Restoring p53 by Antagonizing MDM2-p53 in Soft Tissue Sarcoma

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ESMO = European Society for Medical Oncology.

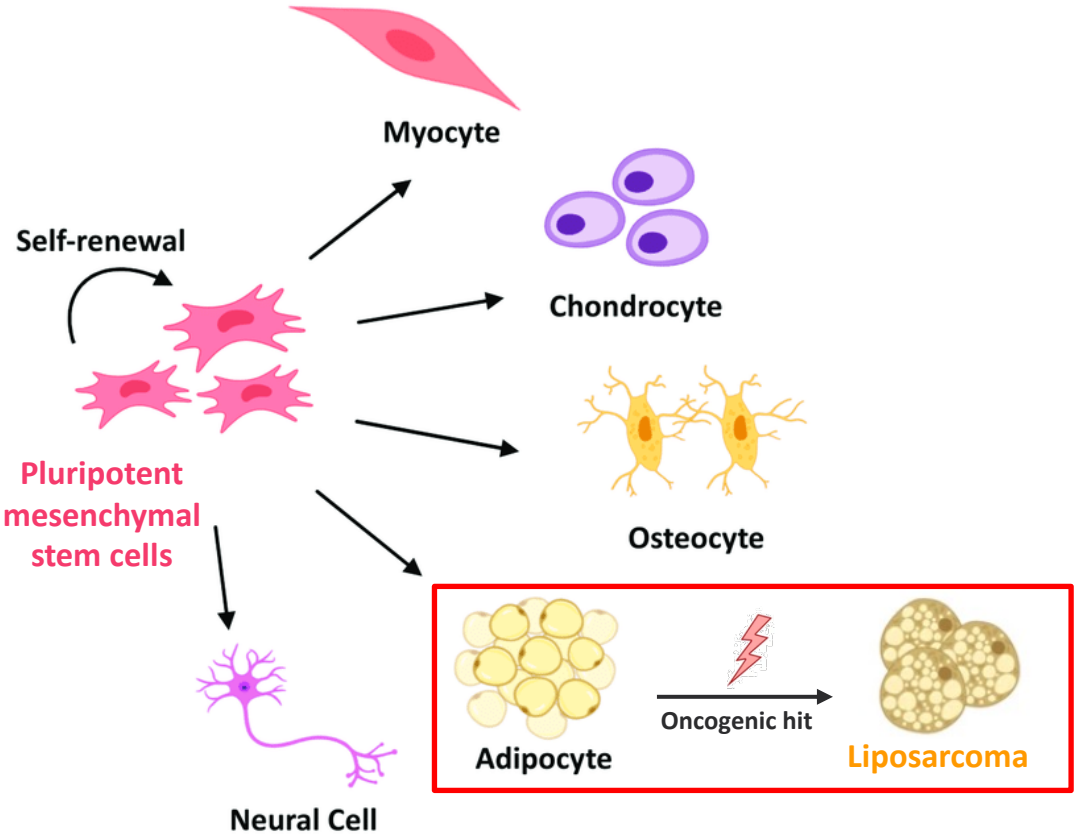
Overview of STS

STS = soft tissue sarcoma.

STS Encompasses a Group of Rare Tumors With High Unmet Need[1]

- Rare, heterogeneous group of tumors that make up 1% of all adult malignancies[1]
  - The incidence of STS is 4.7/100,000 per year in Europe[2]
- Debilitating symptoms and poor survival with advanced/recurring STS[1]
- Surgery is the mainstay of treatment for localized sarcomas[3,4]
  - Many patients develop advanced metastatic disease requiring systemic therapy[3,4]

Sarcomas Arise From Mesenchymal Precursors[5,6]



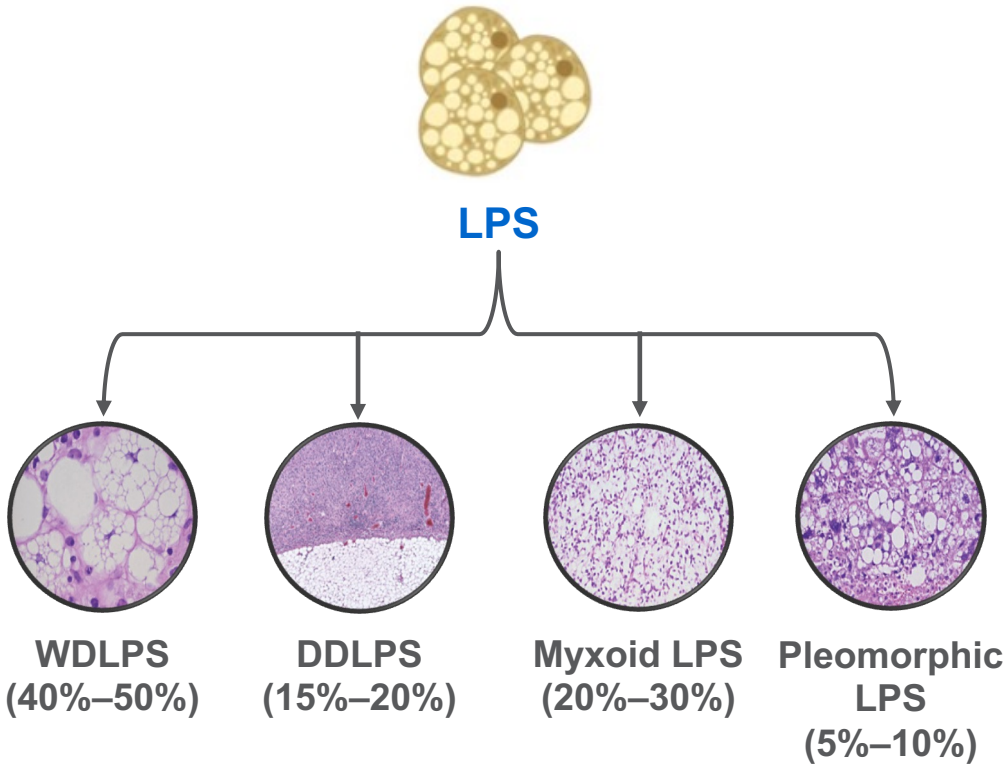
ESMO = European Society for Medical Oncology; STS = soft tissue sarcoma.

1. Gamboa AC, et al. *CA Cancer J Clin.* 2020;70(3):200–229; 2. Liu H, et al. *Front Oncol.* 2022;12:890040; 3. Gronchi A, et al. *Ann Oncol.* 2021;32(11):1348–1365; 4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma V.2.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed September 2023. To view the most recent and complete version of the guideline, go online to NCCN.org; 5. Ravera F, et al. *Molecules.* 2020;25(23):5554; 6. Damerell V, et al. *Signal Transduct Target Ther.* 2021;6(1):246.

LPS Is Composed of 4 Distinct Histologic Subtypes

- LPS is a subtype of STS that arises from adipocytic precursors[1]
- DDLPS is a subtype of LPS that occurs as a focal outgrowth within precursor WDLPS lesions[1]
  - Most aggressive form of LPS with the poorest prognosis[1,2]
  - Highest rates of local and metastatic recurrence[1]

Histologic Subtypes of LPS[3]



DDLPS = dedifferentiated liposarcoma; ESMO = European Society for Medical Oncology; LPS = liposarcoma; STS = soft tissue sarcoma; WDLPS = well-differentiated liposarcoma.

1. Lee ATJ, et al. *J Clin Oncol.* 2018;36(2):151–159; 2. Bock S, et al. *Int J Environ Res Public Health*. 2020;17(8):2710; 3. Schöffski P. *Oncol Res Treat.* 2022;45(9):525–543.

Features of DDLPS

Key Features

- DDLPS is a **high-grade, aggressive disease**[1,2]
  - Local recurrence rate of 40%–60%[2]
  - Metastatic rate of 15%–30%[1]
  - 5-year mortality rate of 30%–40%[2]
- DDLPS has **low responsiveness to doxorubicin (SOC)**
  - ORR<15%[3,4]
  - mPFS: 2–5 months[3,4]
  - mOS: 6–12 months[5,6]

Other Features

***MDM2* amplification is a hallmark of the disease** – the vast majority of cases exhibit *MDM2* amplification and *TP53*wt[1,7,8]

DDLPS occurs most frequently in[9]:
Retroperitoneum > extremities > other regions

Delayed symptoms lead to large size at presentation which is associated with significant morbidity and poorer prognosis[10]

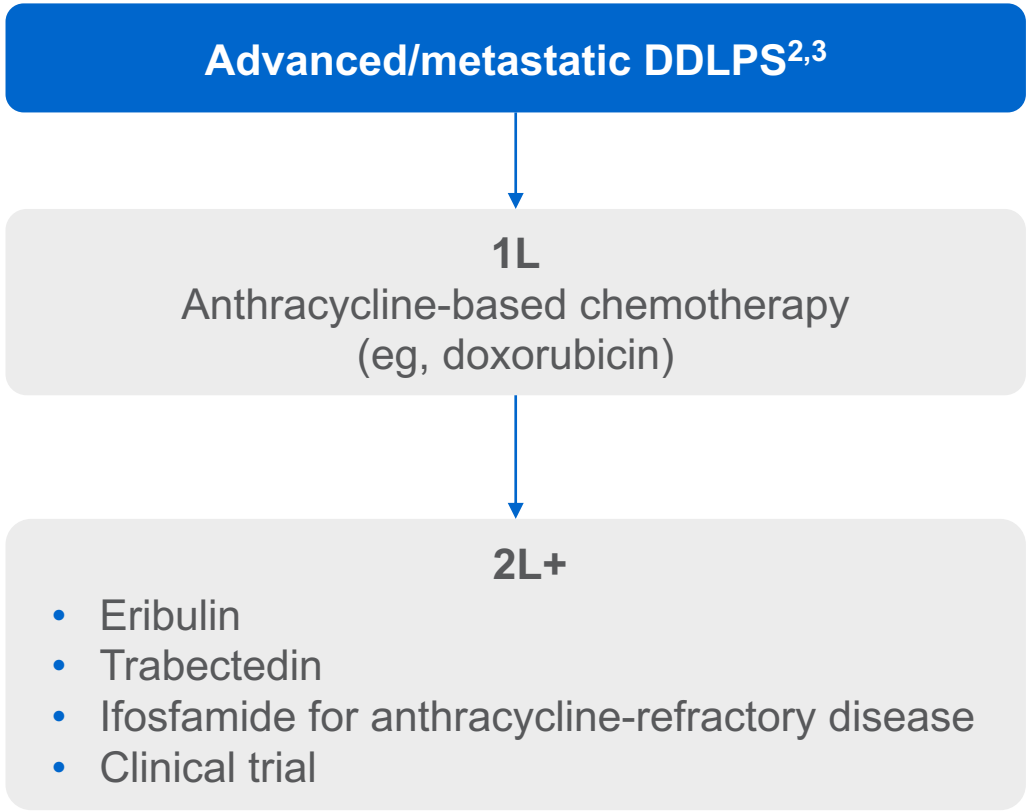
- Wide resection with removal of contiguous viscera is recommended to achieve negative margins[11]
- Complete resection of retroperitoneal DDLPS proves to be difficult due to its proximity to vital organs[2]
- Tumor may become inoperable at a given point then require systemic palliation[12]

DDLPS = dedifferentiated liposarcoma; ESMO = European Society for Medical Oncology; *MDM2* = mouse double minute 2 homolog; mOS = median overall survival; mPFS = median progression-free survival; ORR = objective response rate; SOC = standard of care; *TP53* = tumor protein p53 gene; WDLPS = well-differentiated liposarcoma; wt = wild type.

