LIPOSARCOMA SUPPORT NETWORK

If you have any questions or need more information on this summary of CTOS2024, please contact us: *support@liposarcomasupport.org*

Presentation #1: INTRATUMORAL HETEROGENEITY GOVERNS IMMUNE ORGANIZATION LINKED TO CLINICAL OUTCOME IN DEDIFFERENTIATED LIPOSARCOMAS

My takeaways:

- DDLPS is not a single entity, and there are multiple subtypes - there are often well-differentiated, low-grade dedifferentiated (LGD), high-grade dedifferentiated (HGD), and mixed areas - within any DDLPS tumor(s). These subtypes describe how mature the cancerous cells are developed and how they function. Well-differentiated describes cells that are more mature and look more “normal” under a microscope. This is in contrast to dedifferentiated which is on the other end of the spectrum where cells don’t look normal and don’t resemble earlier stages of cell development (this means they can easily change function).
- LGD areas often have more “tertiary lymphoid structures” (TLS), which are areas of inflammation, and these may be associated with better response to a certain type of drug family known as immune check-point inhibitors (ICI) and may have better outcomes.
- HGD areas are associated with stem cell and fibroblast signatures, known for their immature appearance and early development, which may contribute to difficulty in treatment with immune checkpoint inhibitors and lack of immune cells
- TLS are associated with improved responses to anti-PD1 treatment, a specific immune targeted therapy that helps the immune system recognize and attack the cancer
- Soft-tissue sarcoma patients with more TLS have historically increased responses to immunotherapy from 2 to 30%! This is because they have a recognizable target that drugs can attack.
- **Impact for patients:** Ask your doctor about this paper, what the different type of cells within your tumor looks like (i.e. if you have low and high-grade dediff areas), and the potential use of immunotherapies

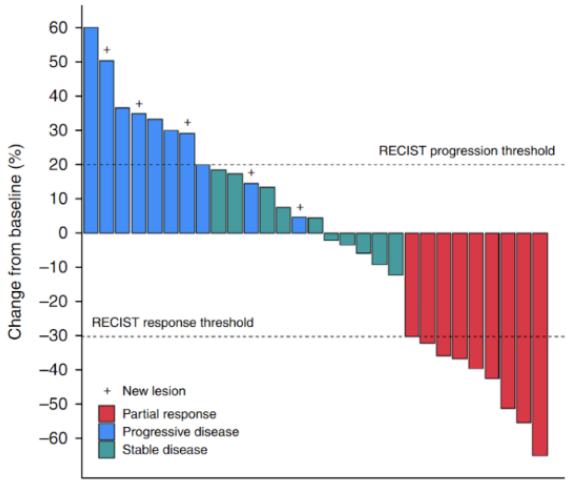
Conclusion

- High-grade regions are characterized by lower immune infiltration and reduced TLS formation.
- TLS and low-grade regions are associated with better prognosis in liposarcoma patients.
- Transcriptomic analyses reveal genetic differences between tumor cells in high-grade versus low-grade regions, which may differentially influence the microenvironment.

Presented by:

Théo Bouloudani PhD student

Perspectives



Italiano, A. et al. P. Nat Med (2022).

TLS are associated with improved responses to anti-PD1 treatment.

Selecting STS patients on the basis of the presence of TLS increases response from 2-30%.

Does intratumour heterogeneity have an impact on response to immunotherapy and could it explain why some TLS positive patients do not respond ?

