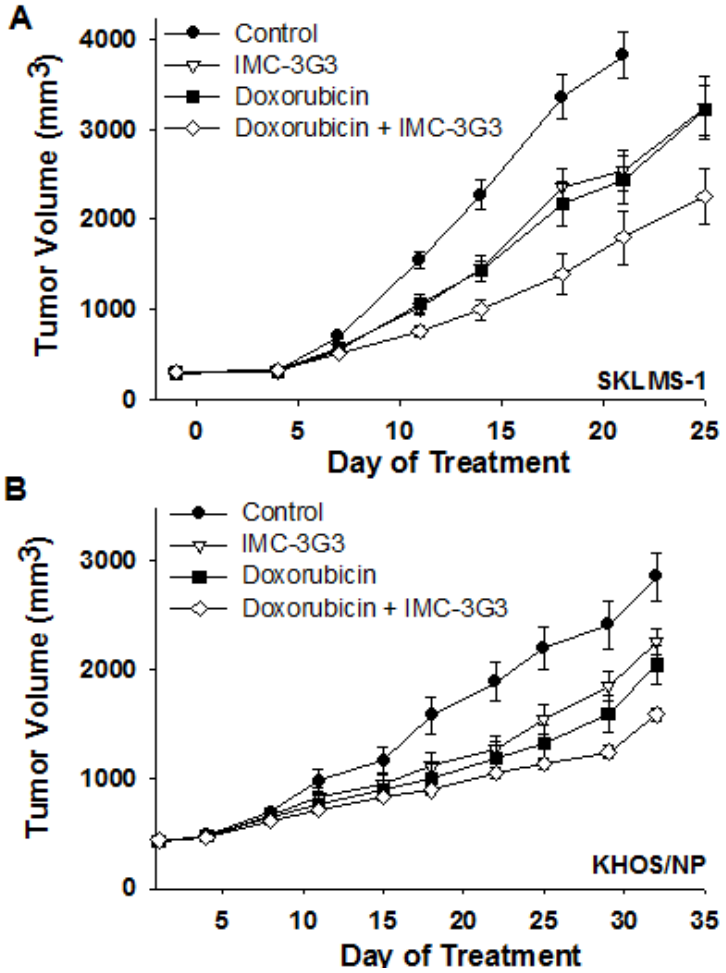
PDGFR-α in the cancer world





Andrae J. Role of platelet-derived growth factors in physiology and medicine. Genes Dev. 2008;22:1276-1312.

Preclinical activity



- **Olaratumab increases the antitumor effects of doxorubicin in the SKLMS-1 leiomyosarcoma model (p=0.05)**

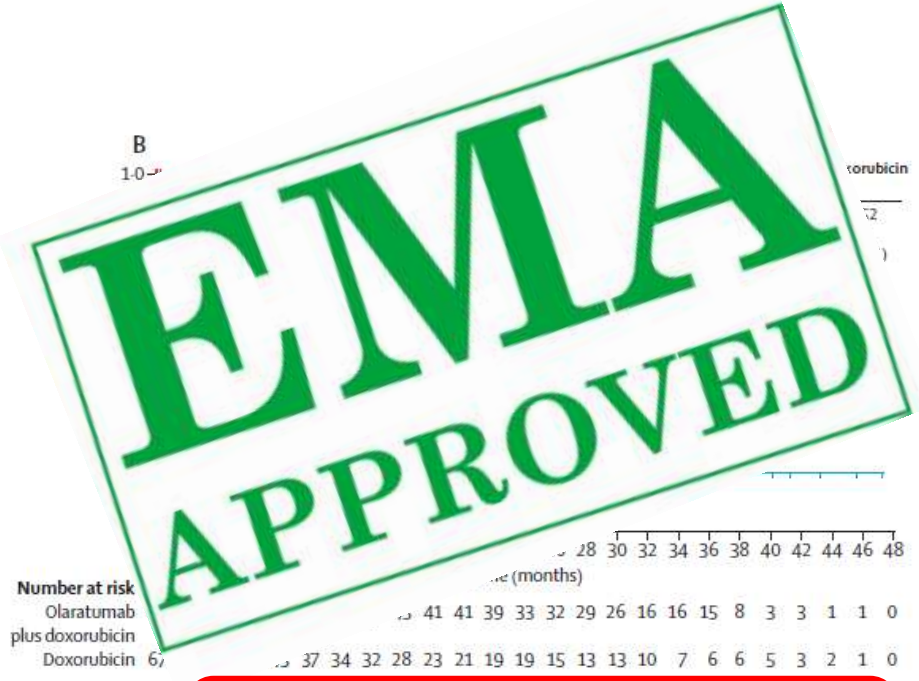
- **Olaratumab increases the antitumor effects of doxorubicin in the KHOS/NP osteosarcoma model (p=0.05)**

Loizos et al. *Mol Cancer Ther* 2005;4(3):369-79

Olaratumab in STS

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 Ilar... Jan Cosaert, Gary K Schwartz



FDA APPROVED

EMA APPROVED

PFS ≈ +2.5 months

OS ≈ +12 months

Lancet 2016; 388: 488–97

Agencies' announcement

Agenzia Italiana del Farmaco
AIFA

Pillole dal Mondo

Cari Colleghi,

Vi segnalo oggi che l'Agenzia Europea per i Medicinali (EMA) ha raccomandato la concessione di un'autorizzazione all'immissione in commercio condizionata per olaratumab per il trattamento di pazienti adulti affetti da sarcoma dei tessuti molli.

Buona lettura,
Luca Pani

@AIFA_ufficiale
@Luca_Pani

3 ottobre 2016

EMA raccomanda un nuovo trattamento per il sarcoma dei tessuti molli

L'Agenzia Europea per i Medicinali (EMA) ha raccomandato la concessione di un'autorizzazione all'immissione in commercio condizionata per Lartruvo (olaratumab) per il trattamento di pazienti adulti affetti da sarcoma dei tessuti molli, un raro tipo di cancro. Lartruvo deve essere utilizzato in combinazione con doxorubicina (un farmaco chemioterapico) nei pazienti con sarcoma dei tessuti molli avanzato, per i quali la chirurgia o la radioterapia risultino inidonee e che non siano stati precedentemente trattati con doxorubicina.

Vai sul sito AIFA per la notizia originale

3 ottobre 2016

EMA Conditional Marketing Authorization

Conditional marketing authorisation

Share

The European Medicines Agency (EMA) supports the development of medicines that address unmet medical needs of patients. In the interest of public health, applicants may be granted a conditional marketing authorisation for such medicines where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required, based on the scope and criteria defined in legislation and guidelines.

Medicines for human use are eligible if they are aimed at treating, preventing or diagnosing **seriously debilitating or life-threatening diseases**. This includes orphan medicines.

For products intended for use in emergency situations, less comprehensive pharmaceutical and non-clinical data may also be accepted.

Conditional marketing authorisations may be granted if the CHMP finds that **all the following requirements** are met:

- the benefit-risk balance of the product is positive;
- it is likely that the applicant will be able to provide comprehensive data;
- unmet medical needs will be fulfilled;
- the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data.

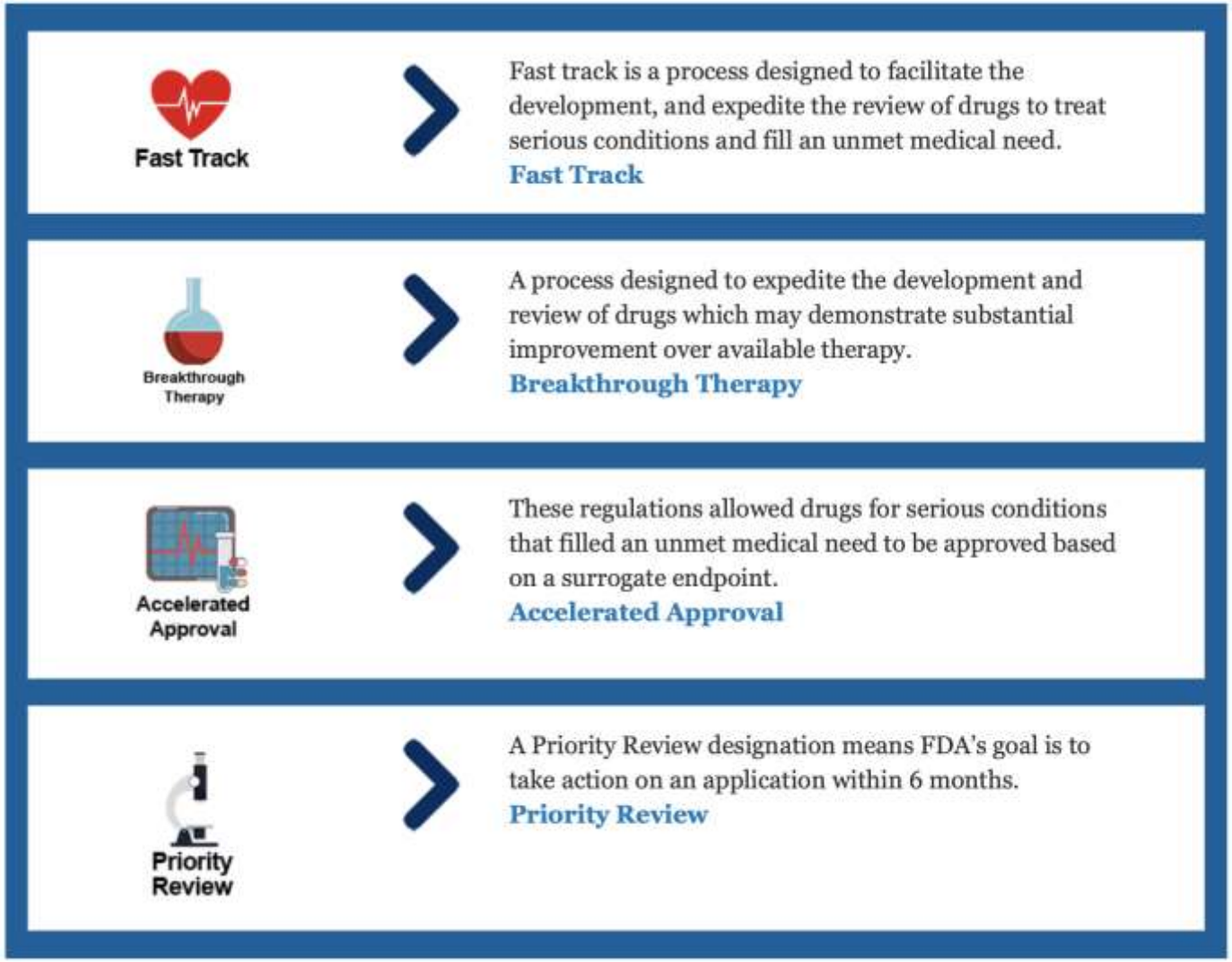
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA's olaratumab approval

On October 19, 2016, the U.S. Food and Drug Administration granted accelerated approval to olaratumab (LARTRUVO, Eli Lilly and Company) for the treatment of patients with soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery and with a histologic subtype for which an anthracycline-containing regimen is appropriate.

FDA granted olaratumab **fast track** and **breakthrough therapy** designation, **priority review status**, and **accelerated approval** for this indication. As a condition of the accelerated approval, Eli Lilly and Company is required to conduct a randomized, controlled trial to verify and further describe the clinical benefit of olaratumab given with doxorubicin in patients with STS. Olaratumab also received **orphan drug designation**.

FDA’s expedited programs



FDA's accelerated approval

"address unmet medical need in the treatment of a serious or life-threatening condition."

"help ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies' benefits justify their risks."

"in settings in which the disease course is long and an extended period of time would be required to measure the intended clinical benefits of a drug."