1. Nishio J, et al. *J Clin Med*. 2021;10(15):3230; 2. Nguyen K, et al. *Surg Case Rep*. 2021;4(2):2–7; 3. Jones RL, et al. *Eur J Cancer*. 2005;41(18):2853–2860; 4. Italiano A, et al. *Ann Oncol*. 2012;23(6):1601–1607; 5. Savina M, et al. *BMC Med*. 2017;15(1):78; 6. Langmans C, et al. *Oncol Res Treat*. 2019;42(7-8):396–404; 7. Asano N, et al. *Oncotarget*. 2017;8(8):12941–12952; 8. Somiah N, et al. *Oncotarget*. 2018;9(28):19891–19899; 9. Lee ATJ, et al. *J Clin Oncol*. 2018;36(2):151–159; 10. Goldberg BR. *Orthop Nurs*. 2007;26(1):4–11; 11. Thway K. *Semin Diagn Pathol*. 2019;36(2):112–121; 12. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma V.2.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed September 2023. To view the most recent and complete version of the guideline, go online to NCCN.org.

There Has Been No Change in 1L Treatment in Advanced DDLPS in Nearly 5 Decades

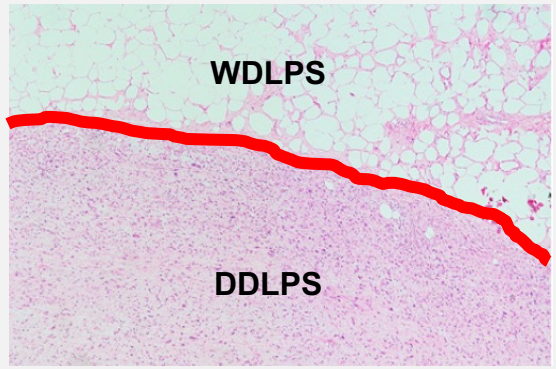
- Treatment recommendations for advanced DDLPS are generally not distinct from LPS or other STS[1–3]
- SOC for 1L treatment is anthracycline-based therapy: doxorubicin[1–3]
- SOC for 2L+ in LPS: trabectedin and eribulin[1–3]
- There has been a lack of advances in the treatment landscape[4]
  - Doxorubicin approved in 1974[5]
  - No targeted agents are recommended for routine use in DDLPS[1–3]



1L = first-line; 2L= second-line; DDLPS = dedifferentiated liposarcoma; ESMO = European Society for Medical Oncology; LPS = liposarcoma; PFS = progression-free survival; SOC = standard of care; STS = soft tissue sarcoma.

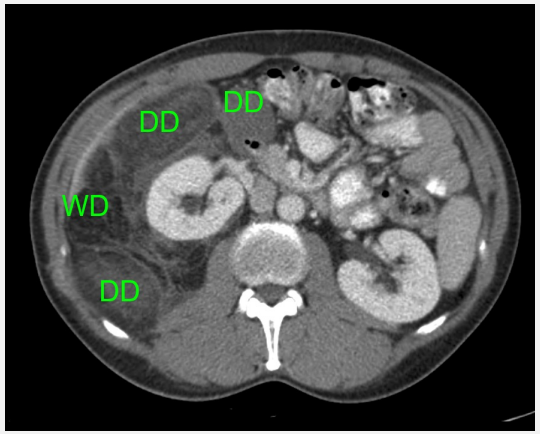
1. Nishio J, et al. *J Clin Med.* 2021;10(15):3230; 2. Gronchi A, et al. *Ann Oncol.* 2021;32(11):1349–1365; 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma V.2.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed September 2023. To view the most recent and complete version of the guideline, go online to NCCN.org; 4. Gamboa AC, et al. *CA Cancer J Clin.* 2020;70(3):200–229; 5. European Medicines Agency. https://www.ema.europa.eu/en/documents/ withdrawal-report/withdrawal-assessment-report-doxorubicin-hydrochloride-tillomed_en.pdf. Accessed August 2023.

Diagnosis of DDLPS Can be Challenging Due to Intratumor Heterogeneity



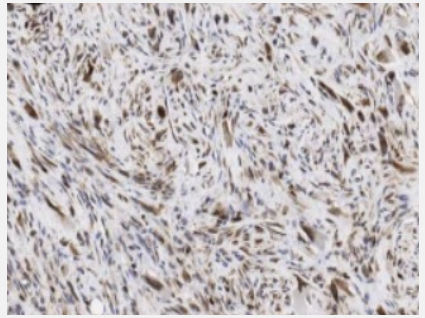
Histology

The histologic hallmark of DDLPS is the **abrupt transition** from WDLPS to DDLPS[1]



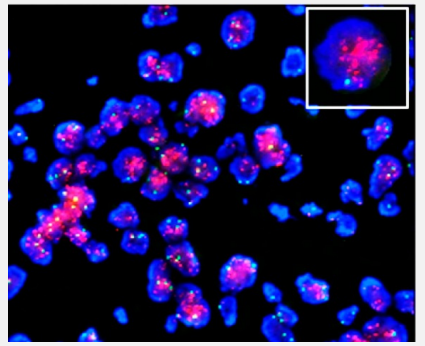
CT scan

- WD = well differentiated component of the tumor
- DD = more dedifferentiated component of the tumor, which typically has **2 morphologic "faces"**



IHC

Can be used to detect biomarkers that can help distinguish DDLPS and WDLPS from other adipocytic tumors[1,2,3]



FISH

Can serve as a useful **diagnostic adjunct** for DDLPS by identifying status of ***MDM2* amplification (red signals)**[1,2,4]

NGS

Can be used to detect markers (eg, MDM2 amp) in a large number of samples[5]

Image courtesy of P. Schöffski, University Hospitals Leuven, Leuven, Belgium.

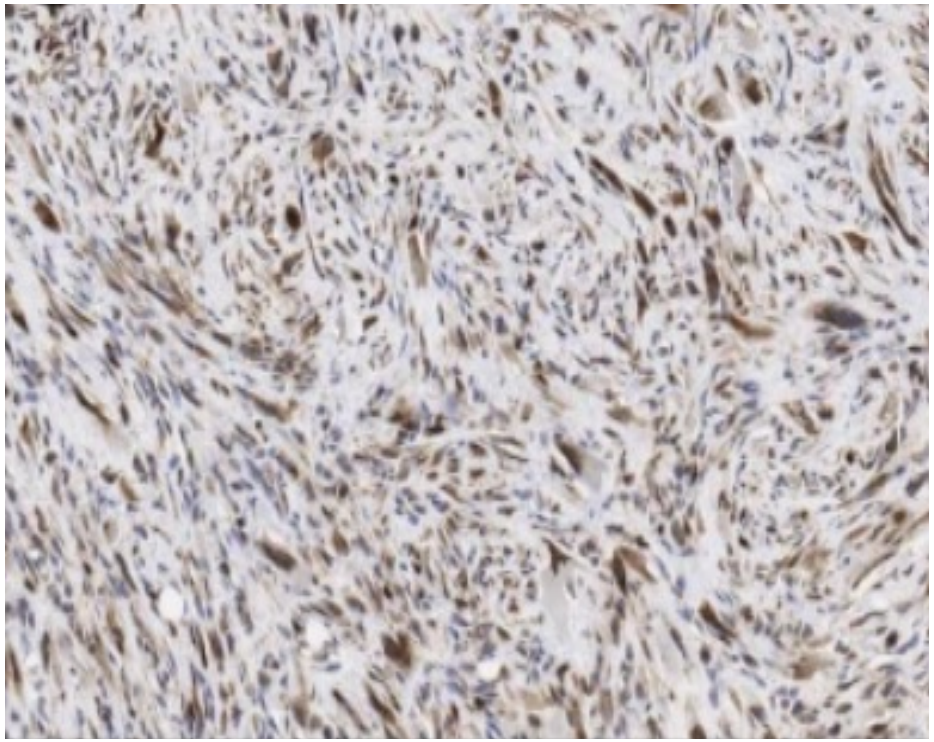
CT = computed tomography; DDLPS = dedifferentiated liposarcoma; ESMO = European Society for Medical Oncology; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; MDM2 = mouse double minute 2 homolog; NGS = next-generation sequencing; WDLPS = well-differentiated liposarcoma.

1. Nishio J, et al. *J Clin Med*. 2021;10(15):3230; 2. Thway K. *Semin Diagn Pathol*. 2019;36(2):112–121; 3. Lokka S, et al. *BMC Clin Pathol*. 2014;14:36; 4. Gambella A, et al. *Int J Mol Sci*. 2023;24:1342; 5. Qin D, et al. *Cancer Biol Med*. 2019;16(1):4–10.

Molecular Biomarkers for DDLPS

- DDLPS and WDLPS are characterized by the amplification of several cancer-related genes in the q13-15 region of chromosome 12[1–3]
  - *MDM2*—distinguishes DDLPS and WDLPS from benign lipomas[2]
  - *CDK4*—co-amplification with *MDM2* is sensitive and specific marker for diagnosis of DDLPS/WDLPS[2]
  - *HMG2A*—amplified in 60% of DDLPS cases[2]
  - *CPM*, *YEATS4*—implicated in dedifferentiation[1]

IHC Staining Showing MDM2 Overexpression in DDLPS[4]



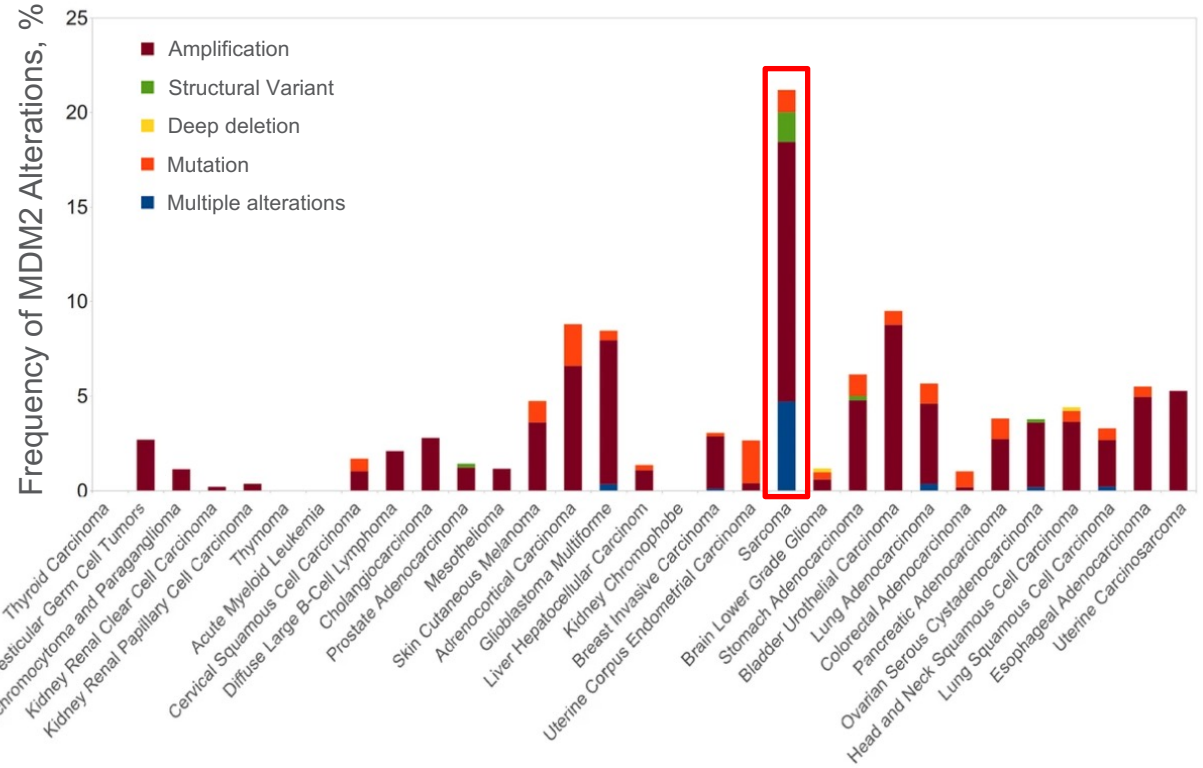
CDK4 = cyclin-dependent kinase 4; *CPM* = carboxypeptidase M; DDLPS = dedifferentiated liposarcoma; ESMO = European Society for Medical Oncology; *HMG2A* = high mobility group AT hook 2; IHC = immunohistochemistry; *MAP3K5* = mitogen-activated protein kinase Scoffs kinase 5; MDM2 = mouse double minute 2 homolog; WDLPS = well-differentiated liposarcoma; *YEATS4* = YEATS containing domain 4.