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Presented by:

Théo Bouloudani PhD student

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Presentation #2 - DEFINING NOVEL BENCHMARK VALUES FOR OUTCOMES OF COMPREHENSIVE RESECTION OF PRIMARY RETROPERITONEAL LIPOSARCOMA

My takeaways:

- This study analyzed outcomes following full surgical removal of primary WDLPS / DDLPS - and sets goals around outcomes after surgery that could potentially be made "standards" that are applicable across care centers, geographies - that can help us define what a "successful" retroperitoneal surgery is.
- The study discusses the difference between "high volume centers" (more than 13 patients with primary retroperitoneal liposarcoma every year) and "low volume centers" (<13 patients every year).
- These "outcome" include: duration of surgery, blood loss during surgery, transfusion rate during surgery, R0/R1 resection, length of hospital stay, major complications after surgery, and deaths.
- **Impact for patients:** While this study is likely more relevant for surgeons and researchers - get your sarcoma surgeries done at high-volume sarcoma centers! Multidisciplinary care at high volume sarcoma centers improves outcomes.

Presentation #3 - BRIGIMADLIN VERSUS STANDARD-OF-CARE DOXORUBICIN AS FIRST-LINE TREATMENT IN PATIENTS WITH ADVANCED DEDIFFERENTIATED LIPOSARCOMA (DDLPS): BRIGHTLINE-1

My takeaways:

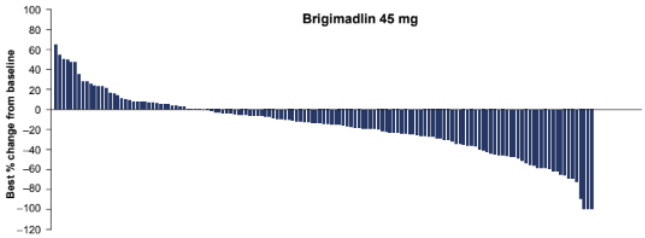
- This was considered the "big presentation of the conference" - I know many of you were on this drug, too! This is/was considered the first potential major breakthrough for DDLPS drugs in several decades.
- An investigative DDLPS drug, brigmidalin (BI 907828), was compared to doxorubicin as a potential first treatment for DDLPS - these are the results of the Phase II / Phase III analysis.
- Phase I results: 19% had a complete or partial shrinkage of their tumor, 67% had no change in disease, and preliminary time until progression was 8.1 months.
- Phase II results: The tumor response and disease control rates showed that brigimadlin may be superior to doxorubicin.
- However, the trial did not demonstrate that brigimadlin changed the time until progression of disease which was their primary goal of the study. While brigimadlin was numerically superior in tumor shrinkage and patients that remained stable, that did not appear to change the duration of time it took for patients to progress in their disease and therefore, it was unlikely to change survival outcomes compared to doxorubicin.

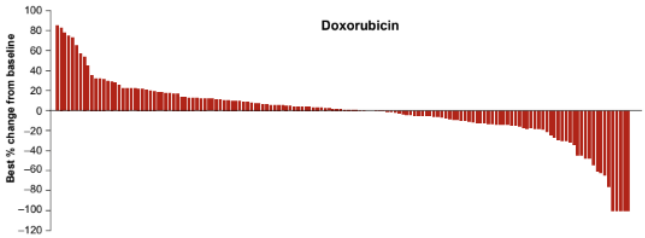
- The results seemed controversial amongst doctors/attendees: i.e. some that the study setup was not ideal - i.e. specifically comparing brigmidalin vs. doxorubicin was the wrong comparator and they should've tried to become a second treatment after patients fail Doxorubicin treatment. This makes the future of the drug development of Brigmidalin uncertain.
- **Impact for patients:** Ask your doctors about brigmidalin and make sure we don't lose this potentially helpful drug from being developed further - Also, join the Liposarcoma Support Network so we can show large-scale support for the feasibility of another trial that has a better design to show success.