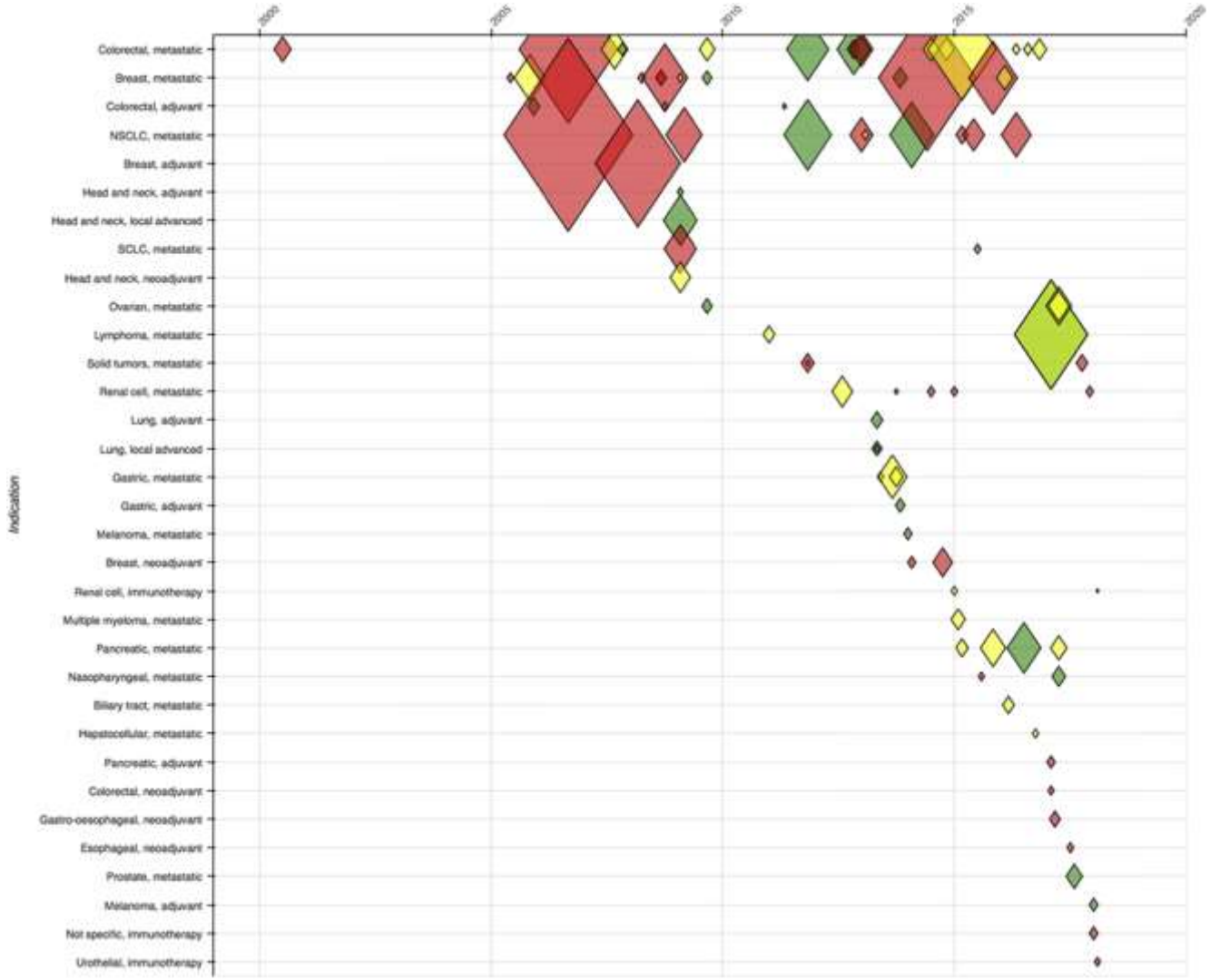
Surrogate endpoint

«A surrogate endpoint used for accelerated approval is a marker - a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Likewise, an intermediate clinical endpoint is a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality (IMM).»

The problem of surrogate endpoints

A systematic review of trial-level meta-analyses measuring the strength of association between surrogate end-points and overall survival in oncology

Alyson Haslam [a,*], Spencer P. Hey [b], Jennifer Gill [a], Vinay Prasad [c,d,e,f]



European Journal of Cancer 106 (2019) 196–211

OS benefit from new FDA approved drugs is marginal

JAMA Oncology | Original Investigation

Assessment of Overall Survival, Quality of Life, and Safety Benefits Associated With New Cancer Medicines

Sebastian Salas-Vega, MSc; Othon Iliopoulos, MD; Elias Mossialos, MD, PhD

IMPORTANCE There is a dearth of evidence examining the impact of newly licensed cancer medicines on therapy. This information could otherwise support clinical practice, and promote value-based decision-making in the cancer drug market.

OBJECTIVE To evaluate the comparative therapeutic value of all new cancer medicines approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) between 2003 and 2013.

DESIGN, SETTING, AND PARTICIPANTS We used a narrative synthesis approach to systematically synthesize and analyze English, French, and Australian health technology assessments (HTAs) of all new cancer medicines licensed in the United States and Europe between 2003 and 2013.

INTERVENTIONS Sixty-two new molecular entities with a primary oncology indication.

MAIN OUTCOMES AND MEASURES Overall survival (OS), quality of life (QoL), and safety.

RESULTS Of the 62 new active cancer molecules approved by the FDA and EMA between 2003 and 2013, 53 were appraised by English, French, or Australian HTA agencies through May 2015. Of these 53 drugs, 23 (43%) increased OS by 3 months or longer, 6 (11%) by less than 3 months, and 8 (15%) by an unknown magnitude; there was no evidence to suggest that the remaining 16 (30%) increased OS over best alternative treatments. Where overall survival gains could be quantified, all new cancer drugs were associated with a mean (SE) total increase in OS of 3.43 (0.63) months over the treatments that were available in 2003. Drug-related improvements in OS were, however, widely distributed across therapeutic targets—ranging between 0 (thyroid, ascites) and 8.48 months (breast cancers)—and were sometimes based on modeled data, indirect or nonactive comparisons, or nonvalidated evidence. Although 22 (42%) of 53 new medicines were associated with an increase in QoL, 24 (45%) were also associated with reduced patient safety. Of the 53 new cancer drugs, 42 (79%) were associated with at least some improvement in OS, QoL, or safety.

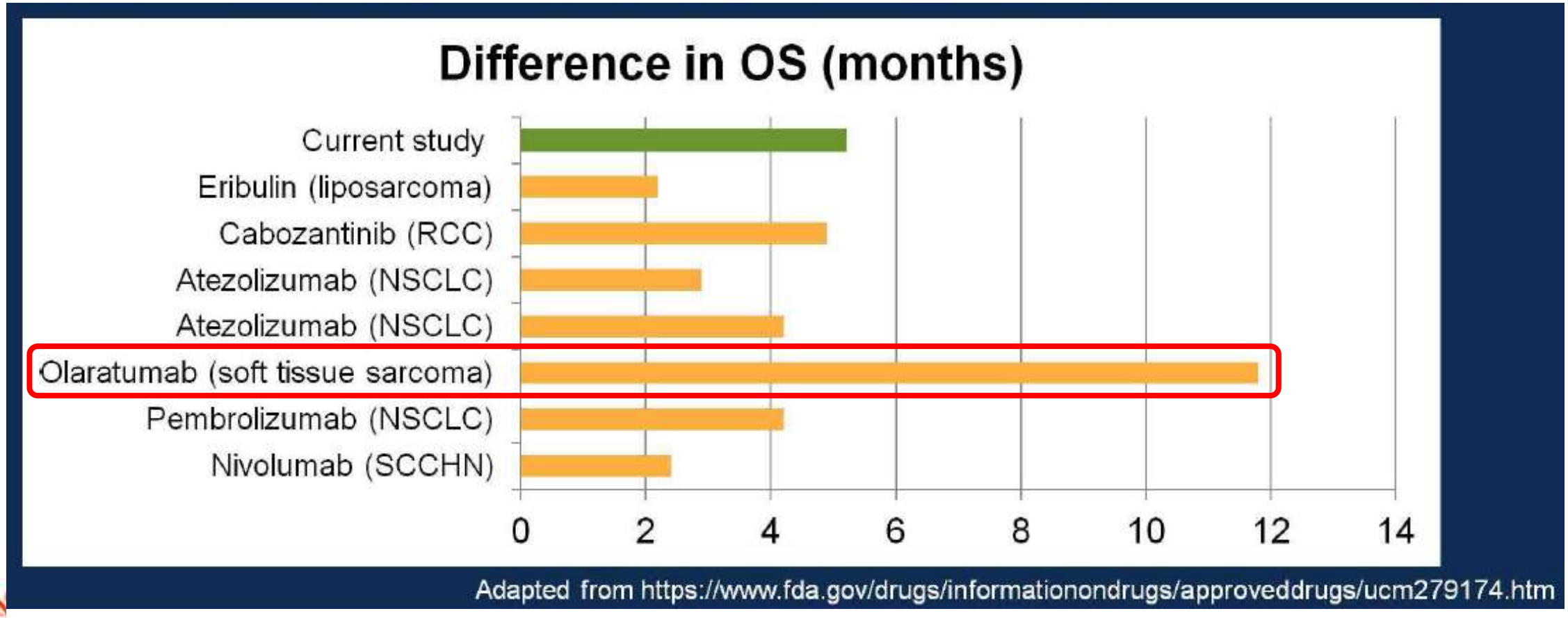
CONCLUSIONS AND RELEVANCE Although innovation in the oncology drug market has contributed to improvements in therapy, the magnitude and dimension of clinical benefits vary widely, and there may be reasons to doubt that claims of efficacy reflect real-world effectiveness exactly. These findings raise important questions for clinical decision-making and value-based policy.

Supplemental content

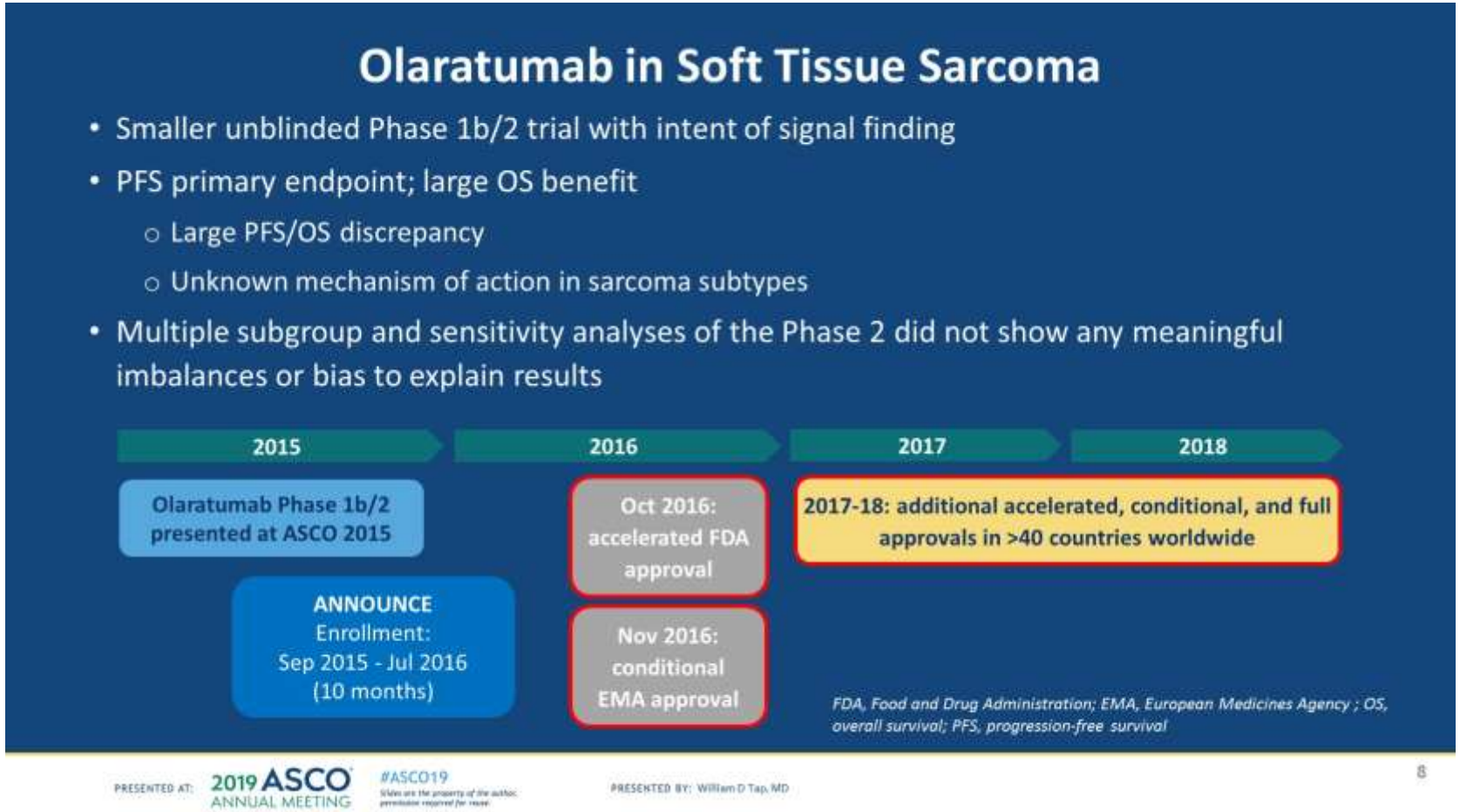
Author Affiliations: London Schc of Economics and Political Scienc London, England (Salas-Vega,