1. Lee ATJ, et al. *J Clin Oncol*. 2018;36(2):151–159; 2. Jagosky MH, et al. *Cancer Med*. 2023;12(6):7029–7038; 3. Yang L, et al. *J Cancer*. 2020;11(1):100–107; 4. Lokka S, et al. *BMC Clin Pathol*. 2014;14:36.

MDM2 Is Amplified in DDLPS and Other Malignancies, Providing a Potential Target in Cancer Therapy

- Overall, the frequency of *MDM2* amplification across different cancers varies between 3.5% and 4.4%[1]
  - The highest rates have been observed in the sarcoma family[2]
  - >90% of patients with WDLPS/DDLPS have *TP53*wt and *MDM2* amplification[3–8,a]
  - The vast majority of DDLPS cases have *TP53*wt and *MDM2* amplification[9–10]
- This serves as a rationale to target the MDM2-p53 pathway in DDLPS and selected LPS

Frequency of *MDM2* Alterations Across Tumor Types[2,b]



[a]*MDM2* amplification is mutually exclusive of *TP53* mutations at copy number ≥12.[9] [b]Data were obtained from The Cancer Genome Atlas.[2]

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1. Sciot R. *Diagnostics (Basel).* 2021;11:496; 2. Haronikova L, et al. *Cell Mol Biol Lett.* 2021;26:53; 3. Pilotti S, et al. *J Pathol.* 1997;181:14–24; 4. Thway K. *Semin Diagn Pathol.* 2019;36(2):112–121; 5. Kim YJ, et al. *Lab Invest.* 2019;99:1309–1320; 6. Sirvent N, et al. *Am J Surg Pathol.* 2007;31:1476–1489; 7. Lee SE, et al. *Histol Histopathol.* 2014;29:127–138; 8. Tirunagaru VG, et al. AACR 2022. Abstract 1174; 9. Asano N, et al. *Oncotarget.* 2017;8(8):12941–12952; 10. Somiah N, et al. *Oncotarget.* 2018;9(28):19891–19899.

MDM2-p53 Antagonism as a Therapeutic Strategy in DDLPS

MDM2 = mouse double minute 2 homolog; p53 = tumor protein 53.

The Tumor Suppressor Protein p53 Maintains Genomic Integrity During Cellular Stress or Injury

- p53 is known as “the guardian of the genome” because it regulates processes that avert or repair DNA damage and prevent tumor initiation and progression[1,2]

ESMO = European Society for Medical Oncology; p53 = tumor protein 53.

1. Zhao Y, et al. *Acta Biochim Biophys Sin (Shanghai)*. 2014;46:180–189; 2. Joerger A, Fersht AR. *Annu Rev Biochem*. 2016;85:375–404.

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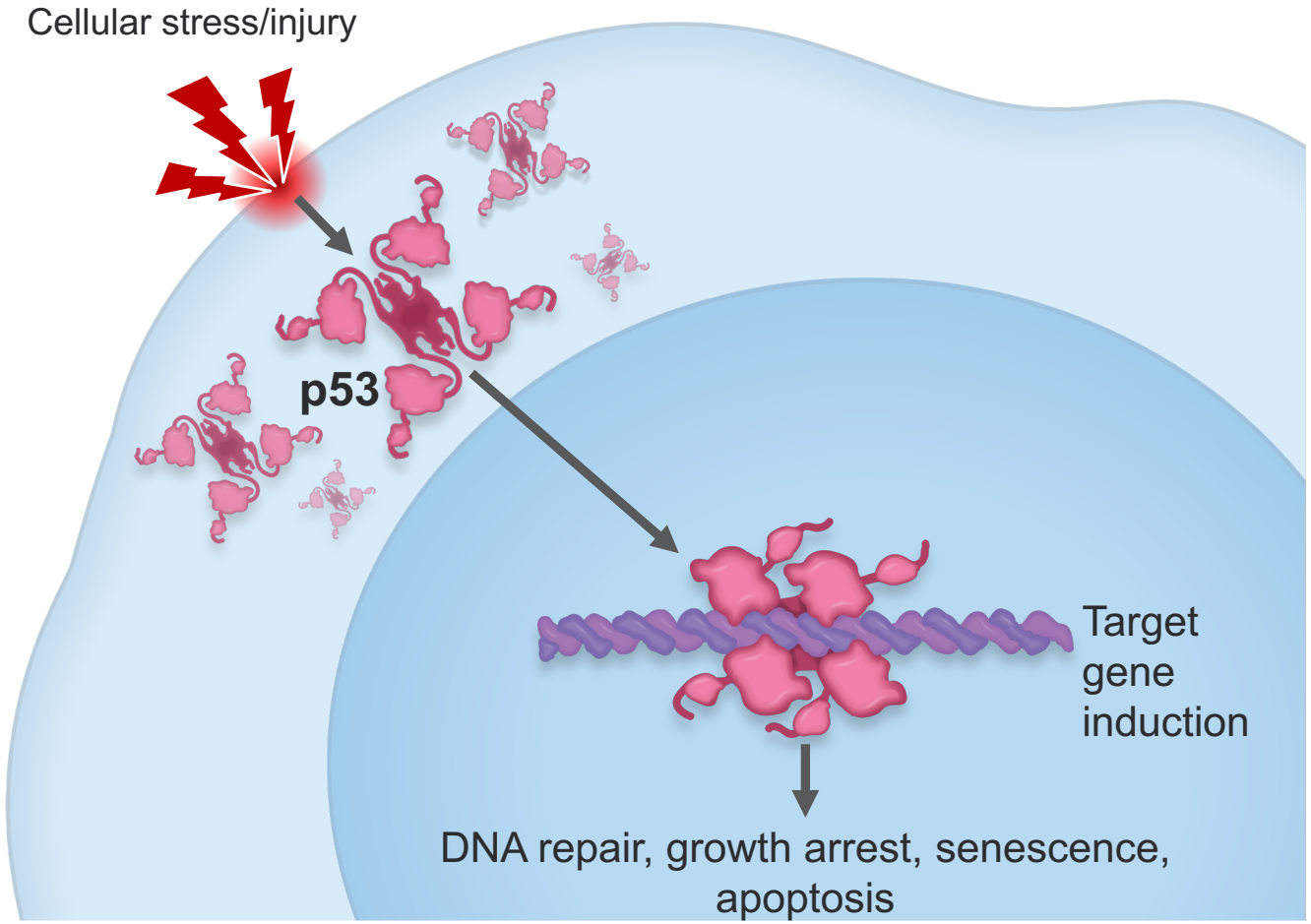
- In response to cell stress, p53 is activated and facilitates gene transcription to promote DNA repair, cell cycle arrest, senescence, and apoptosis[1,2]

Physiologic p53 Function[1,2]



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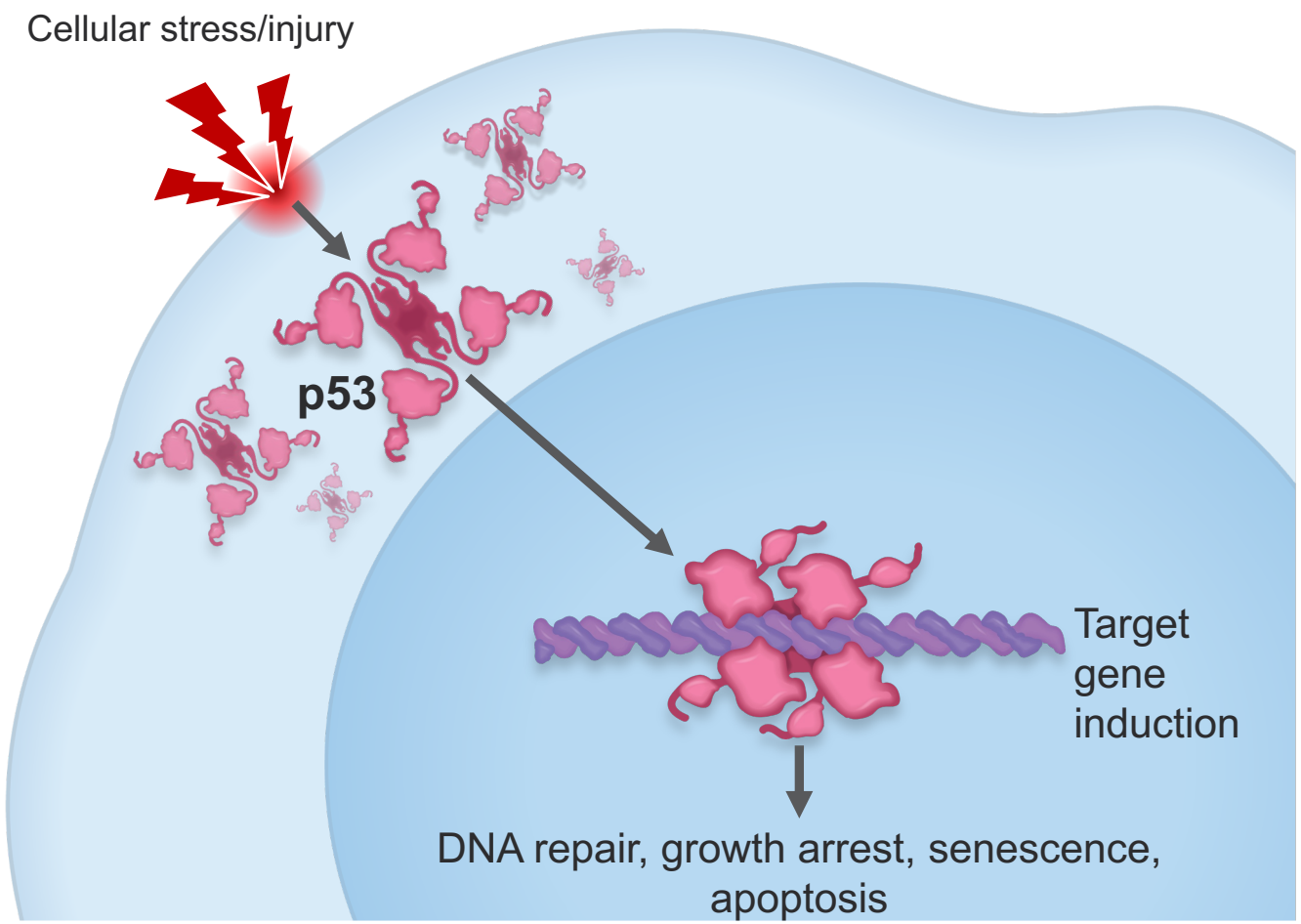
- In response to cell stress, p53 is activated and facilitates gene transcription to promote DNA repair, cell cycle arrest, senescence, and apoptosis[1,2]
- A key mechanism by which tumor cells promote survival and proliferation is by inactivation of p53 through[1,2]
  - *TP53* mutations
  - Downregulation of p53wt

Physiologic p53 Function[1,2]