OBJECTIVE RESPONSE (BICR) AND ASSESSMENT OF TARGET LESIONS

Response, n (%)	Brigimadlin 45 mg (n=148)	Doxorubicin (n=162)
Objective response	33 (22.3)	14 (8.6)
Complete response	2 (1.4)	2 (1.2)
Partial response	31 (20.9)	12 (7.4)
Disease control	128 (86.5)	117 (72.2)

- The objective response and disease control rates were numerically superior with brigimadlin vs doxorubicin
  - Response endpoint not formally met due to hierarchical ranking of endpoints





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Presented by:
Patrick Schöffski

BICR, blinded independent central review

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CONCLUSIONS

- Brightline-1 is the largest prospective DDLPS trial ever performed
- The primary PFS endpoint was not met: HR 0.79 (95% CI 0.60, 1.06), p=0.0956
- Doxorubicin showed longer PFS than expected
- Trend to benefit with brigimadlin seen across pre-defined patient subgroups
- Greater PFS benefit based on investigator assessment vs BICR
- Numerically superior ORR and DCR with brigimadlin vs doxorubicin
- Efficacy data in first line are comparable with results from the previous Phase Ia/Ib study with brigimadlin
- Preliminary NGS data did not help identify biomarkers for response/resistance to brigimadlin treatment
- Brightline-1 provides a new prospective benchmark for PFS with doxorubicin in first-line DDLPS

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Presented by:
Patrick Schöffski

CI, confidence interval; DCR, disease control rate; DDLPS, dedifferentiated liposarcoma; HR, hazard ratio; NGS, next-generation sequencing; ORR, objective response rate; PFS, progression-free survival

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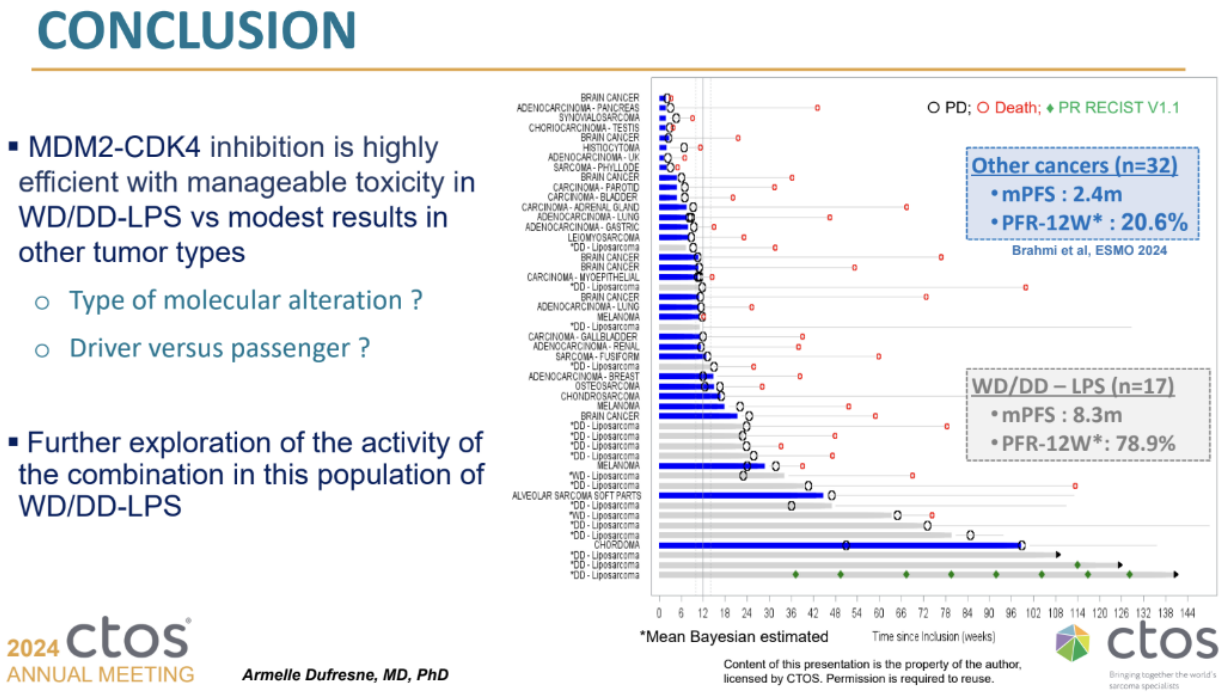
Presentation #4 - COMBINATION OF MDM2 AND CDK4/6 INHIIBITOR IN PATIENTS WITH ADVANCED WELL AND DE-DIFFERENCIATED LIPOSARCOMA AND OTHER CANCERS: COHORT ANALYSIS FROM THE MEGAMOST PHASE II BASKET STUDY