Figure 2. Analysis of Improvements in Overall Survival

Olaratumab enthusiasm



Worldwide olaratumab approval



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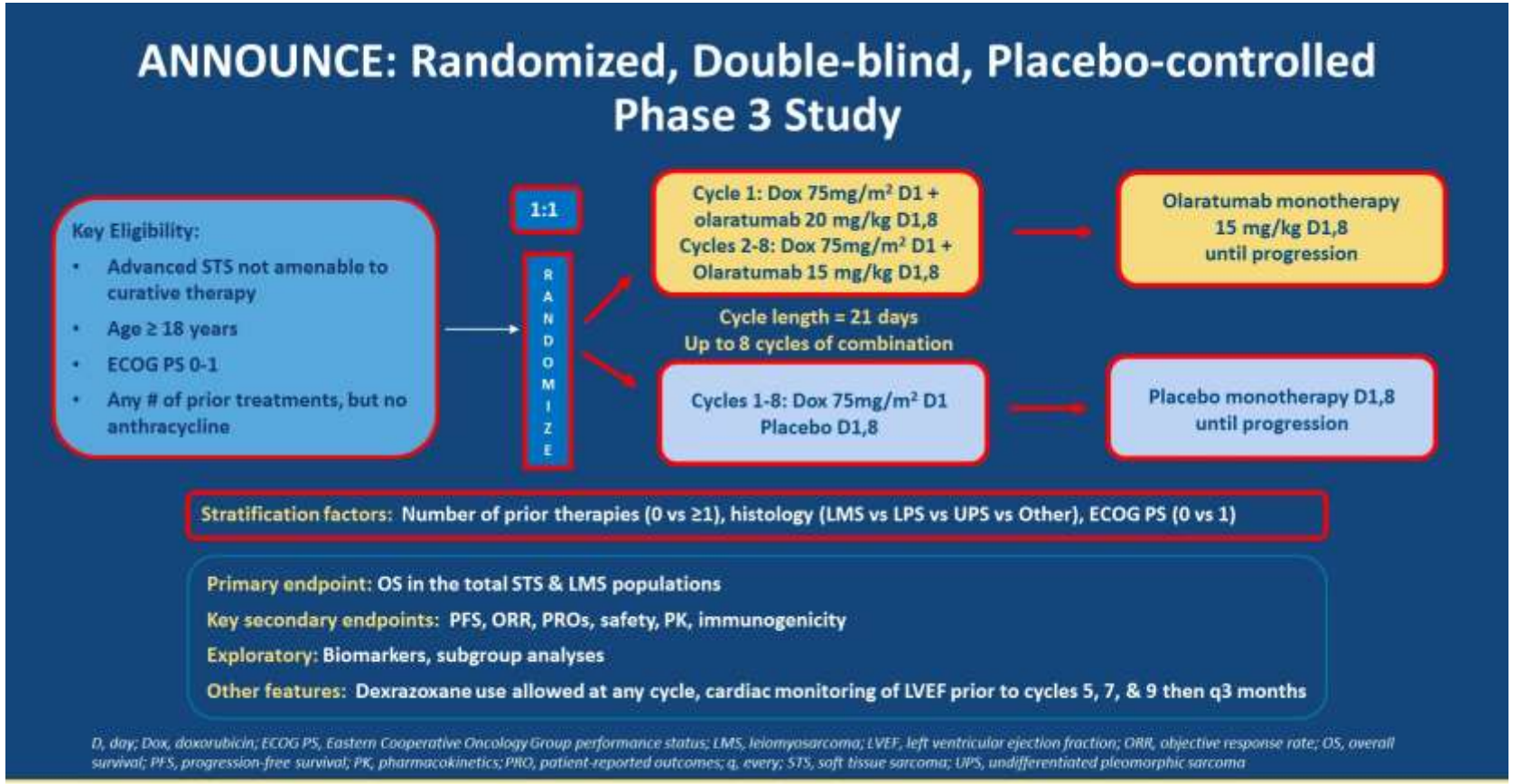
ANNOUNCE trial



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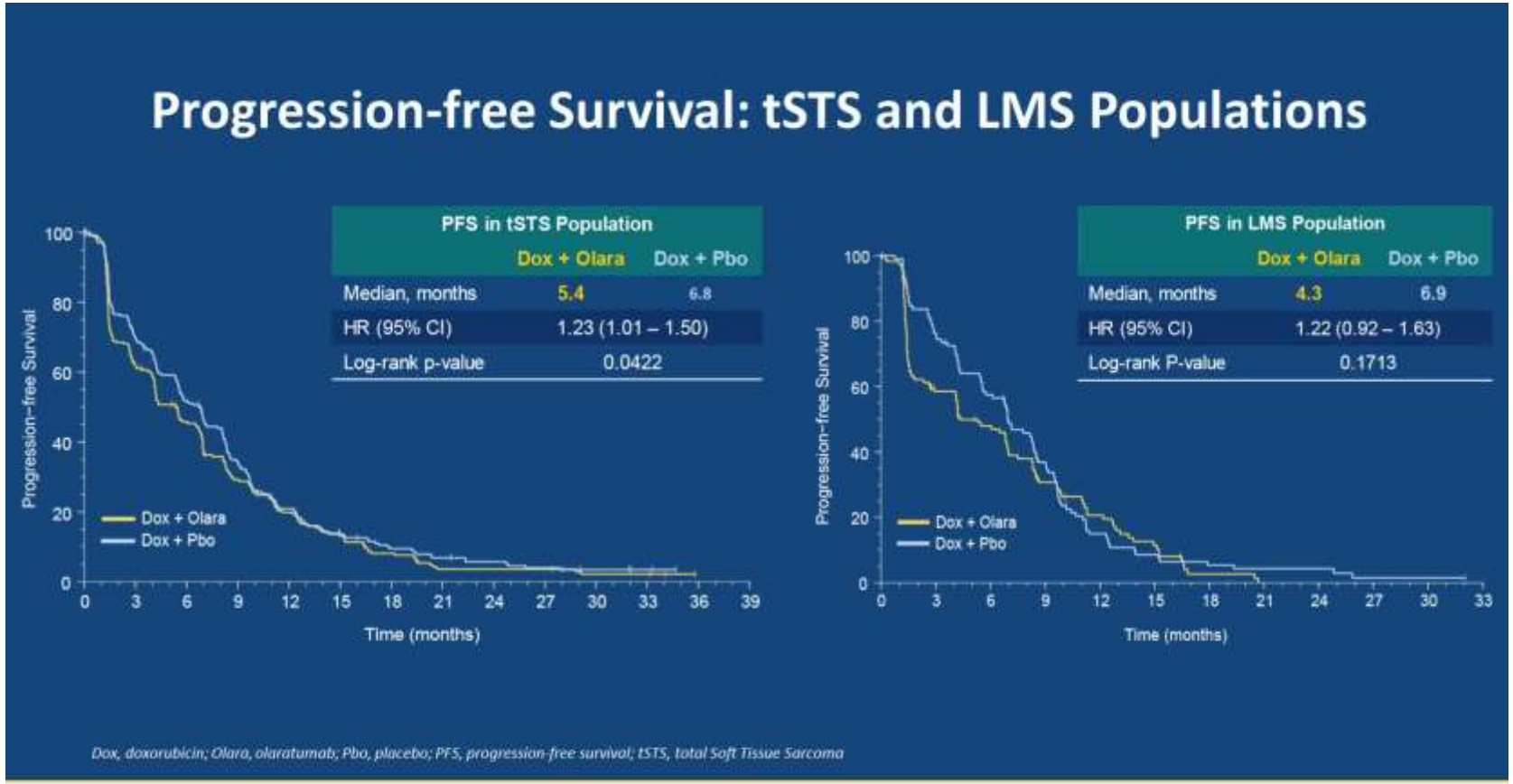
Progression-free survival



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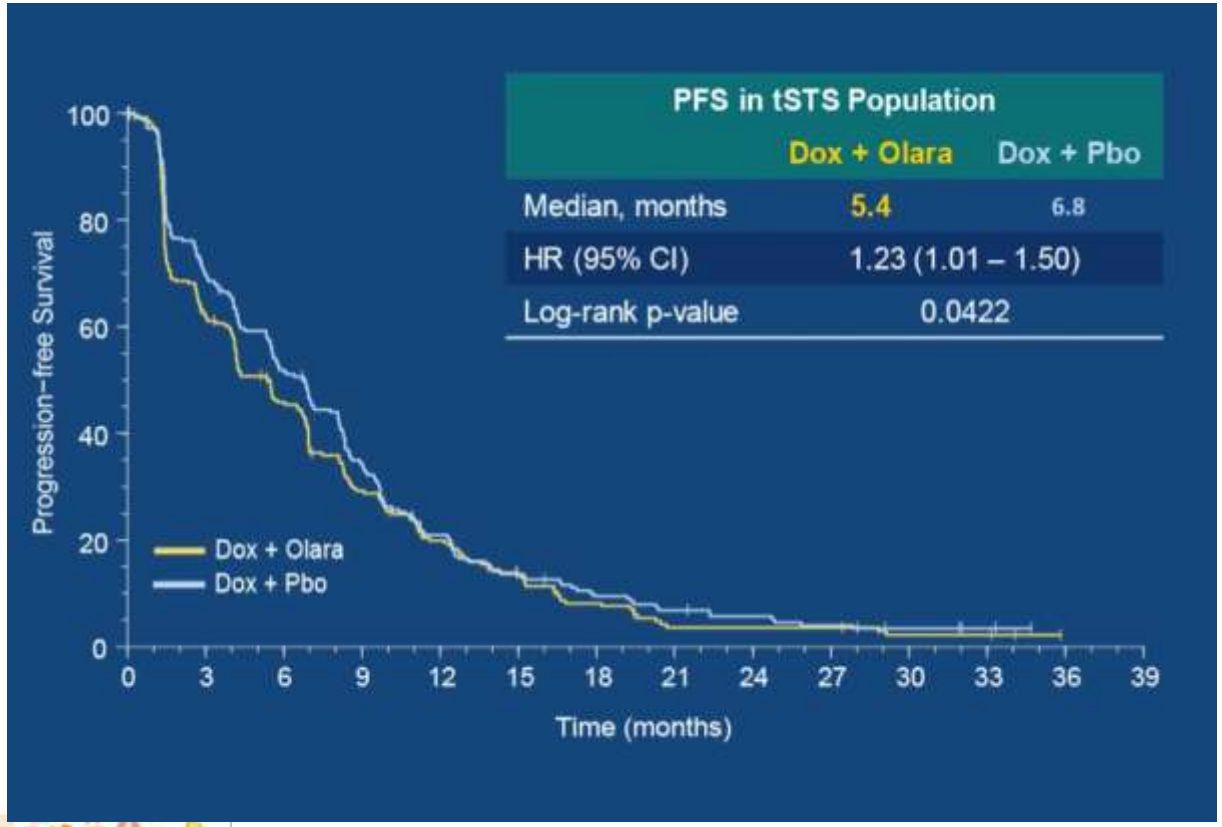
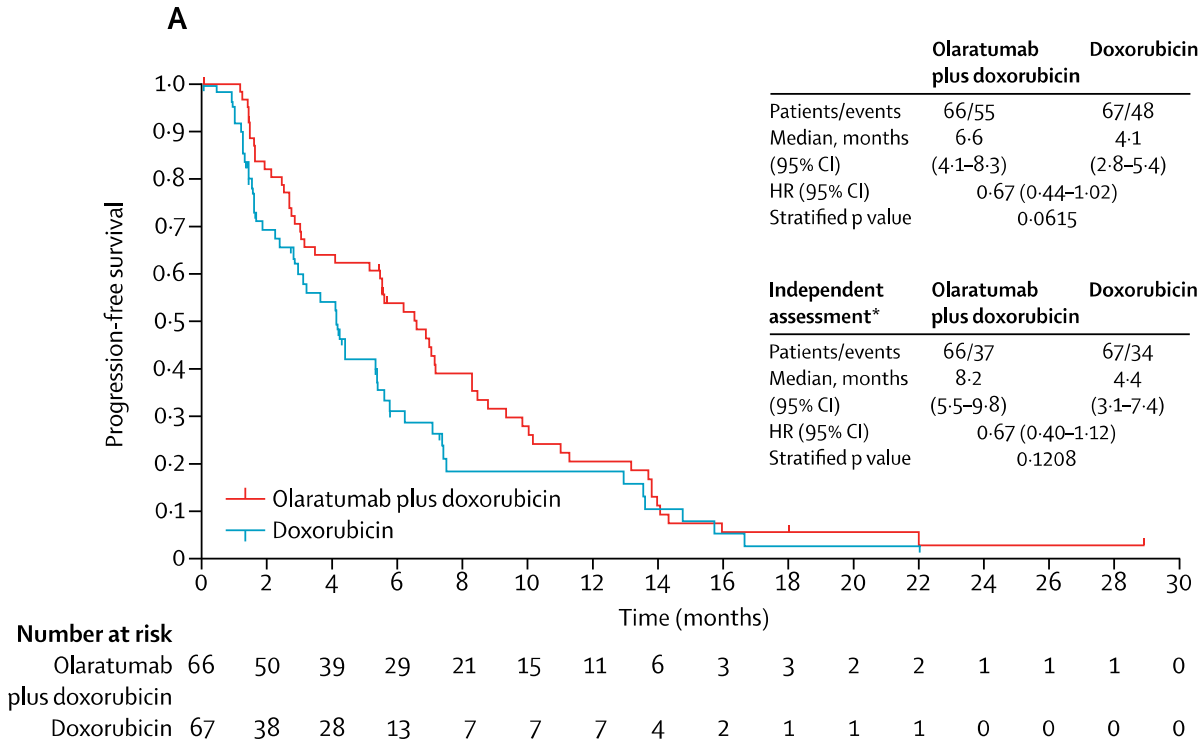
Progression-free survival