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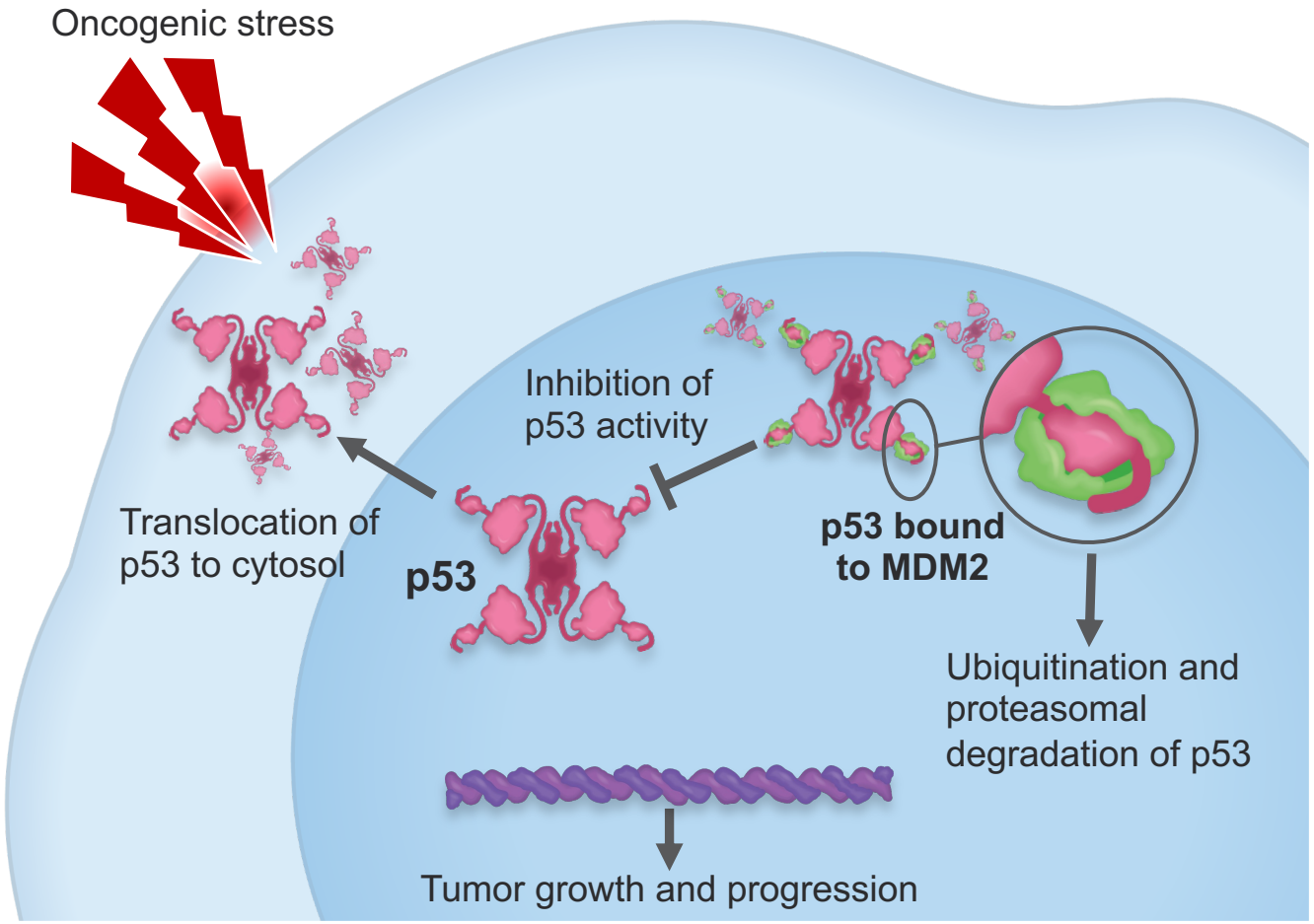
1. Zhao Y, et al. *Acta Biochim Biophys Sin (Shanghai)*. 2014;46.:180–189; 2. Joerger AC, Fersht AR. *Annu Rev Biochem*. 2016;85:375–404.

MDM2-Mediated Loss of p53 Function in Cancer

- MDM2 is the primary negative regulator of p53, ensuring in physiologic conditions that p53 is only active at the appropriate times[1]
- MDM2 inactivates p53 through direct binding and inhibition of p53 activity and through degradation of p53[1,2]
- Tumors can inactivate p53wt by increasing levels of MDM2 through[1,2]:
  - *MDM2* amplification
  - MDM2 overexpression
- Blocking the MDM2-p53 interaction to restore p53wt function is therefore a potential therapeutic strategy in cancers with wt or functional p53[2]

MDM2 Inhibition of p53 in Malignancy[1,2]



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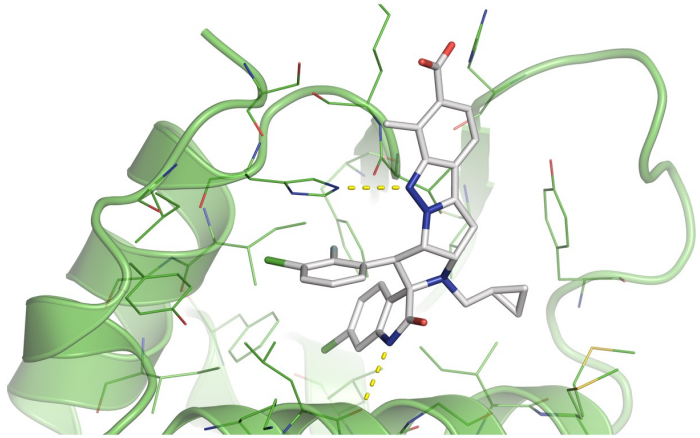
Brigimadlin Is a Highly Potent, Orally Available MDM2-p53 Antagonist

Brigimadlin was optimized to address key challenges of targeting the MDM2-p53 interaction[1]

Challenge: Overcoming protein-protein binding

The strong binding constant and the large binding interface between protein molecules can be hard to overcome with a small molecule[2]

Solution: Optimized structure for binding MDM2[1]



X-ray co-crystal structure of brigimadlin in human MDM2

Challenge: Cytopenia from MDM2 inhibition

Inhibition of the MDM2-p53 interaction may impair the development of neutrophils and platelets, leading to cytopenias that prevent patients remaining on treatment[3]

Solution: Optimized PK that allows intermittent dosing[1]

Preliminary human PK parameters of brigimadlin 45 mg p.o. Q3W (dose expansion, cycle 1, n = 27)

Median t_{max}, h	5.0
C_{max}, nM (gCV [%])	2,880 (56.7)
$AUC_{0-\infty}$, nmol*h/L (gCV [%])	173,000 (77.1)
$t_{1/2}$, h (gCV [%])	42.0 (52.7)

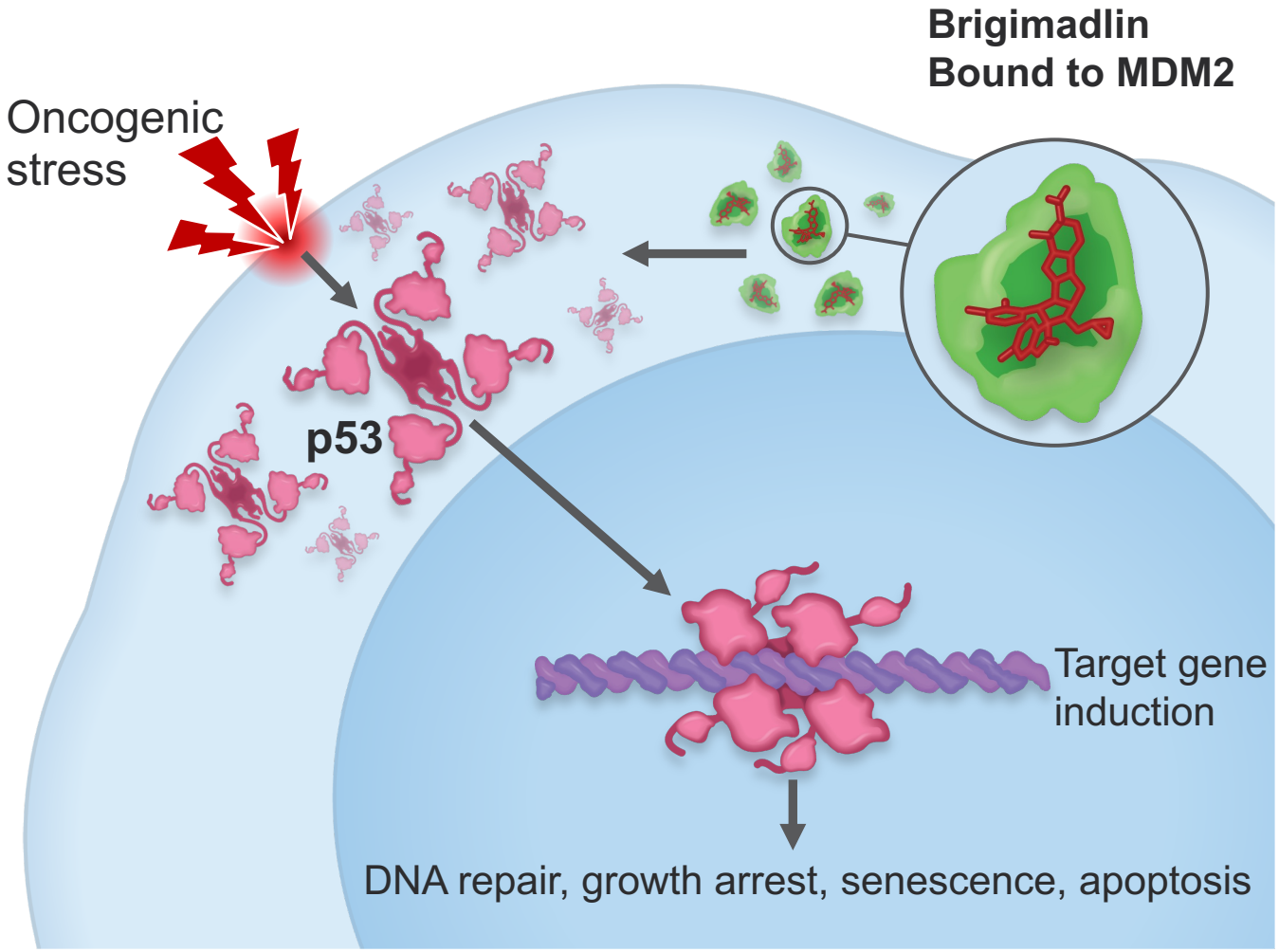
This compound is an investigational agent. Its safety and efficacy have not been established.

$AUC_{0-\infty}$ = area under the concentration-time curve at time points 0 to infinity; C_{max} = maximum serum concentration; ESMO = European Society for Medical Oncology; gCV = geometric coefficient of variance; MDM2 = mouse double minute 2 analog; PK = pharmokinetics; p.o. = by mouth; Q3W = every 3 weeks; $t_{1/2}$ = half-life; t_{max} = time to reach C_{max}.

1. Gollner A, et al. AACR 2023. Poster LB003; 2. Lu H, et al. *Signal Transduct Target Ther.* 2020;5(1):213; 3. Iancu-Rubin C, et al. *Exp Hematol.* 2014;42(2):137–145.