My takeaways:

- This Phase II trial combined Ribociclib (oral CDK4/6 inhibitor) and DM201 (a HDM2-p53 interaction inhibitor) on WDLPS / DDLPS patients
- These MDM2 inhibitors are a new way to treat WDLPS/DDLPS and would be the first of its kind.
- This MDM2-CDK4 inhibitor combination was considered highly efficient in WD/DD LPS patients - where 78.9% of patients had 3 months without any recurrence, and 8.3 months without progression and an extra 23.0 months of survival.
- This was higher than in other sarcoma subtypes and suggestive that the WD/DD LPS population may be of particular interest in the development of MDM2 inhibitors
- **Impact for patients:** If you have WD/DDLPS, ask your doctors about ribociclib (CDK4/6 inhibitors) + MDM2 inhibitor combinations



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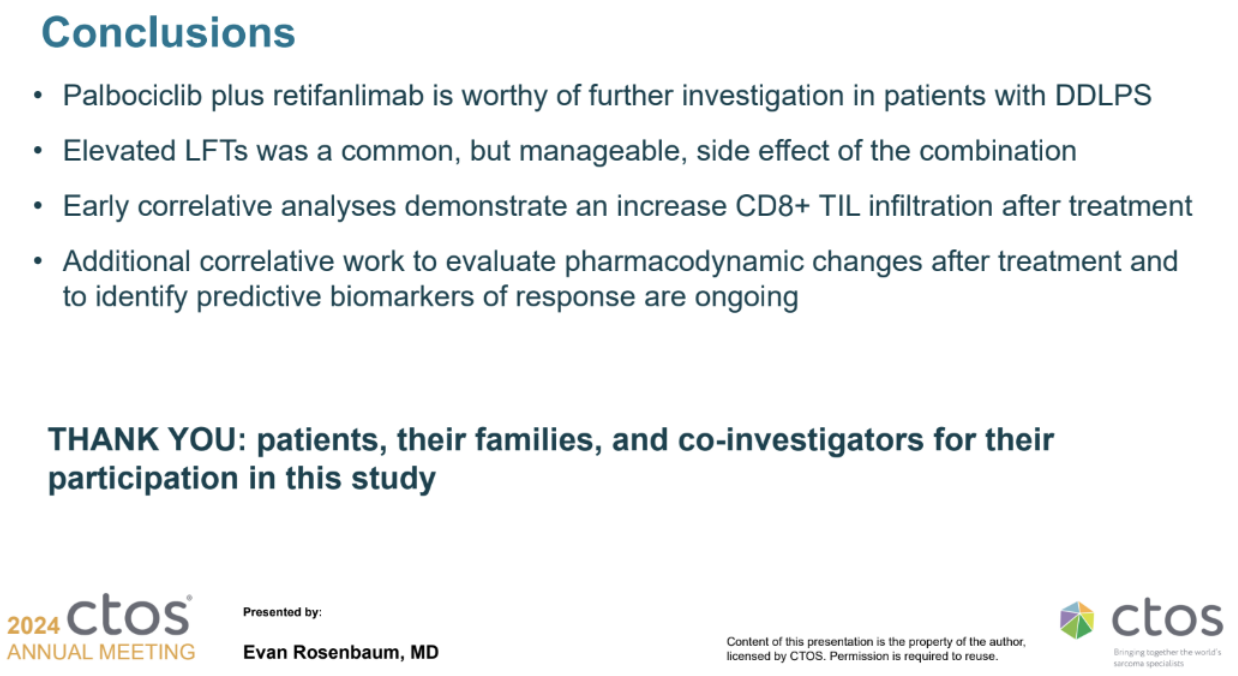
Presentation #5 - A PHASE II STUDY OF PALBOCICLIB COMBINED WITH THE PD-1 INHIBITOR RETIFANLIMAB IN PATIENTS WITH ADVANCED DEDIFFERENTIATED LIPOSARCOMA