Phase 3



Phase 2



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Overall Response Rate

Overall Response Rate: tSTS and LMS Populations

Response rate, %	tSTS		LMS	
	Doxorubicin + Olaratumab (N=258)	Doxorubicin + Placebo (N=251)	Doxorubicin + Olaratumab (N=119)	Doxorubicin + Placebo (N=115)
Best overall response				
Complete response (CR)	0.8	0.4	0.8	0
Partial response (PR)	13.2	17.9	12.6	22.6
Stable disease (SD)	53.5	57.4	49.6	60.0
Progressive disease	27.1	20.7	33.6	14.8
Objective response rate	14.0	18.3	13.4	22.6
	p=0.1837		p=0.0890	
Disease control rate (CR+PR+SD)	67.4	75.7	63.0	82.6
	p=0.0595		p=0.0011	

LMS, leiomyosarcoma; tSTS, total soft tissue sarcoma

Overall Response Rate

Phase 3

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LMS, leiomyosarcoma; tSTS, total soft tissue sarcoma

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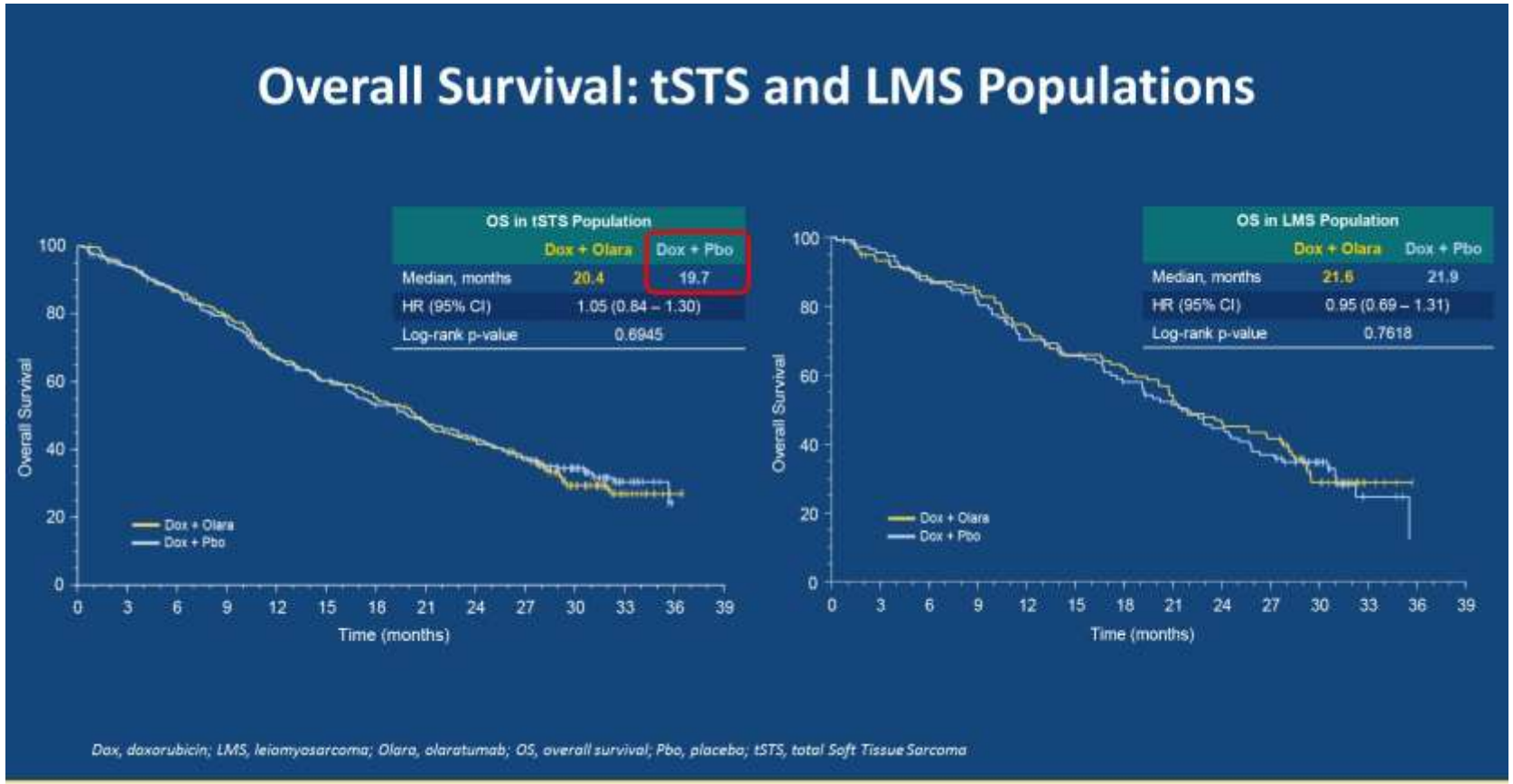
Phase 2

Supplementary Table S3. Response to Treatment (Phase 2) Investigator and Independent Assessments

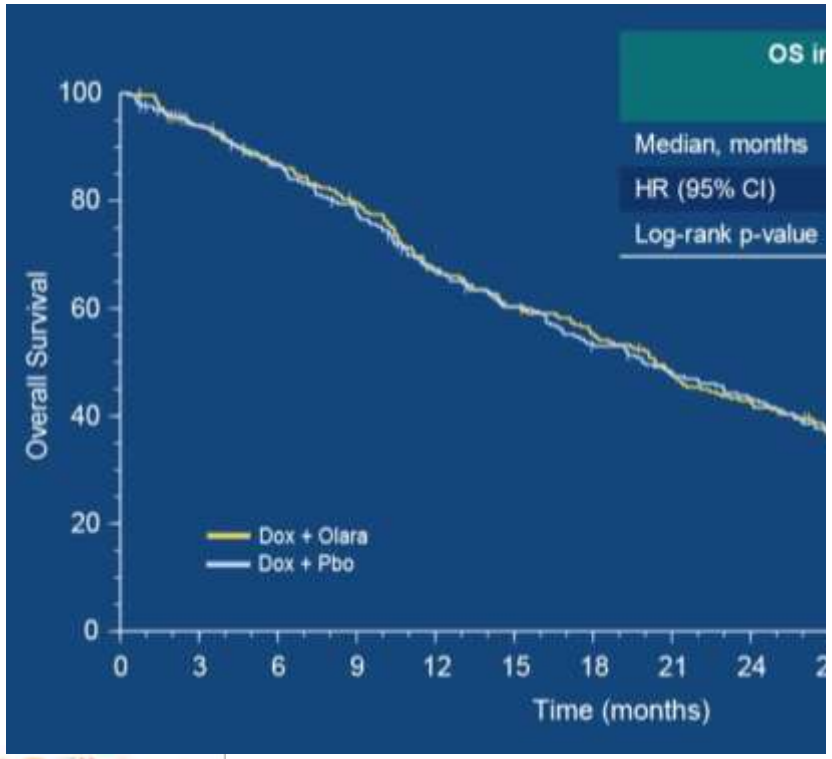
Characteristic	Investigator Assessment		Independent Assessment	
	Olaratumab + Doxorubicin (N=66)	Doxorubicin (N=67)	Olaratumab + Doxorubicin (N=66)	Doxorubicin (N=67)
Best overall response—no. (%)				
Complete response	2 (3.0)	1 (1.5)	3 (4.5)	1 (1.5)
Partial response	10 (15.2)	7 (10.4)	9 (13.6)	4 (6.0)
Stable disease	39 (59.1)	34 (50.7)	37 (56.1)	36 (53.7)
Progressive disease	11 (16.7)	15 (22.4)	11 (16.7)	15 (22.4)
Not evaluable	4 (6.1)	10 (14.9)	6 (9.1)	11 (16.4)
Disease control[a]				
No. of patients (%)	51 (77.3)	42 (62.7)	49 (74.2)	41 (61.2)
95% CI	65.3, 86.7	50.0, 74.2	62.0, 84.2	48.5, 72.9
Objective response[b]				
No. of patients (%)	12 (18.2)	8 (11.9)	12 (18.2)	5 (7.5)
95% CI	9.8, 29.6	5.3, 22.	9.8, 29.6	2.5, 16.6
P value (Fisher's exact test)	0.3421		0.0740	
Duration of response—mo.				
Median	8.3	8.2		
95% CI	2.7, 12.7	2.8, 14.5		