MDM2-p53 Antagonism With Brigimadlin (BI 907828)

- Brigimadlin binds to MDM2 and blocks the MDM2-p53 interaction. This prevents MDM2 from inactivating p53, thereby restoring p53 function[1]
- Increased p53 levels resulting from MDM2 inhibition reinstitutes cell cycle arrest and apoptosis in response to oncogenic stress[2]



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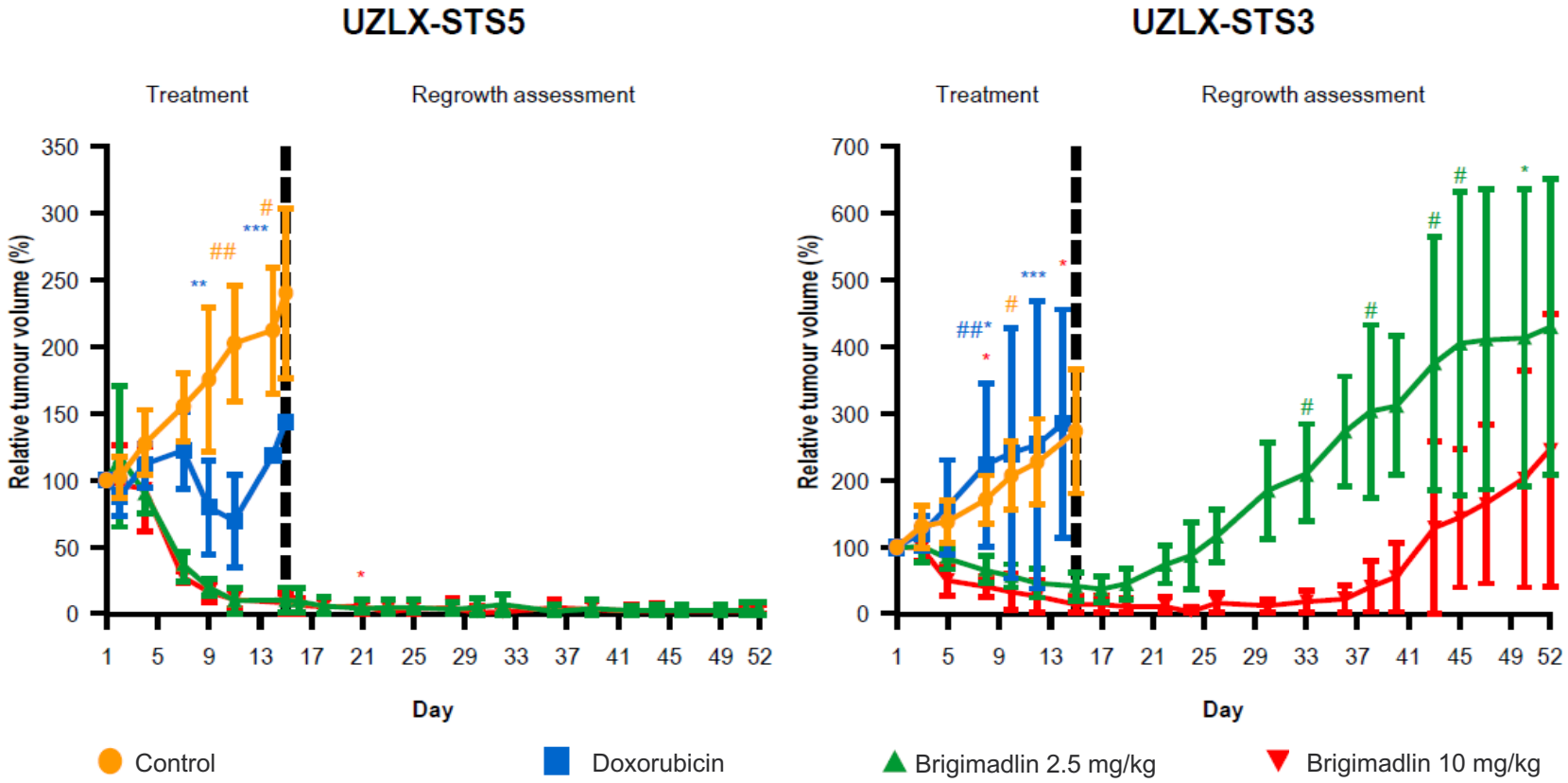
1. Schöffski P, et al. ESMO Sarcoma and Rare Cancers 2023. Presentation 420; 2. Burgess A, et al. *Front Oncol*. 2016;6:7.

Antitumor Activity of Brigimadlin in Preclinical Models of DDLPS Provided a Rationale for Clinical Development

Brigimadlin showed strong antitumor activity in xenograft models derived from patients with *TP53*wt, *MDM2*-amplified DDLPS[2]



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Cornillie J, et al. *Clin Transl Oncol*. 2020;22(4):546–554.

Phase Ia/Ib, Dose-Escalation/Expansion Study of Brigimadlin in Patients With Advanced/Metastatic Solid Tumors (1403-0001)[1,2]

Key inclusion criteria:

- Known *TP53*wt status[a] and *MDM2* amplification (expansion phase only)
- ECOG PS 0–1
- Patients with PD/relapse, no proven treatment available, or *MDM2*-amplified sarcomas who require 1L treatment (expansion phase only)

Key exclusion criteria:

- Previous administration of any MDM2-p53 or MDMX (MDM4)-p53 antagonist

Phase 1a (dose escalation): completed
N = 54 patients with locally advanced/metastatic solid tumors

Arm A
Brigimadlin on Day 1 of 21-day cycles

Arm B
Brigimadlin on Days 1 and 8 of 28-day cycles

RDE: Brigimadlin 45 mg Q3W

Phase 1b (dose expansion): ongoing

Cohort 1
*TP53*wt, *MDM2*-amplified sarcomas (any line)

Brigimadlin p.o.

Cohort 2
*TP53*wt, *MDM2*-amplified solid tumors; NSCLC, gastric, urothelial, pancreatic, biliary tract (≥2L)

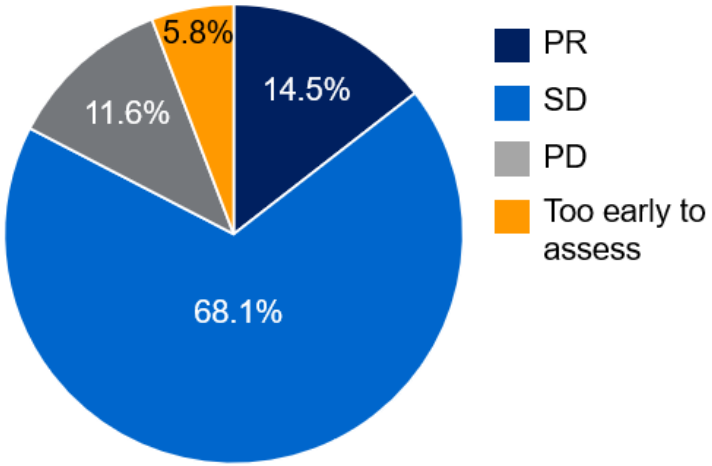
Brigimadlin p.o.

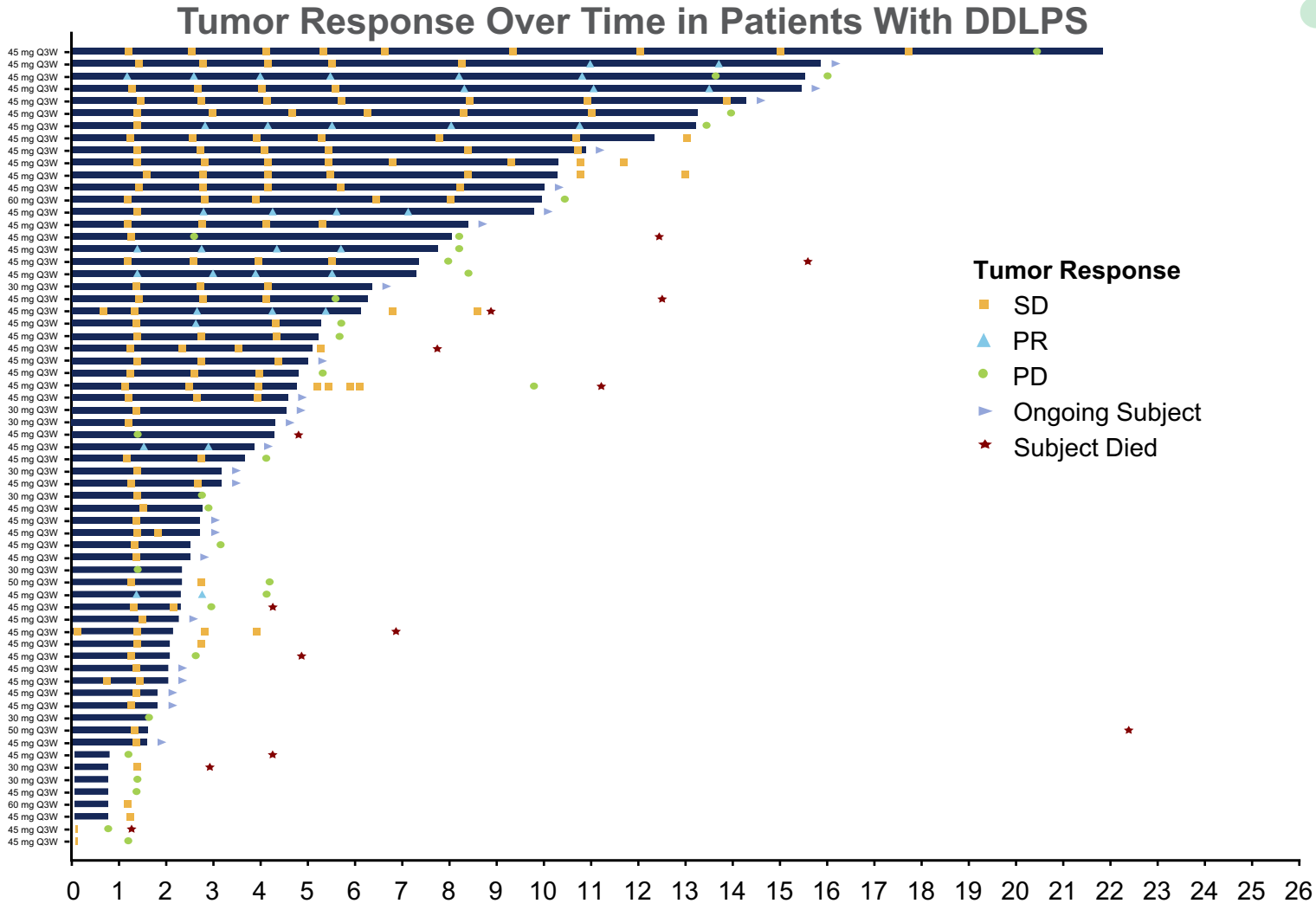
Phase 1b
Primary endpoint: PFS
Secondary endpoints: OR, OS, grade ≥3 TRAEs, PK

[a]If *TP53* status cannot be evaluated, patients may be included if agreed by the investigator and sponsor.
1L = first-line; 2L = second-line; ECOG PS = Eastern Cooperative Oncology Group performance status; ESMO = European Society for Medical Oncology; *MDM2* = mouse double minute 2 homolog; MDMX (MDM4) = mouse double minute 4 homolog; NSCLC = non–small cell lung cancer; OR = objective response; OS = overall survival; p53 = tumor protein 53; PD = progressive disease; PK = pharmacokinetics; PFS = progression-free survival; p.o. = by mouth; PR = partial response; Q3W = every 3 weeks; RDE = recommended dose for expansion; *TP53* = tumor protein p53 gene; TRAE = treatment-related adverse event; wt = wild type.
1. LoRusso P, et al. ASCO 2023. Abstract 11554; 2. Clinicaltrials.gov. https://clinicaltrials.gov/study/NCT03449381. Accessed September 2023.