My takeaways:

- The study combined the use of palbociclib with retifanlimab in patients with DDLPS.
- The primary endpoint was tumor shrinkage - and this study met its primary endpoint, because of a subset of patients had significant tumor shrinkage that was longstanding
- **Impact for patients:** Ask your doctors about this ongoing work to combine Palbociclib + Retifanlimab if you have DDLPS.



Presentation #6 - SINGLE CELL ATLAS OF WELL DIFFERENTIATED/DEDIFFERENTIATED LIPOSARCOMA SUGGESTS UNDERLYING EPIGENETIC PROGRAMS DRIVING TRANSTION BETWEEN WELL- AND DE-DIFFERENTIATED STATES

My takeaways:

- Researchers believe well-differentiated deprograms into dedifferentiated, and this study assesses the underlying biology of the transition.
- YAP1 signaling activity may be contributing to deprograming (known as dedifferentiation).
- **Impact for patients:** This furthers the understanding of the relationship between subtypes and while not directly applicable to our care currently, this appears to be relevant primarily for researchers / drugmakers understanding what drives dedifferentiation from WDLPS.

Presentation #7 - TARGETING DEDIFFERENTIATED LIPOSARCOMA CELL OF ORIGIN WITH TGF-BETA INHIBITION

My takeaways:

- This study discusses the origins and mechanisms which drive the aggressive nature of dedifferentiation/deprogramming.
- DDLPS originates from early adipocyte stem cells, an immature version of fat cells, that further gives rise to the well-differentiated / dedifferentiated components.
- This study provides rationale for evaluating TF-beta inhibitors in patients with dedifferentiated liposarcoma.
- **Impact for patients:** This may provide future options and lays the foundation for more treatment targets.

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Presentation #8 - PLANNED ANALYSIS OF THE PIVOTAL IGNYTE-ESO TRIAL OF LETE-CEL IN PATIENTS WITH SYNOVIAL SARCOMA OR MYXOID/ROUND CELL LIPOSARCOMA.

My takeaways:

- Lete-cel is an autologous engineered T-cell receptor therapy designed to target the NY-ESO-1 cancer testis antigen in myxoid/round cell liposarcoma (MRCLS) - this study of IGNYTE-ESO substudy 2 studied efficacy, demonstrating tumor shrinkage.
- The study reached the primary success criterion, demonstrating that 40% of patients with MRCLS met the criteria of tumor shrinkage.
- **Impact for patients:** If you have MRCLS, ask your provider about lete-cel as a potential treatment option.

Conclusions

- IGNYTE-ESO substudy 2 met the primary endpoint for efficacy
- At this primary analysis, lete-cel demonstrated 42% ORR (41% for SyS and 43% for MRCLS) by independent review
  - The median duration of response was 12.2 months overall, 18.3 months in SyS, and 12.2 months in MRCLS
  - The median PFS was 5.3 months overall, 3.9 months in SyS, and 7.7 months in MRCLS
- All patients experienced treatment-emergent AEs:
  - Cytopenias, CRS and rash were common and manageable
- These results support the advancement of lete-cel as a novel therapy for patients with unresectable or metastatic SyS and MRCLS; Biologics License Application to the FDA planned
- Further analyses of translational correlates are pending

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AE, adverse event; CRS, cytokine release syndrome; FDA, US Food and Drug Administration; ICANS, immune effector cell–associated neurotoxicity; lete-cel, letetresgene autoleucel; MRCLS, myxoid/round cell liposarcoma; ORR, overall response rate; SyS, synovial sarcoma.

Presented by:
Sandra P. D'Angelo, MD

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