Overall Survival

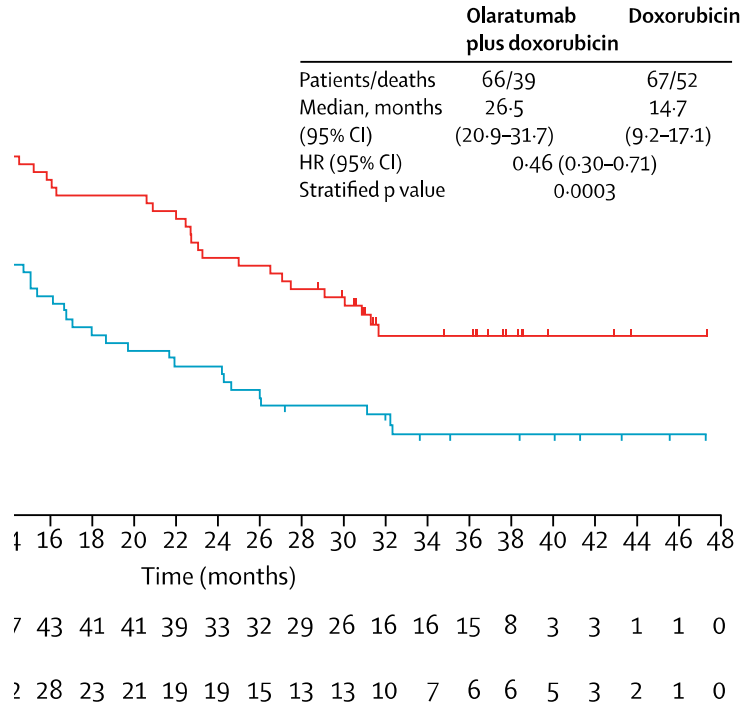


Overall Survival

Phase 3

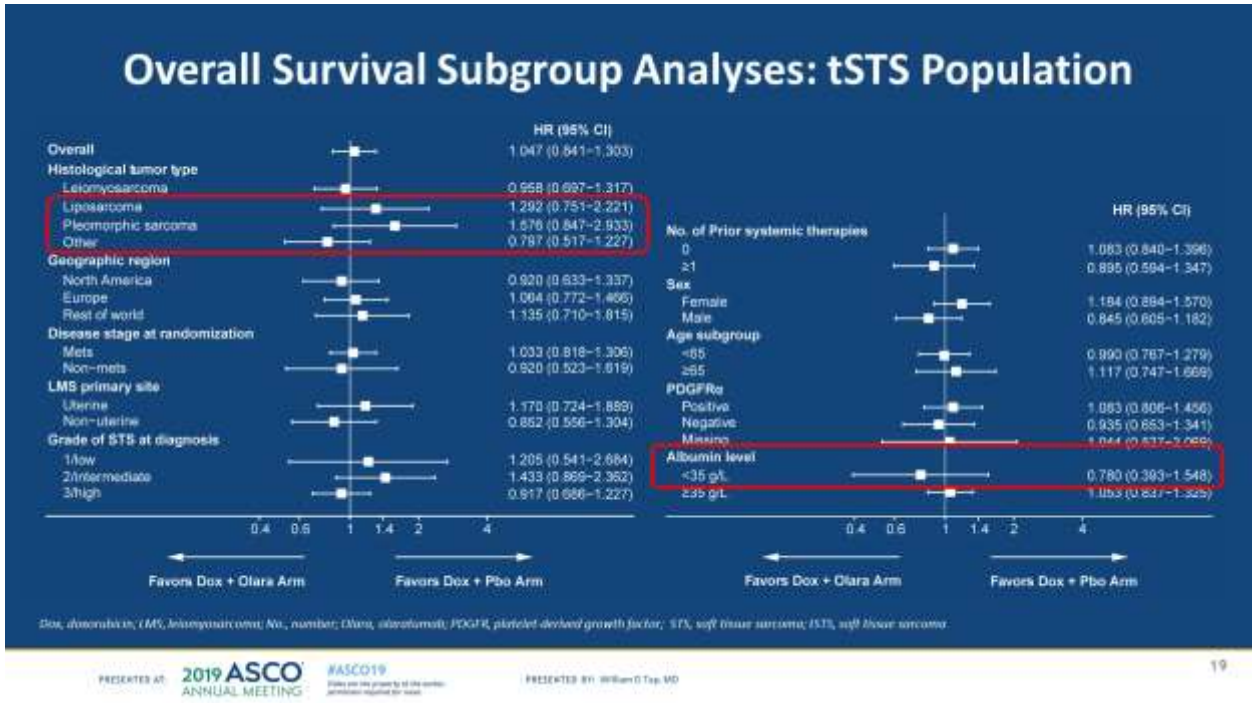


Phase 2



Subgroups?...same story

Phase 3



Phase 2

Subgroup	Investigational arm Number of events	Investigational arm n	Control arm Number of events	Control arm n	HR (95% CI)
PDGFRα (exploratory assay)					
Positive	14	18	17	19	0·64 (0·31–1·33)
Negative	19	37	26	37	0·40 (0·21–0·73)
Number of lines of previous treatment					
0	21	40	36	47	0·47 (0·27–0·81)
1 or more	18	26	16	20	0·55 (0·28–1·10)
Histological tumour type					
Leiomyosarcoma	16	24	24	27	0·47 (0·25–0·90)
Other	23	42	28	40	0·56 (0·32–0·97)
ECOG PS					
0	20	36	30	38	0·51 (0·29–0·91)
1	16	26	19	26	0·46 (0·24–0·91)
Sex					
Men	16	26	28	33	0·55 (0·30–1·02)
Women	23	40	24	34	0·53 (0·30–0·94)
Age (years)					
18–<65	30	48	33	43	0·54 (0·33–0·89)
≤65	9	18	19	24	0·48 (0·22–1·07)
Weight (kg)					
<81·4	19	29	31	37	0·53 (0·30–0·94)
≥81·4	20	37	21	30	0·56 (0·30–1·04)
Duration of disease (months)					
<14·95	20	33	29	34	0·38 (0·21–0·68)
≥14·95	19	33	23	33	0·68 (0·37–1·25)
Duration of most recent previous systemic treatment (months)					
<4·12	8	11	10	12	0·48 (0·18–1·26)
≥4·12	10	15	6	8	0·69 (0·25–1·91)
Grade					
Grade 1–2	5	12	10	15	0·46 (0·16–1·35)
Grade 3	21	29	25	29	0·58 (0·32–1·04)
Unknown/not assessed	13	25	17	23	0·42 (0·20–0·87)
Albumin at baseline (g/L)					
<38·0	22	29	30	37	0·60 (0·34–1·05)
≥38·0	17	37	22	30	0·46 (0·24–0·87)
Liver metastases					
Yes	17	26	19	22	0·45 (0·22–0·89)
No	22	40	33	45	0·51 (0·30–0·88)
Platelets at baseline (×10⁹/L)					
≤300	26	49	29	41	0·50 (0·29–0·86)
>300	13	17	23	26	0·73 (0·37–1·44)
White blood cell count at baseline (×10⁹/L)					
≤10	34	59	38	52	0·55 (0·34–0·87)
>10	5	7	14	15	0·74 (0·26–2·06)

0·1 0·5 1 2·1

Favours investigational arm Favours control arm

Looking behind OS data

Phase 3

Post-Discontinuation Therapy

Patients, n (%)	Doxorubicin + Olaratumab (N=258)	Doxorubicin + Placebo (N=251)	Total (N=509)
Surgery	32 (12.4)	28 (11.2)	60 (11.8)
Radiation	39 (15.1)	70 (27.9)	109 (21.4)
Systemic therapy			
Overall	178 (69.0)	169 (67.3)	347 (68.2)
Gemcitabine	72 (27.9)	82 (32.7)	154 (30.3)
Trabectedin	65 (25.2)	67 (26.7)	132 (25.9)
Pazopanib	55 (21.3)	57 (22.7)	112 (22.0)
Olaratumab	1 (0.4)	1 (0.4)	2 (0.4)

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Phase 2

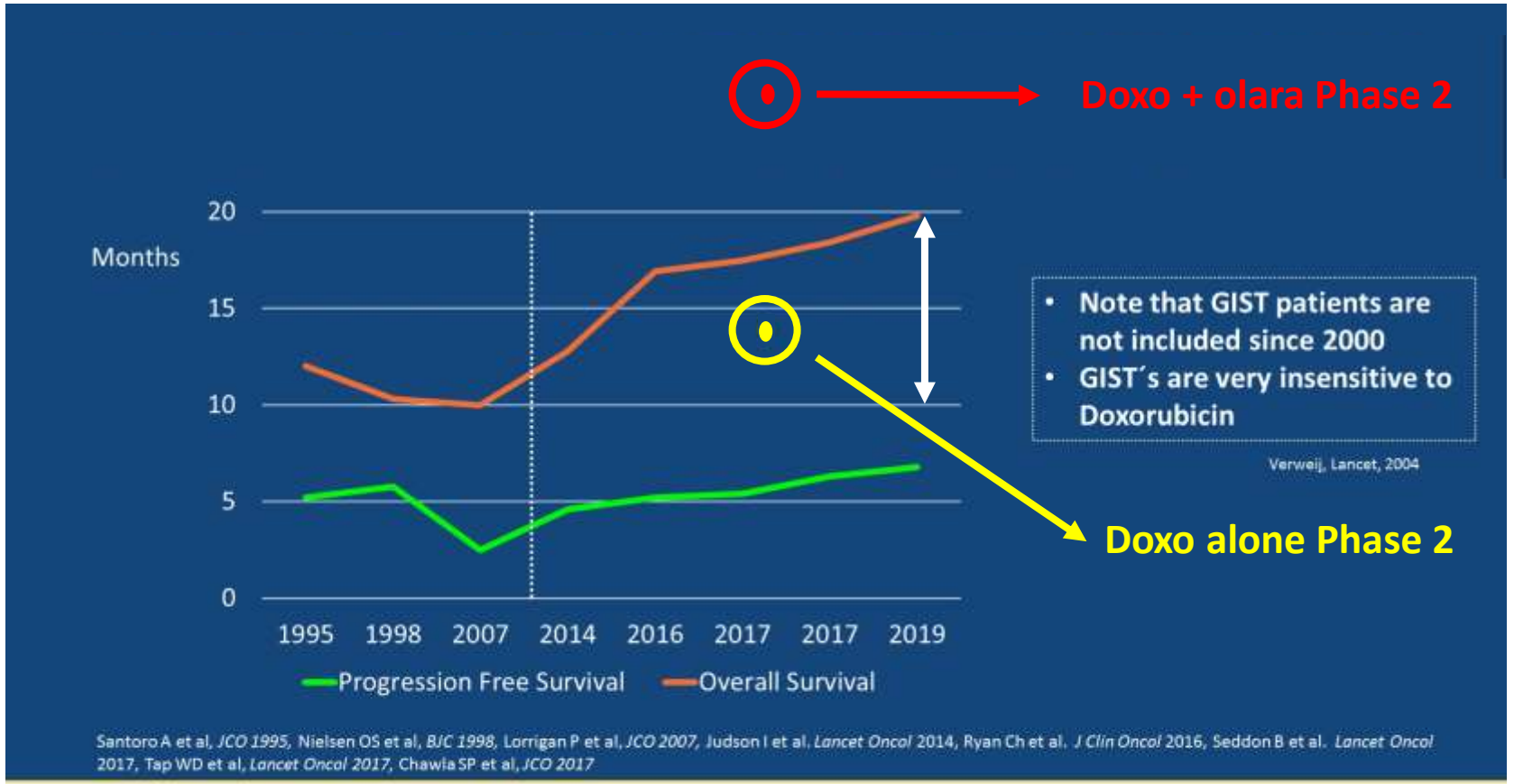
	Olaratumab plus doxorubicin (n=66)	Doxorubicin* (n=67)
Any additional treatment	44 (67%)	33 (49%)
1	18 (27%)	16 (24%)
2	12 (18%)	10 (15%)
3	9 (14%)	2 (3%)
4	1 (2%)	1 (2%)
>4	4 (6%)	4 (6%)

*Olaratumab monotherapy was not counted as a regimen for patients in the doxorubicin arm who elected to receive olaratumab monotherapy upon disease progression during doxorubicin treatment.

Table 2: **Total number of post-study anticancer treatments received (phase 2)**

Doxo alone -18%!!

Did doxo change through the years?



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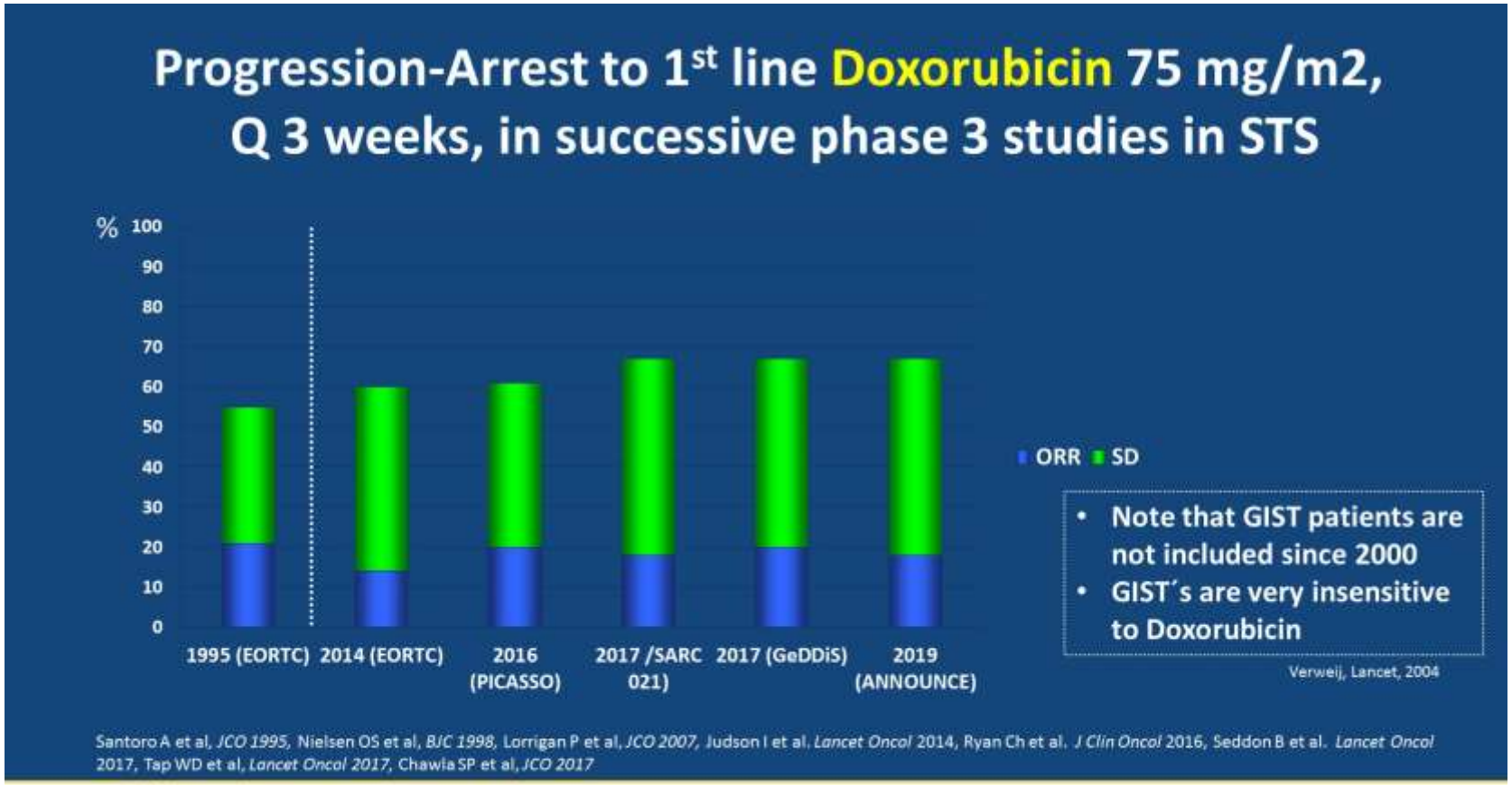
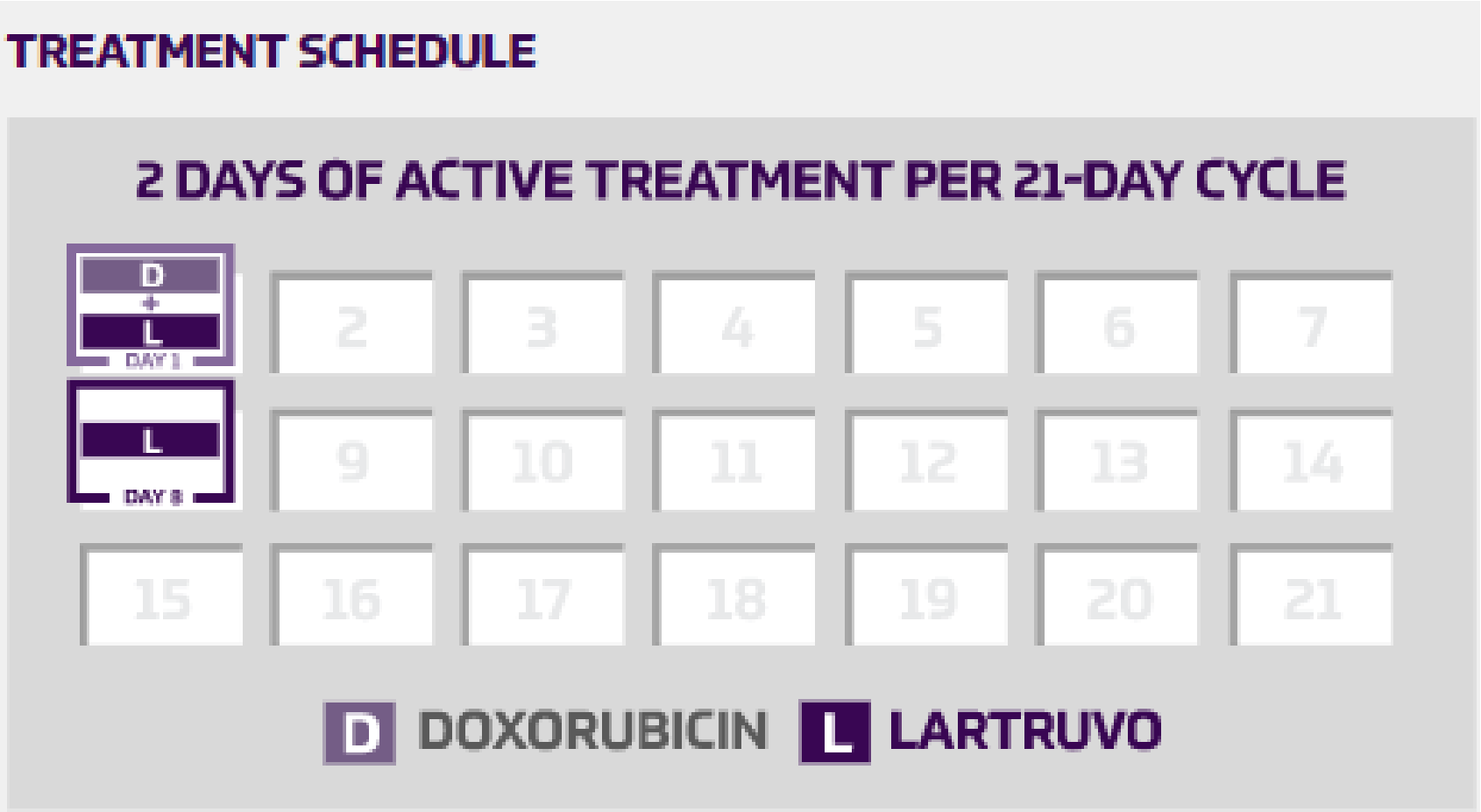