Preliminary Efficacy Seen in Patients With DDLPS

- In patients with *MDM2*-amplified DDLPS (69 patients), preliminary median PFS was 7.9 months (95% CI: 4.2–9.9) and ORR was 14.5%
  - 10/69 (14.5%) patients achieved a PR
  - A further 47 (68.1%) patients had SD
  - DCR was 82.6%

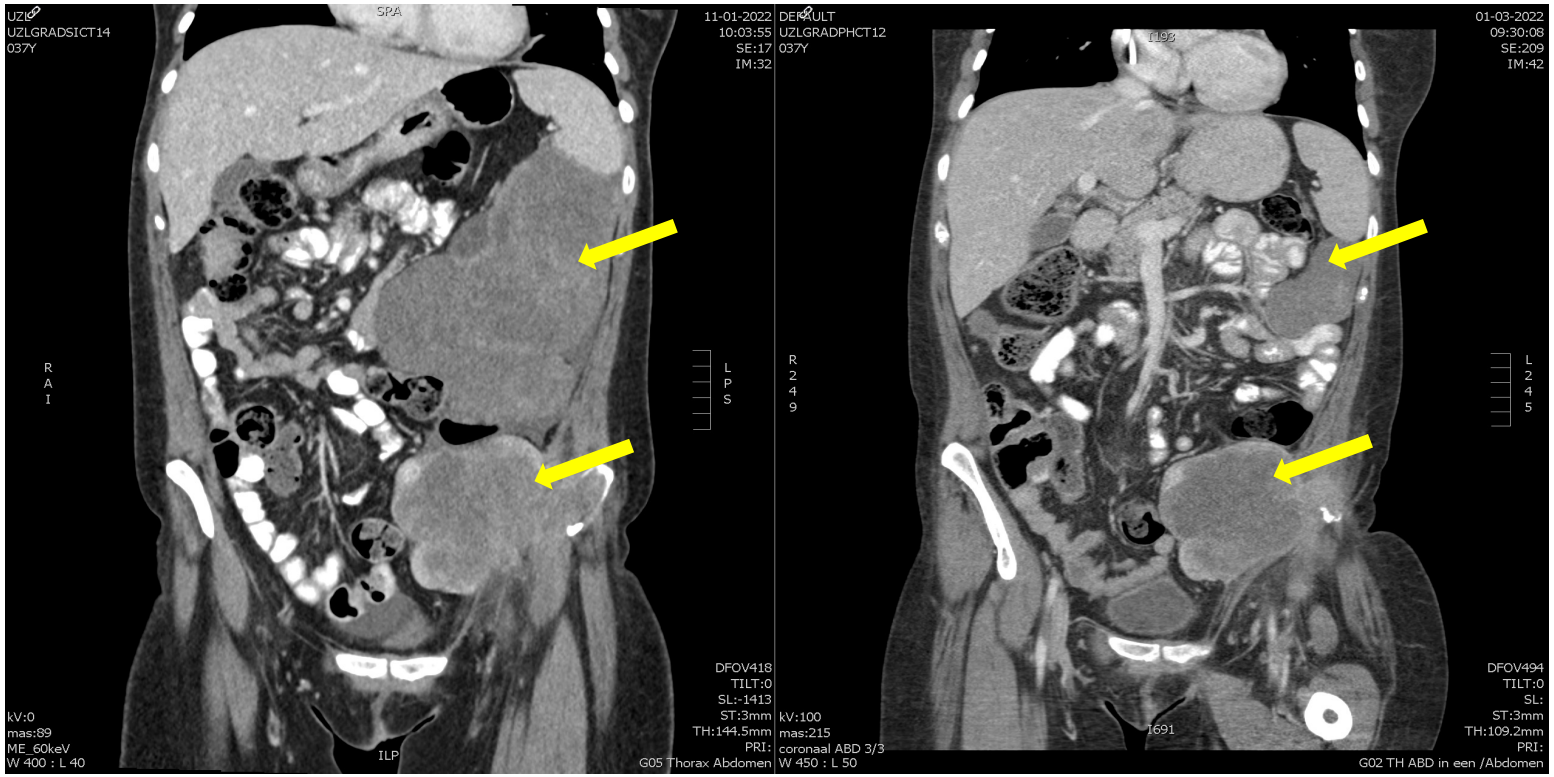




DCR = disease control rate; DDLPS = dedifferentiated liposarcoma; ESMO = European Society for Medical Oncology; *MDM2* = mouse double minute 2 homolog; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

LoRusso P, et al. ASCO 2023. Abstract 11554.

Patient Case 1: Patient With DDLPS With a Striking Partial Response



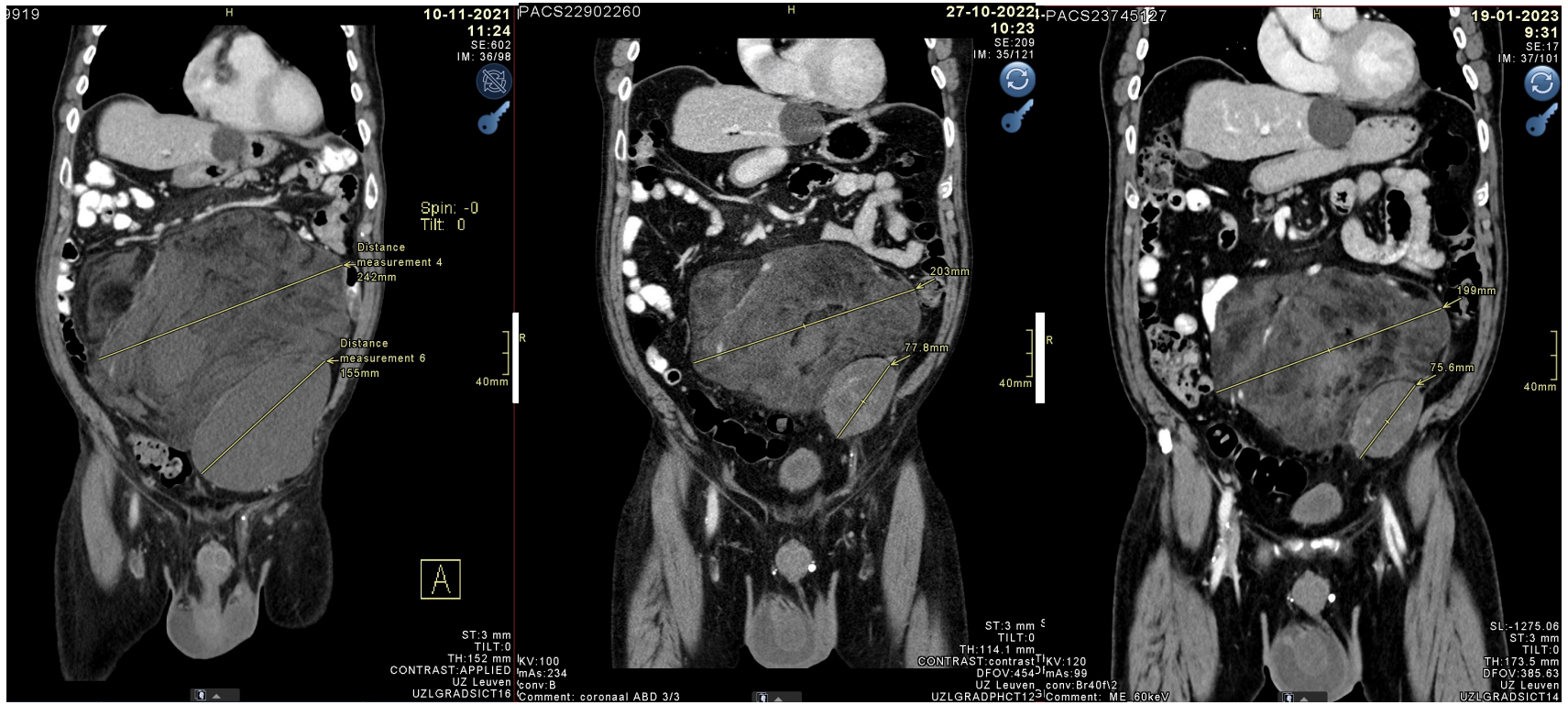
Baseline CT scan (01/2022)

On-treatment CT scan after only 2 administrations of brigimadlin (03/2022)

- Female patient, 37 years of age, with metastatic pelvic DDLPS, *TP53*wt, *MDM2*-amplified
- Never responded to doxorubicin/ ifosfamide, eribulin, or trabectedin
- Early benefit observed with RECIST PR (–43%) after only 2 administrations of brigimadlin 45 mg Q3W, confirmed over a total treatment duration of >8 months
- Response of peritoneal, lung, and pleural metastasis
- Patient came off study in 09/2022 with RECIST PD

Images courtesy of P. Schöffski, University Hospitals Leuven, Leuven, Belgium.
CT = computed tomography; DDLPS = dedifferentiated liposarcoma; ESMO = European Society for Medical Oncology; *MDM2* = mouse double minute 2 homolog; PD = progressive disease; PR = partial response; Q3W = once every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; *TP53* = tumor protein p53 gene; wt = wild type.
Schöffski P, et al. ESMO Sarcoma and Rare Cancers 2023. Presentation 420.

Patient Case 2: Patient With DDLPS With Progressive Tumor Shrinkage and Delayed Partial Response



Baseline CT scan (11/2021) **CT scan (10/2022)** **CT scan (01/2023)**

- Male patient, 67 years of age, with metastatic pelvic DDLPS, *TP53*wt, *MDM2*-amplified
- RECIST PD after 4 cycles of doxorubicin
- Received brigimadlin Q3W since 11/2021 with progressive shrinkage of the target lesions
- Achieved RECIST PR in 10/2022 with 36% shrinkage
- Patient still on treatment

Images courtesy of P. Schöffski, University Hospitals Leuven, Leuven, Belgium.
CT = computed tomography; DDLPS = dedifferentiated liposarcoma; ESMO = European Society for Medical Oncology; *MDM2* = mouse double minute 2 homolog; PD = progressive disease; PR = partial response; Q3W = once every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; *TP53* = tumor protein p53 gene; wt = wild type.
Schöffski P, et al. ESMO Sarcoma and Rare Cancers 2023. Presentation 420.

Preliminary Safety Profile in All Patients Who Received Brigimadlin Every 3 Weeks

- Nausea was the most common TRAE[1–3]; antiemetic prophylaxis or antiemetic prophylaxis strategies were implemented[2–3]
- Neutropenia and thrombocytopenia were the most common grade ≥3 TRAEs[1]
- DLTs were mainly thrombocytopenia and neutropenia[2]
  - The MTD of brigimadlin was 60 mg Q3W
  - The RDE was selected as 45 mg Q3W
- Thrombocytopenia was not associated with bleeding and typically recovered within 1–3 weeks[2,3]
- The overall AE profile was similar for patients with DDLPS (n = 39)[3]
  - Thrombocytopenia was not associated with bleeding and typically recovered within 1 to 3 weeks
  - Dose reductions occurred in 15% of patients and only 5% discontinued treatment

AEs, n (%)	45 mg Q3W cohort (N = 97)	
Any-grade TRAE	90 (92.8)	
Grade ≥3 TRAE	46 (47.4)	
AEs leading to dose reduction/ discontinuation	34/3 (35.1/3.1)	
Most common TRAEs[a]	**Any grade**	**Grade ≥3**
Nausea	70 (72.2)	5 (5.2)
Fatigue	58 (59.8)	4 (4.1)
Neutropenia	47 (48.5)	26 (26.8)
Thrombocytopenia	42 (43.3)	22 (22.7)
Vomiting	38 (39.2)	2 (2.1)
Decreased appetite	32 (33.0)	1 (1.0)
Anemia	28 (28.9)	13 (13.4)
Leukopenia	23 (23.7)	10 (10.3)

[a]Any-grade TRAEs occurring in >30% of patients or grade 3/4 AEs occurring in >5% of patients.

AE = adverse event; DDLPS = dedifferentiated liposarcoma; DLT = dose-limiting toxicity; ESMO = European Society for Medical Oncology; MTD = maximum tolerated dose; Q3W = every 3 weeks; RDE = recommended dose for expansion; TRAE = treatment-related adverse event.

1. LoRusso P, et al. ASCO 2023. Abstract 11554; 2. Gounder MM, et al. CTOS 2022. Paper 19; 3. Schöffski P, et al. ESMO Sarcoma and Rare Cancers 2023. Presentation 420.

Preliminary Mutational Analysis in Patients Who Received Brigimadlin

- A longitudinal mutational analysis of *TP53* was done to determine if mutations in *TP53* can be associated with possible acquired resistance to brigimadlin[1]
  - ctDNA from patients in study 1403-0001 was analyzed using tumor-specific NGS[1,a]
- Among patients with DDLPS, *TP53*wt was found in 5/6 (83%) patients at baseline and 4/10 (40%) patients at last available sample[1]
  - Note: patients with previously known *TP53* mutations were excluded from study 1403-0001[2]
- No clear association of induction of mutations could be identified for any brigimadlin dose or dosing schedule, treatment duration, or tumor type[1]

_TP53_ Mutations in Patients With DDLPS in Study 1403-0001

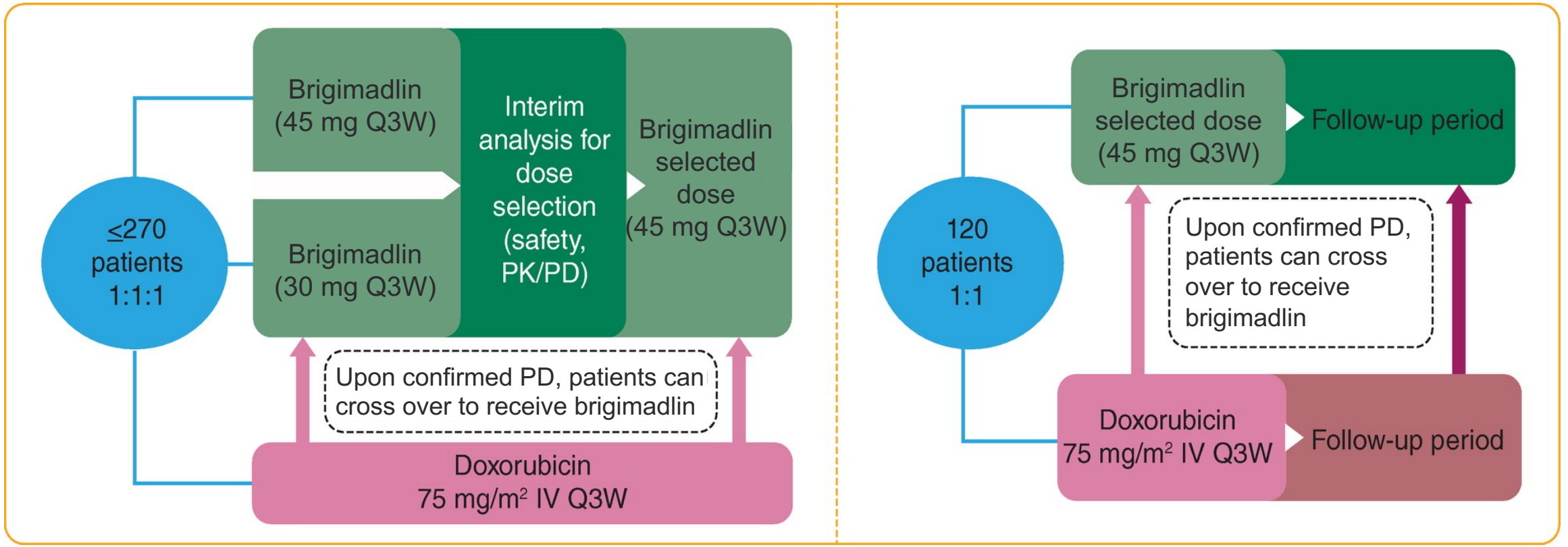
TP53 mutation/s at baseline	*TP53* mutation/s at last available sample	Brigimadlin dose level and schedule
NA	None	45 mg Q3W
NA	None	20 mg D1D8Q4W
NA	None	15 mg D1D8Q4W
None	C275Y, I195N	45 mg Q3W
None	Y220C, R175H	45 mg Q3W
None	K373fs, Y234D, Y220C, H168R	30 mg D1D8Q4W
None	NA	45 mg Q3W
NA	H193Y	45 mg D1D8Q4W
None	V143M	50 mg Q3W
K373fs, S362fs	H179R	50 mg Q3W
NA	None	45 mg Q3W

[a]Custom-made 8-gene panel using KAPA HyperCap technology, including *TP53*.
C = cysteine; ctDNA = circulating tumor DNA; D = aspartic acid; D1D8Q4W = on days 1 and 8 every 4 weeks; DDLPS = dedeifferentiated liposarcoma; ESMO = European Society for Medical Oncology; fs = frameshift; H = histidine; I = isoleucine; K = lysine; LAS = last available sample; M = methionine; N = asparagine; NA = no sample available; NGS = next-generation sequencing; Q3W = every 3 weeks; R = arginine; S = serine; *TP53* = tumor protein p53 gene; V = valine; wt = wild type; Y = tyrosine.

1. Peltzer A, et al. ASCO 2023. Poster 3036; 2. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03449381. Accessed August 2023.

Brightline-1 Study Design

A phase 2/3, randomized, open-label, multicenter study of brigimadlin compared with doxorubicin as first-line treatment of patients with advanced DDLPS[1,2]



Brightline-1 is now fully enrolled.[1]

DDLPS = dedifferentiated liposarcoma; ESMO = European Society for Medical Oncology; IV = intravenous; PD = pharmacodynamics; PK = pharmacokinetics; Q3W = every 3 weeks.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05218499. Accessed September 2023; 2. Schöffski P, et al. *Future Oncol*. 2023;19(9):621–629.

Brigimadlin in Other Solid Tumors

Phase 1a/1b, Dose-Escalation/Expansion Study of Brigimadlin in Patients With Advanced/Metastatic Solid Tumors (1403-0001)[1,2]

Key inclusion criteria:

- Known *TP53*wt status[a] and *MDM2* amplification (expansion phase only)
- ECOG PS 0–1
- Patients with PD/relapse, no proven treatment available, or *MDM2*-amplified sarcomas who require first-line treatment (expansion phase only)

Key exclusion criteria:

- Previous administration of any MDM2-p53 or MDMX (MDM4)-p53 antagonist

Phase 1a (dose escalation): completed
N = 54 patients with locally advanced/metastatic solid tumors

Arm A
Brigimadlin on Day 1 of 21-day cycles

Arm B
Brigimadlin on Days 1 and 8 of 28-day cycles

RDE: Brigimadlin 45 mg Q3W

Phase 1b (dose expansion): ongoing

Cohort 1
*TP53*wt, *MDM2*-amplified sarcomas (any line)

Brigimadlin p.o.

Cohort 2
*TP53*wt, *MDM2*-amplified solid tumors; NSCLC, gastric, urothelial, pancreatic, biliary tract (≥2L)

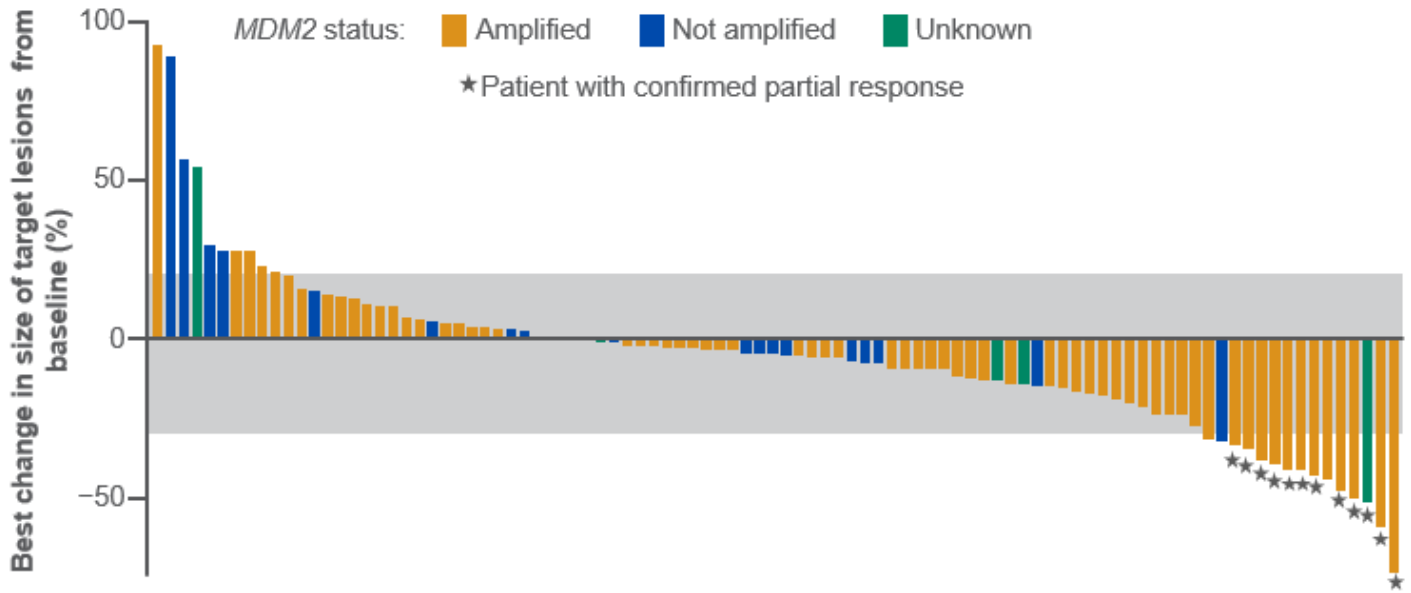
Brigimadlin p.o.

Phase 1b
Primary endpoint: PFS
Secondary endpoints: OR, OS, grade ≥3 TRAEs, PK

[a]If *TP53* status cannot be evaluated, patients may be included if agreed by the investigator and sponsor.
1L = first-line; 2L = second-line; ECOG PS = Eastern Cooperative Oncology Group performance status; ESMO = European Society for Medical Oncology; *MDM2* = mouse double minute 2 homolog; MDMX (MDM4) = mouse double minute 4 homolog; NSCLC = non–small cell lung cancer; OR = objective response; OS = overall survival; p53 = tumor protein 53; PD = progressive disease; PK = pharmacokinetics; PFS = progression-free survival; p.o. = by mouth; PR = partial response; Q3W = every 3 weeks; RDE = recommended dose for expansion; *TP53* = tumor protein p53 gene; TRAE = treatment-related adverse event; wt = wild type.
1. LoRusso P, et al. ASCO 2023. Abstract 11554; 2. Clinicaltrials.gov. https://clinicaltrials.gov/study/NCT03449381. Accessed September 2023.