Presented By Jaap Verweij at 2019 ASCO Annual Meeting

Phase 1b/2 *vs.* Phase 3



Was the Phase 3 run correctly?

Validation of Study Conduct and Data Integrity

Verification

- Treatment assignment code
- Placebo vs olaratumab correctly labeled
- No olaratumab in placebo PK patient samples
- Proper PK levels in olaratumab patient samples
- Olaratumab vials contained “active drug” (met biologic specifications)

Results were not Influenced by

- Doxorubicin source
- Timing of dexrazoxane introduction
- Differences in premedication due to amendment
- Geographic region

Presented By William Tap at 2019 ASCO Annual Meeting

The original sin…no biomarker

Articles

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

alone included neutropenia (37 [58%] *vs* 23 [35%]), mucositis (34 [53%] *vs* 23 [35%]), nausea (47 [73%] *vs* 34 [52%]), vomiting (29 [45%] *vs* 12 [18%]), and diarrhoea (22 [34%] *vs* 15 [23%]). The number of infusion-related reactions in the olaratumab plus doxorubicin arm was (eight [13%] *vs* 0 for doxorubicin).

Treatment-related adverse events of grade 3 or higher and serious adverse events of grade 3 or higher were more frequent in patients treated with olaratumab plus doxorubicin than in those treated with doxorubicin (table 3). Fatigue and neutropenia of grade 3 or higher were more frequent with olaratumab plus doxorubicin (six [9%] and 34 [53%]) than with doxorubicin (two [3%] and 21 [32%]). However, the incidence of febrile neutropenia was similar in both groups: olaratumab plus doxorubicin (eight [13%] of 64) versus doxorubicin (nine [14%] of 65). The percentage of patients who discontinued treatment because of an adverse event was lower in the olaratumab plus doxorubicin group (eight [13%] of 64) than in the doxorubicin group (12 [18%] of 65).

Of the 129 treated patients in the phase 2 part of the

serum concentrations re
cessation of treatment at th

Analysis of PDGFRα expres
tumours in patient treate
doxorubicin and 8% of tumo
doxorubicin were PDGFRα p
this assay was subsequent
specificity for PDGFRα by
precluding meaningful data a
tumour samples with an assay
for PDGFRα showed that 33
treated with olaratumab plus
tumours in patients treated
positive for PDGFRα, consiste
interaction effect between PD
or negative) and treatment
either overall (p=0·3209) or
(p=0·5924).

Discussion

The combination of olaratumab plus doxorubicin improved both progression-free and overall survival

precluding meaningful data analysis. Reanalysis of study tumour samples with an assay that had better specificity for PDGFRα showed that 33% of tumours in patients treated with olaratumab plus doxorubicin and 34% of tumours in patients treated with doxorubicin were positive for PDGFRα, consistent with a 2015 study.[14] The interaction effect between PDGFRα expression (positive or negative) and treatment was not significant for

http://dx.doi.org/10.1016/S0140-6736(16)30587-6

Olaratumab and its "target"

ORIGINAL ARTICLE

Annals of Oncology 28: 541–546, 2017
doi:10.1093/annonc/mdw659
Published online 14 February 2017

A phase II study of a human anti-PDGFRα monoclonal antibody (olaratumab, IMC-3G3) in previously treated patients with metastatic gastrointestinal stromal tumors

A. J. Wagner[1*], H. Kindler[2], H. Gelderblom[3], P. Schöffski[4], S. Bauer[5], P. Hohenberger[6], H.-G. Kopp[7], J. A. Lopez-Martin[8], M. Peeters[9], P. Reichardt[10], A. Qin[11], J. Nippgen[12], R. L. Ilaria[11] & P. Rutkowski[13]

ORR 0%

Table 3. Progression-free survival estimated by Kaplan–Meier method (mITT population)[a]

	Cohort 1 (PDGFRα mutant) (*N*=7)	Cohort 2 (PDGFRα wild-type) (*N*=14)
Median (90% CI), weeks	32.1 (5.0–35.9)	6.1 (5.7–6.3)
12-week PFS rate (90% CI), %	51.4 (17.0–77.9)	14.3 (3.4–32.7)
24-week PFS rate (90% CI), %	51.4 (17.0–77.9)	NE

[a]This analysis censored data from two patients in cohort 1 who had no documented progressive disease during the study.
CI, confidence interval; mITT, modified intent-to-treat; NE, not evaluable; PDGFRα, platelet-derived growth factor receptor α; PFS, progression-free survival.

The oncologist's best skill

Biological rationale

Median time to the elaboration of a biological rationale to explain **ANY unexpected finding**:

90 seconds (anonymous, NCI, ~ 1980)

Courtesy of Paolo Bruzzi

Hitting PDGFR-α with olaratumab

Direct tumor effect

- **Genetically altered**

  and/or overexpressed in multiple tumor types including certain sarcomas

- Expression associated with **increased metastatic potential**

- **growth of tumor cells**

  via autocrine and paracrine functions

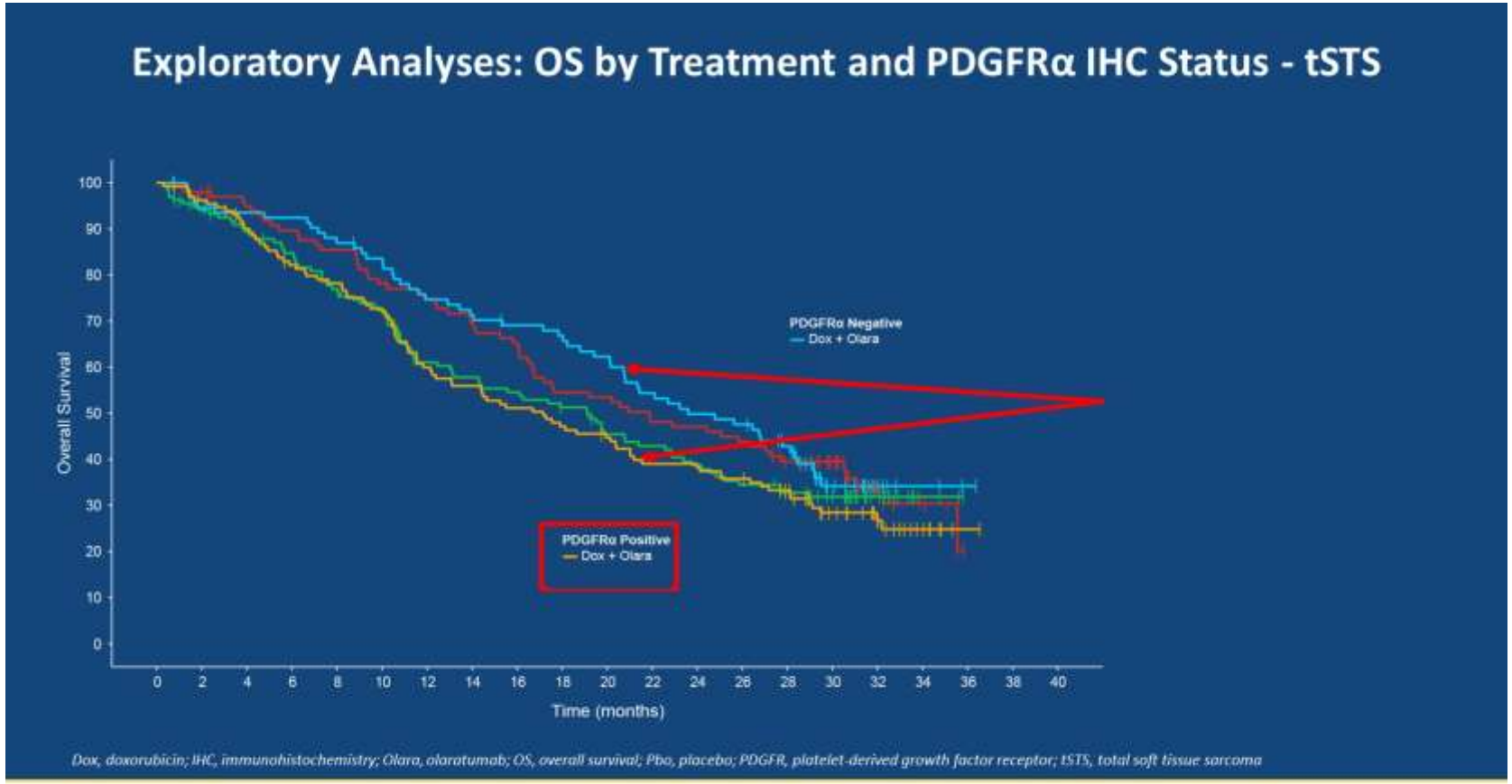
Direct stromal effect

- PDGF stimulation of PDGFRα-positive stromal cells **enhances tumor growth**

- **Angiogenesis**

?

ANNOUNCE trial: PDGFRα positive pts did worse



Presented By William Tap at 2019 ASCO Annual Meeting

Are expedited programs correct?

FDA Accelerated Approval (AA)

Clinical Review & Education

JAMA Oncology | Review

A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics

A Review

Julia A. Beaver, MD; Lynn J. Howie, MD; Lorraine Pelosof, MD, PhD; Tamy Kim, PharmD; Jinzhong Liu, MD; Kirsten B. Goldberg, MA; Rajeshwari Sridhara, PhD; Gideon M. Blumenthal, MD; Ann T. Farrell, MD; Patricia Keegan, MD; Richard Pazdur, MD; Paul G. Kluetz, MD

IMPORTANCE Accelerated approval (AA) is a US Food and Drug Administration (FDA) expedited program intended to speed the approval of drugs and biologics that may demonstrate a meaningful advantage over available therapies for diseases that are serious or life-threatening.

OBSERVATIONS This review describes all malignant hematology and oncology AAs from inception of the program on December 11, 1992, to May 31, 2017. During this period, the FDA granted AA to 64 malignant hematology and oncology products for 93 new indications. Of these AAs, 53 were for new molecular entities. Overall, the end point of response rate, including hematologic response rates, accounted for most AAs (81 [87%]), followed by time-to-event end points of progression-free survival or time to progression (8 [9%]) and disease-free survival or recurrence-free survival (4 [4%]). Single-arm trial designs provided the data for 67 (72%) of the initial AA indications. Of the 93 AAs, 51 (55%) have fulfilled their postmarketing requirement and verified benefit in a median of 3.4 years after their initial AA. Thirty-seven (40%) indications have not yet completed confirmatory trial(s) or verified benefit, and 5 indications receiving AA (5%) have been withdrawn from the market.