Preliminary Efficacy of Brigimadlin in Patients with Advanced or Metastatic Solid Tumors (Study 1403-0001)

- At data cutoff,[a] 107 patients had received brigimadlin, including 4 patients with BTC
- Of 94 evaluable patients,[b] 79 achieved at least stable disease (DCR=84.0%)
- 12 patients achieved a confirmed partial response; majority were *MDM2*-amplified (ORR=12.8%), including those with non-sarcoma solid tumors:
  - 1 patient with pancreatic adenocarcinoma
  - 2 patients with BTC



Data update will be presented at this conference
Title: A Phase I dose-escalation and expansion study evaluating the safety and efficacy of the MDM2–p53 antagonist BI 907828 in patients (pts) with solid tumours
Presentation number: 673P
Date & Time: 23 October 2023 (Monday), 12:00PM–1:00PM
Authors: Dr. Patrick Schöffski, et al

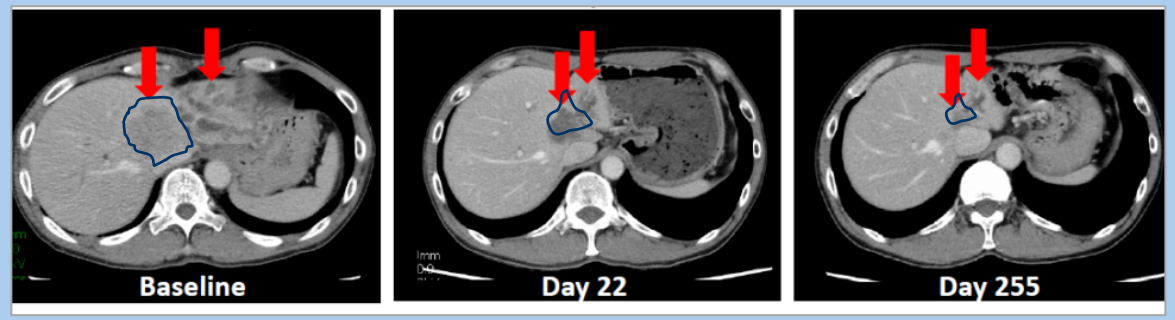
[a]Data cutoff July 2022. [b]These patients were enrolled in phase 1a or Cohort 1 of phase 1b.
BTC = biliary tract cancer; DCR = disease control rate; ESMO = European Society for Medical Oncology; *MDM2* = mouse double minute 2 analog; ORR = objective response rate.
Schöffski P, et al. ESMO 2022. Abstract 4520.

MDM2 Amplification in BTC

- *TP53* is one of the most frequently mutated genes in BTC, but p53 function can also be lost in BTC tumors due to the amplification of its negative regulator ***MDM2*, a key driver in BTC**[1,2]
  - 5−6% of BTC cases have *MDM2* amplification[2]

Case Report: Brigimadlin in BTC[3,4]

- Male Asian patient, 51 years of age
- ***MDM2*-amplified cholangiocarcinoma**
- 3 prior lines of therapy
- Brigimadlin monotherapy at 80 mg Q3W then dose reduction to 45 mg on cycle 2
- **PR (–73%) at Day 22 until Day 404**



BTC = biliary tract cancer; ESMO = European Society for Medical Oncology; *MDM2* = mouse double minute 2 homolog; p53 = tumor protein 53; PR = partial response; Q3W = every 3 weeks; *TP53* = tumor protein p53 gene.

1. Mirallas O, et al. *ESMO Open*. 2022;7:100503; 2. Kim SJ, et al. *Am J Surg Pathol*. 2018;42(4):512–521; 3. Yamamoto N, et al. ASCO Gastrointestinal Cancers Symposium 2023. Abstract 543; 4. LoRusso P, et al. *Cancer Discov*. 2023;13(8):1802−1813.

Brightline-2: A Phase 2a/2b Trial of Brigimadlin for Locally Advanced/Metastatic, *MDM2*-amplified, *TP53*wt BTC and Other Selected Solid Tumors[1,2]

Brigimadlin monotherapy Q3W

MDM2 amplified/*TP53*wt locally advanced/metastatic tumors without treatment options

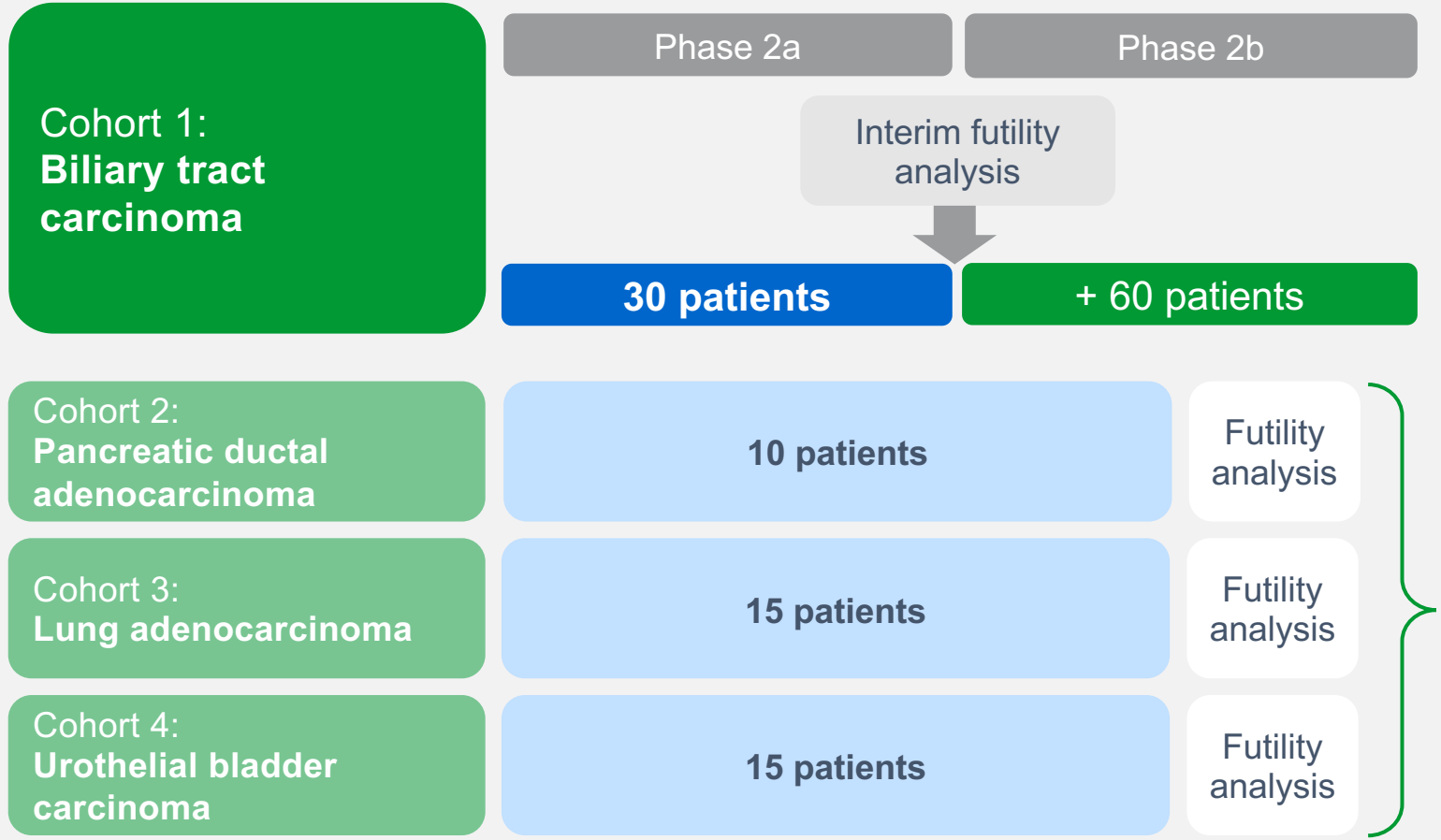
Primary endpoint:

- ORR

Secondary/further endpoints:

- DOR (key secondary)
- PFS
- OS
- PRO
- Safety
- PK

Clinicaltrials.gov identifier
NCT05512377



BTC = biliary tract cancer; DOR = duration of response; ESMO = European Society for Medical Oncology; *MDM2* = mouse double minute 2 homolog; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PRO = patient-reported outcome; *TP53* = tumor protein p53 gene; wt = wild type.

1. Goyal L, et al. ASCO 2023. Abstract TPS4179; 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05512377. Accessed August 2023.

Key Trials for Brigimadlin

Study	Phase	Treatment	Patient population	Status
Study 1403-0001[1]	1	Brigimadlin	Advanced solid tumors	Recruiting
Study 1403-0002[2]	1	Brigimadlin + ezabenlimab (PD-1 inhibitor)	Advanced solid tumors	Recruiting
Brightline-1[3]	2/3	Brigimadlin vs doxorubicin	Advanced DDLPS	Active, not recruiting
Brightline-2[4]	2	Brigimadlin	*MDM2*-amplified BTC and other solid tumors (pancreatic, urothelial, lung)	Recruiting
Brightline-4[5]	3	Brigimadlin	Advanced DDLPS	Not yet recruiting
Study 1403-0007[6]	0/1a	Brigimadlin	Newly diagnosed glioblastoma	Recruiting

BTC = biliary tract cancer; DDLPS = dedifferentiated liposarcoma; ESMO = European Society for Medical Oncology; *MDM2* = mouse double minute 2 homolog; PD-1 = programmed death protein 1.

1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03964233. Accessed August 2023; 2. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03449381. Accessed August 2023; 3. ClinicalTrials.gov. https://www.clinicaltrials.gov/study/NCT05218499. Accessed August 2023; 4. ClinicalTrials.gov. https://www.clinicaltrials.gov/study/NCT05512377. Accessed August 2023; 5. ClinicalTrials.gov. https://www.clinicaltrials.gov/study/NCT05376800. Accessed August 2023.

Summary

- p53 protects genomic integrity during times of cellular stress/injury. Some tumors inactivate p53wt by amplifying or overexpressing MDM2, the primary negative regulator of p53[1,2]
- The MDM2-p53 antagonist brigimadlin was developed with optimized drug, metabolism, and pharmacokinetic properties, allowing Q3W dosing to mitigate hematologic toxicities associated with this drug class[3,4]
- Patients with advanced DDLPS have a poor prognosis and there has been no change in first-line treatment in nearly five decades. The vast majority of DDLPS are *MDM2*-amplified, *TP53*wt[5–11]
- In a phase 1 study, preliminary signs of efficacy (ORR 14.5%, DCR 82.6%, median PFS 7.9 months) and manageable safety were seen with brigimadlin monotherapy[12,13]
- Brightline-1, assessing brigimadlin as first-line treatment in advanced DDLPS compared with doxorubicin, has fully enrolled and the US FDA has granted Fast Track Designation[12,13]
- Brigimadlin is being clinically developed in other tumor types based on early signs of efficacy. Enrollment is ongoing globally for Brightline-2, a phase 2 study assessing brigimadlin in *MDM2*-amplified biliary tract cancer and other *MDM2*-amplified solid tumors[14,15]

DCR = disease control rate; DDLPS = dedifferentiated liposarcoma; ESMO = European Society for Medical Oncology; LPS = liposarcoma; *MDM2* = mouse double minute 2 homolog; ORR = objective response rate; p53 = tumor protein 53; PFS = progression-free survival; *TP53* = tumor protein p53 gene; Q3W = every 3 weeks; US FDA = United States Food and Drug Administration; wt = wild type.

1. Zhao Y, et al. *Acta Biochim Biophys Sin (Shanghai).* 2014;46(3):180–189; 2. Joerger AC, Fersht AR. *Annu Rev Biochem.* 2016;85:375–404; 3. Gollner A, et al. AACR 2023. Poster LB003; 4. Iancu-Rubin C, et al. *Exp Hematol.* 2014;42(2):137–145; 5. Lee ATJ, et al. *J Clin Oncol.* 2018;36(2):151–159; 6. Nishio J, et al. *J Clin Med.* 2021;10(15):3230; 7. Gronchi A, et al. *Ann Oncol.* 2021;32(11):1348–1365; 8. Gamboa AC, et al. *CA Cancer J Clin.* 2020;70(3):200229; 9. European Medicines Agency. https://www.ema.europa.eu/en/documents/ withdrawal-report/withdrawal-assessment-report-doxorubicin-hydrochloride-tillomed_en.pdf. Accessed August 2023; 10. Asano N, et al. *Oncotarget.* 2017;8(8):12941–12952; 11. Somiah N, et al. *Oncotarget.* 2018;9(28):19891–19899; 12. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05218499. Accessed April 2022; 13. Boehringer Ingelheim. https://www.boehringer-ingelheim.com/oncology/brigimadlin-bi-907828. Accessed October 2023; 14. Schöffski, P, et al. ESMO 2022. Abstract 4520; 15. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05512377. Accessed August 2023.