CONCLUSIONS AND RELEVANCE The use of the AA program during the past 25 years has increased over time, and only a small portion of indications under the AA program fail to verify clinical benefit. For patients with serious or life-threatening oncologic diseases, AA brings products to the market years before confirmatory trials are typically completed.

JAMA Oncol. 2018;4(6):849-856. doi:10.1001/jamaoncol.2017.5618
Published online March 1, 2018.

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 894

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Corresponding Author: Julia A. Beaver, MD, Office of Hematology and Oncology Products, US Food and Drug Administration, 10903 New Hampshire Ave, Building 22, Room 2100, Silver Spring, MD 20993 (julia.beaver@fda.hhs.gov).

FDA granted AA for 64 products for 93 new indications:

- **Common endpoints RR (87%), PFS (9%)**
- **55% fulfilled postmarketing requirements.**
  Median 3.4 yrs
- **40% not yet completed**
- **5% withdrawn from the market**

FDA AA - challenges

JAMA Internal Medicine | Original Investigation

Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval

Bishal Gyawali, MD, PhD; Spencer Phillips Hey, PhD; Aaron S. Kesselheim, MD, JD, MPH

Invited Commentary
pages 913 and 922

IMPORTANCE The US Food and Drug Administration's (FDA's) accelerated approval pathway allows investigational cancer drugs to be approved by demonstrating a beneficial effect on a surrogate measure (eg, progression-free survival) that is expected to predict a real clinical benefit (eg, overall survival). However, these drugs must undergo postapproval confirmatory studies to evaluate their actual clinical benefits. In an assessment of the accelerated approval pathway published in 2018, the FDA concluded that this pathway was successful because only 5 (5%) of 93 accelerated drug approvals had been withdrawn or revoked over the last 25 years.

OBJECTIVE To compare the end points used in preapproval trials leading to accelerated approval with the end points used in the required confirmatory trials that verified clinical benefit and to update the outcomes of accelerated approvals with confirmatory trials that were ongoing at the time of FDA's review.

DESIGN, SETTING, AND PARTICIPANTS A review of the literature on end points used in preapproval and confirmatory trials of cancer drugs that received accelerated approval and a review of the FDA's database of postmarketing requirements and commitments focused on the outcomes of confirmatory trials that were ongoing at the time of FDA's review of cancer drug approvals published in 2018.

MAIN OUTCOMES AND MEASURES End points used as confirmation of clinical benefit in cancer drugs that received accelerated approval, updated status of the confirmatory trials, and regulatory outcomes for cancer drugs that did not meet expectations in the confirmatory trials.

RESULTS The FDA published a review of 93 cancer drug indications for which accelerated approval was granted from December 11, 1992, through May 31, 2017. Of these approvals, the FDA reported that clinical benefit was adequately confirmed in 51 and confirmatory trials for 15 of these indications (16% of the main sample) accelerated approvals reported improvement in overall survival. For 19 approvals (37%), the confirmatory trials used surrogate measures that were the same as those used in the preapproval trials. In this updated review, confirmatory trials for 19 of 93 (20%) cancer drug approvals reported an improvement in overall survival, 19 (20%) reported improvement in the same surrogate used in the preapproval trial, and 20 (21%) reported improvement in a different surrogate. Five confirmatory trials were delayed, 10 were pending, and 9 were ongoing. For 3 recent approvals, the primary end points were not met in the confirmatory trials; however, 1 cancer drug indication still received full approval.

CONCLUSIONS AND RELEVANCE Confirmatory trials for one-fifth (n = 19 of 93) of cancer drug indications approved via the FDA's accelerated approval pathway demonstrated improvements in overall patient survival. Reassessment of the requirements for confirmatory trials may be necessary to obtain more clinically meaningful information.

Author Affiliations: Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Gyawali, Hey, Kesselheim); Department of Oncology, Department of Public Health Sciences, and Division of Cancer Care and Epidemiology,

Updated Total	**93**
Ongoing	9 (10)
Pending	10 (11)
Delayed	5 (5)
Confirmed benefit	58 (62)
+Clinical outcome[b]	19 (20)
+Surrogate outcome, same as preapproval trial[b]	19 (20)
+Surrogate outcome, different from preapproval trial[b]	20 (21)
Did not confirm benefit	8 (9)
Terminated	1 (1)
Not required	1 (1)
Safety study ongoing	1 (1)

We do need surrogate endpoints, but which is the best one?

Is still OS the best endpoint?

Olaratumab AA

Accelerated/Conditional Approval Olaratumab:

Pros:

- Patient access to a potentially significantly life-prolonging agent.
- Additional risks/toxicities fairly minimal.
- Attention given to a disease of great unmet need.

Cons:

- Burden on patient for extra treatment.
- Some patients with life-threatening infusion reactions.
- Costs to patient, insurance, manufacturer.

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19 PRESENTED BY: Rashmi Chugh, MD 9

Presented By Rashmi Chugh at 2019 ASCO Annual Meeting

Olaratumab – Jan 18, 2019

For Release: Immediately
Refer to: Carole Copeland; carole_copeland@lilly.com; 317-610-6196 (media)
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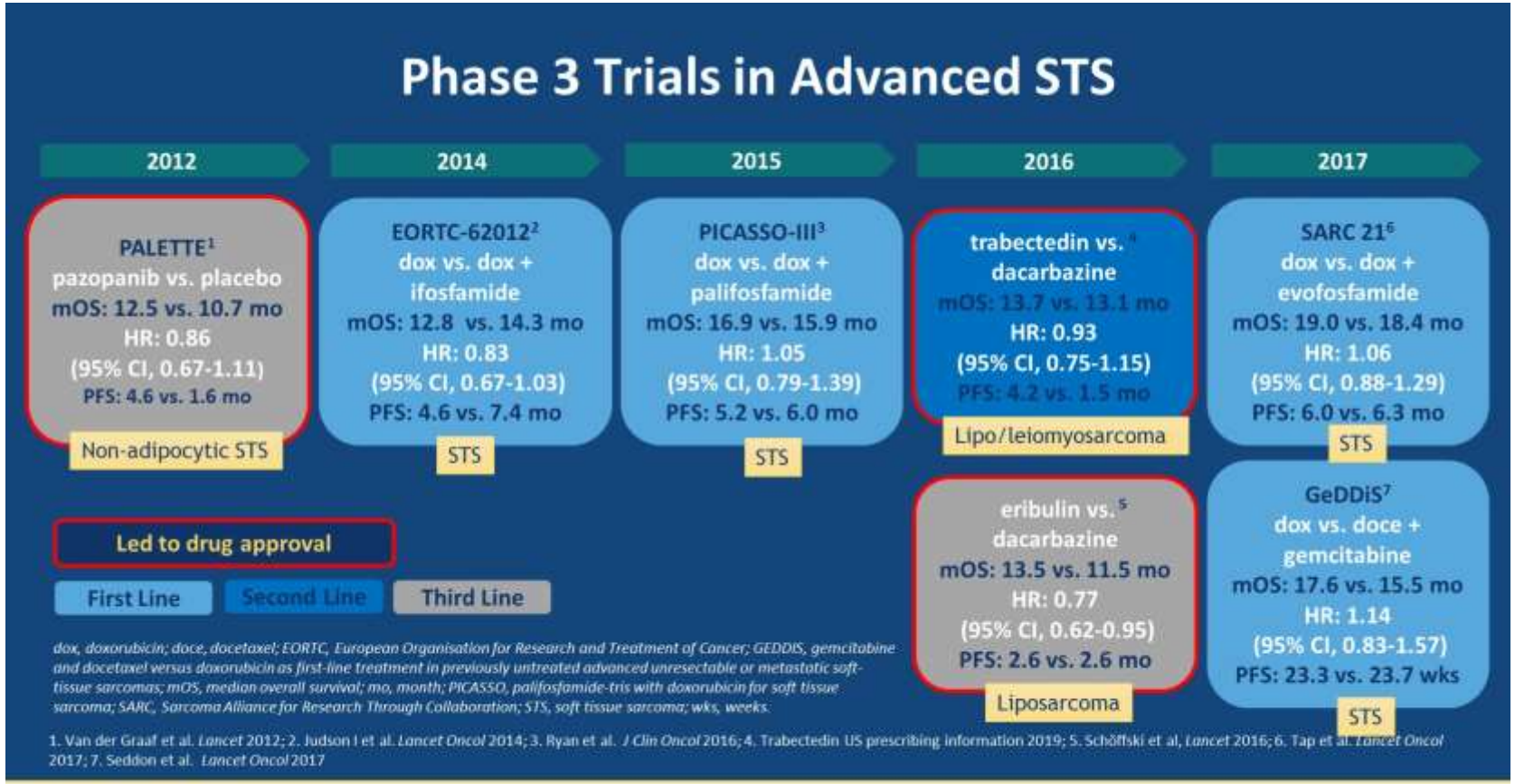
Lilly Reports Results of Phase 3 Soft Tissue Sarcoma Study of LARTRUVO®

- *Study did not meet the primary endpoints of overall survival (OS) in the full study population or in the leiomyosarcoma (LMS) sub-population; there was no difference in survival between the study arms for either population.*
- *There were no new safety signals identified and the safety profile was comparable between treatment arms.*

INDIANAPOLIS, January 18, 2019 – Eli Lilly and Company (NYSE: LLY) today reported that the results of ANNOUNCE, the Phase 3 study of LARTRUVO® (olaratumab), in combination with doxorubicin in patients with advanced or metastatic soft tissue sarcoma (STS), did not confirm the clinical benefit of LARTRUVO in combination with doxorubicin as compared to doxorubicin, a

The challenge of first-line doxo-combos for STS

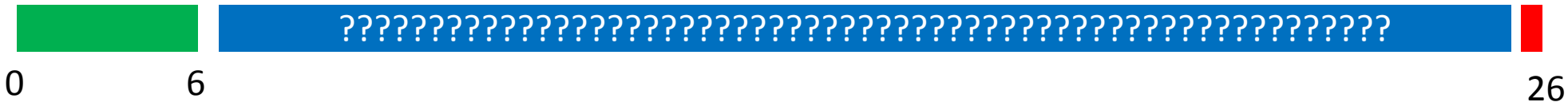


Presented By Rashmi Chugh at 2019 ASCO Annual Meeting

Closing remarks

- **Overall survival is our goal, but don’t forget what happens in between**

Doxo + olaratumab



Closing remarks

- **Overall survival is our goal, but don’t forget what happens in between**
- **BSC is a crucial actor (Phase 2 was probably doxo vs doxo + BSC)**
- **International efforts can run big trials in rare diseases (ANNOUNCE enrolled 50 pts/month)**
- **Sarcomas cannot be considered as a single entity**
- **Doxorubicin is doxorubicin…**
- **To use a target therapy as such, you need a target!!**

THANKS FOR YOUR ATTENTION!

ldambrosio@asl.at.it

BACKUP SLIDES

TABLE 1

The FDA's expedited programs

Program name	Qualifying criteria	Features
Fast track	Treats a serious medical condition and has the potential to address unmet medical need	Acts to expedite development and review, with approval possible after a single Phase 2 study; rolling review
Priority review	Includes drugs that would provide a significant improvement in safety or effectiveness	Has shortened FDA review time of four months; can be combined with other expedited programs
Accelerated approval	Treats a serious condition that generally provides a meaningful advantage over available therapies	Can approve on the basis of a surrogate or intermediate endpoint that is reasonably likely to predict a clinical benefit
Breakthrough therapy	Treats a serous condition; preliminary clincial evidence indicates that the drug may be a substantial improvement over existing therapies	Has all fast track features; intensive guidance on efficient drug development

Sources: Food and Drug Administration, Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (U.S. Department of Health and Human Services, 2014), available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf; Trinia Cain and Stephanie Shapley, "Expedited Programs for Serious Conditions Drugs and Biologics (Draft Guidance)" (Silver Spring, MD: U.S. Food and Drug Administration, 2013), available at http://www.fda.gov/downloads/Drugs/UCM363903.pdf; Aaron S. Kesselheim and others, "Trends in utilization of FDA expedited drug development and approval programs, 1987-2014: cohort study," British Medical Journal 351 (2015).

Supplementary Table S1. Disease at Baseline by Histologic Subtype (Phase 2) (see also Table 2 of main article)

Histological type—no. (%)	Olaratumab + Doxorubicin (N=66)	Doxorubicin (N=67)
Angiosarcoma[a]	4 (6.1)	3 (4.5)
Fibrosarcoma	1 (1.5)	0
Leiomyosarcoma	24 (36.4)	27 (40.3)
Liposarcoma	8 (12.1)	15 (22.4)
Neurofibrosarcoma	1 (1.5)	0
Pleomorphic undifferentiated sarcoma	10 (15.2)	14 (20.9)
Synovial sarcoma	1 (1.5)	2 (3.0)
Other[b]		
Alveolar soft part sarcoma	1 (1.5)	0
Chondrosarcoma bone	0	2 (3.0)
Clear cell sarcoma	1 (1.5)	0
Endometrial stromal sarcoma	1 (1.5)	0
Epithelioid sarcoma	2 (3.0)	0
Extraskeletal chondrosarcoma	0	1 (1.5)
Extraskeletal myxoid chondrosarcoma	1 (1.5)	0
Fibromyxoid sarcoma	1 (1.5)	1 (1.5)
Fibrosarcomatous transformation in a recurrent dermatofibrosarcoma	1 (1.5)	0
Hemangiopericytoma	1 (1.5)	1 (1.5)
Malignant glomus tumor	1 (1.5)	0
Malignant peripheral nerve sheath tumor	1 (1.5)	0
Malignant solitary fibrous tumor	1 (1.5)	0
Myxofibrosarcoma	1 (1.5)	0
Myxoid chondrosarcoma	1 (1.5)	0
Myxoid sarcoma	0	1 (1.5)
Soft tissue undifferentiated round cell carcoma negative for EWS	1 (1.5)	0
Undifferentiated neoplasm	1 (1.5)	0
Undifferentiated uterine sarcoma	1 (1.5)	0

Possible Reasons for ANNOUNCE Outcome

- Olaratumab is not effective with doxorubicin in STS
  - Small sample size, unrecognizable imbalances
    - Numerous represented histologies with disparate clinical behavior
  - Subsequent subtype specific treatments influenced OS

- Olaratumab has some activity in STS patients
  - Heterogeneity of study populations within and between studies
    - Diversity of sarcomas, Disease burden/behavior (albumin), PDGFR-status
  - Differences in study designs
  - ANNOUNCE control arm performed better than expected

ANNOUNCE

- Was a well controlled and conducted Phase 3 trial which failed to meet its overall survival primary endpoint in all STS histologies or the LMS population
- Did not confirm the benefit seen in the Phase 1b/2 trial
- Control arm had the highest OS for dox in any randomized STS trial
  - Entry not limited to first line and allowed up to 600mg/m^2 doxorubicin
- After data read out, the trial sponsor and global regulatory agencies recommended no new patients to be started on olaratumab
  - Withdrawal is in progress
  - Patient Access Program for continuing patients
    - US/Canada Toll Free: 1-833-245-8167
    - Outside US/Canada: 1-917-542-5801
    - Email: LartruvoPatientAccessProgram@iqvia.com

Presented By William Tap at 2019 ASCO Annual Meeting

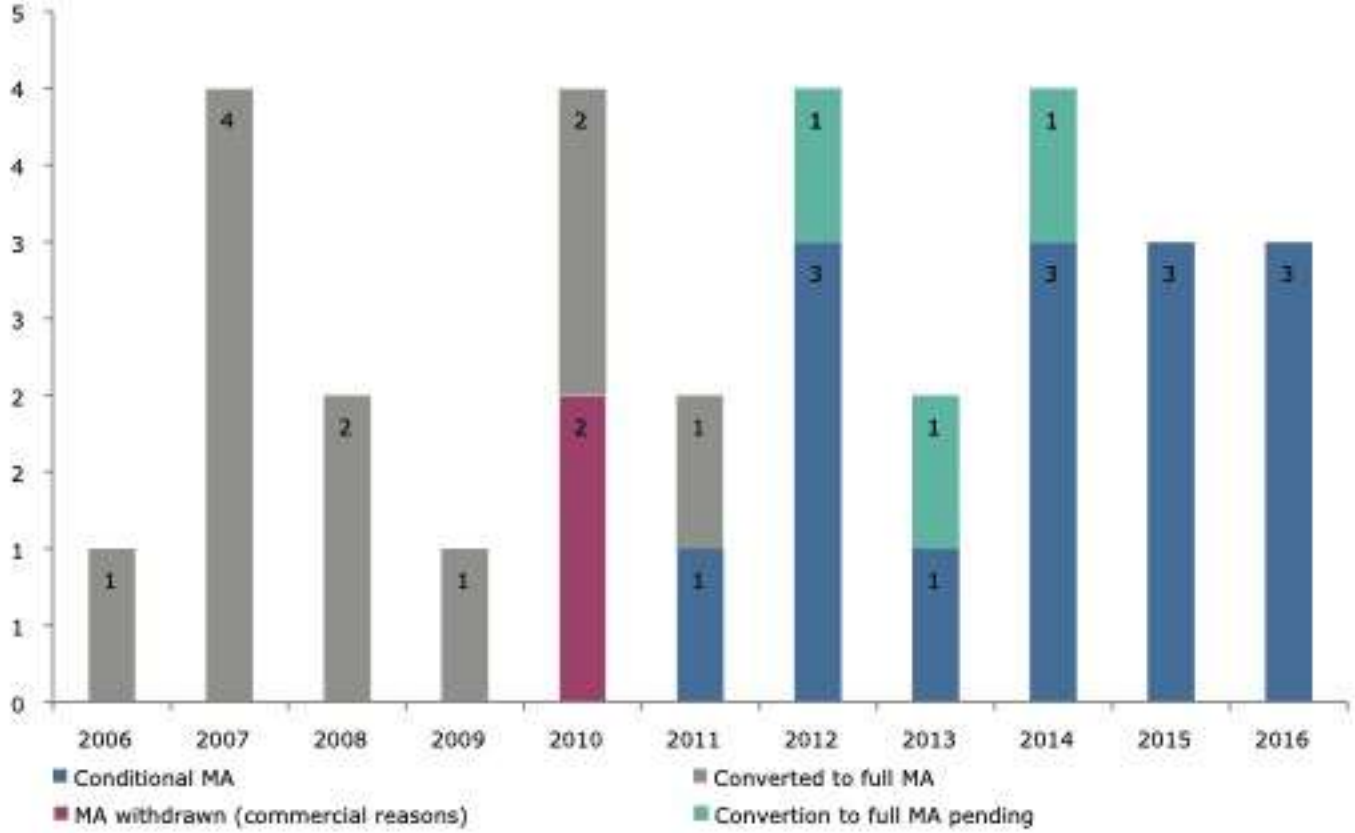
Conditional marketing authorisation EMA

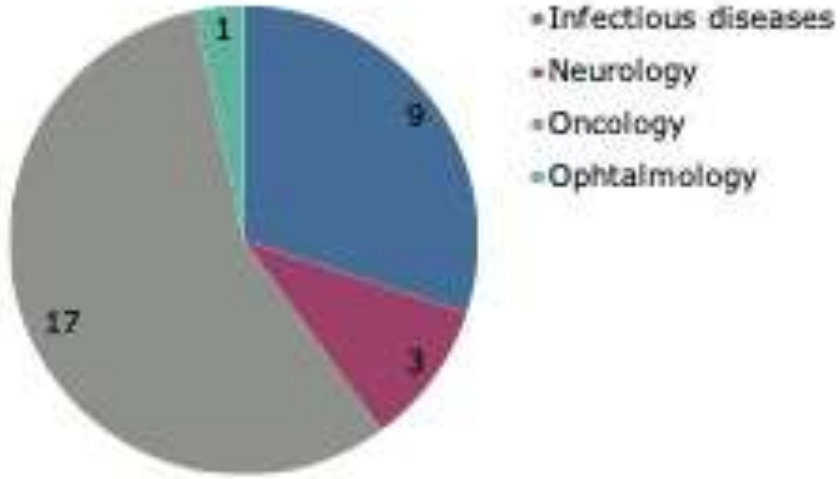
Periodo covered: 2006 - 30th of June 2016

22 CMA unsuccessful
30 CMA granted
- 11 converted into “standard” marketing authorisations
- 2 have withdrawn for commercial reasons
- 17 are still conditional.

None of the marketing authorisation have been revoked or suspended. For the authorisations that are still conditional, none have been authorised for longer than five years

CMA 2006-2016





A long treatment

January	February	March	April	May	June	July	August	September	October	November	December
1 Mo New Year's Day	1 Th	1 Th	1 Su	1 Tu	1 Fr	1 Su	1 We	1 Sa	1 Mo 40	1 Th	1 Sa
[redacted]	2 Fr	2 Fr	2 Mo Easter Monday	2 We	2 Sa	2 Mo 27	2 Th	2 Su	[redacted]	2 Fr	2 Su
3 We	3 Sa	3 Sa	[redacted]	3 Th	3 Su	3 Tu	3 Fr	3 Mo 36	3 We	3 Sa	3 Mo 49
4 Th	4 Su	4 Su	4 We	4 Fr	4 Mo 23	4 We	4 Sa	4 Tu	4 Th	4 Su	[redacted]
5 Fr	5 Mo 6	5 Mo 10	5 Th	5 Sa	[redacted]	5 Th	5 Su	5 We	5 Fr	5 Mo 45	5 We
6 Sa	6 Tu	[redacted]	6 Fr	6 Su	[redacted]	6 Fr	6 Mo 32	6 Th	6 Sa	6 Tu	6 Th
7 Su	7 We	7 We	7 Sa	7 Mo Early May Bank Hol.	7 Th	7 Sa	[redacted]	7 Fr	7 Su	7 We	7 Fr
8 Mo 2	8 Th	8 Th	8 Su	[redacted]	8 Fr	8 Su	8 We	8 Sa	8 Mo 41	8 Th	8 Sa
[redacted]	9 Fr	9 Fr	9 Mo 15	9 We	9 Sa	9 Mo 28	9 Th	9 Su	[redacted]	9 Fr	9 Su
10 We	10 Sa	10 Sa	10 Tu	10 Th	10 Su	[redacted]	10 Fr	10 Mo 37	10 We	10 Sa	10 Mo 50
11 Th	11 Su	11 Su	11 We	11 Fr	11 Mo 24	11 We	11 Sa	[redacted]	11 Th	11 Su	[redacted]
12 Fr	12 Mo 7	12 Mo 11	12 Th	12 Sa	12 Tu	12 Th	12 Su	12 We	12 Fr	12 Mo 46	12 We
13 Sa	[redacted]	[redacted]	13 Fr	13 Su	13 We	13 Fr	13 Mo 33	13 Th	13 Sa	[redacted]	13 Th
14 Su	14 We	14 We	14 Sa	14 Mo [redacted]	14 Th	14 Sa	14 Tu	14 Fr	14 Su	14 We	14 Fr
15 Mo 3	15 Th	15 Th	15 Su	[redacted]	15 Fr	15 Su	15 We	15 Sa	15 Mo 42	15 Th	15 Sa
16 Tu	16 Fr	16 Fr	16 Mo 16	16 We	16 Sa	16 Mo 29	16 Th	16 Su	16 Tu	16 Fr	16 Su
17 We	17 Sa	17 Sa	[redacted]	17 Th	17 Su	[redacted]	17 Fr	17 Mo 38	17 We	17 Sa	17 Mo 51
18 Th	18 Su	18 Su	18 We	18 Fr	18 Mo 25	18 We	18 Sa	[redacted]	18 Th	18 Su	18 Tu
19 Fr	19 Mo 8	19 Mo 12	19 Th	19 Sa	[redacted]	19 Th	19 Su	19 We	19 Fr	19 Mo 47	19 We
20 Sa	[redacted]	20 Tu	20 Fr	20 Su	20 We	20 Fr	20 Mo 34	20 Th	20 Sa	[redacted]	20 Th
21 Su	21 We	21 We	21 Sa	21 Mo 21	21 Th	21 Sa	[redacted]	21 Fr	21 Su	21 We	21 Fr
22 Mo 4	22 Th	22 Th	22 Su	22 Tu	22 Fr	22 Su	22 We	22 Sa	22 Mo 43	22 Th	22 Sa
[redacted]	23 Fr	23 Fr	23 Mo 17	23 We	23 Sa	23 Mo 30	23 Th	23 Su	[redacted]	23 Fr	23 Su
24 We	24 Sa	24 Sa	[redacted]	24 Th	24 Su	24 Tu	24 Fr	24 Mo 39	24 We	24 Sa	24 Mo 52
25 Th	25 Su	25 Su	25 We	25 Fr	25 Mo 26	25 We	25 Sa	25 Tu	25 Th	25 Su	25 Tu Christmas Day
26 Fr	26 Mo 9	26 Mo 13	26 Th	26 Sa	[redacted]	26 Th	26 Su	26 We	26 Fr	26 Mo 48	26 We Boxing Day
27 Sa	27 Tu	[redacted]	27 Fr	27 Su	27 We	27 Fr	27 Mo August Bank Hol.	27 Th	27 Sa	27 Tu	[redacted]
28 Su	28 We	28 We	28 Sa	28 Mo Spring Bank Hol.	28 Th	28 Sa	[redacted]	28 Fr	28 Su	28 We	28 Fr
29 Mo 5	[redacted]	29 Th	29 Su	[redacted]	29 Fr	29 Su	29 We	29 Sa	29 Mo 44	29 Th	29 Sa
[redacted]	[redacted]	30 Fr Good Friday	30 Mo 18	30 We	30 Sa	30 Mo 31	30 Th	30 Su	[redacted]	30 Fr	30 Su
31 We	[redacted]	31 Sa	[redacted]	31 Th	[redacted]	[redacted]	31 Fr	[redacted]	31 We	[redacted]	31 Mo 1