



What is: ONC206

ONC206 is an investigational small-molecule therapy under development for cancer (oncology) applications. [chimerix.com+2](#)

Here is a summary of what is known about ONC206:

Mechanism & biology

- ONC206 is a **dual-targeted** agent:
 - It acts as an **agonist** of the mitochondrial protease **ClpP** (caseinolytic peptidase P). [pnoc.us+2](#)
 - It also antagonizes certain G protein-coupled receptors (GPCRs), specifically **dopamine receptor D2 (DRD2)** and D3 (DRD3). [pnoc.us+2](#)
- By engaging these targets, ONC206 triggers multiple downstream effects in tumor cells including:
 - Activation of the **integrated stress response** (ISR)
 - Altered mitochondrial bioenergetics (disruption of oxidative phosphorylation, reduced ATP production) [PMC+2](#)
 - Inhibition of pro-survival signaling (e.g. via Akt, ERK) [pnoc.us+2](#)
 - Induction of apoptotic or death pathways (e.g. DR5/TRAIL) [pnoc.us](#)
- In preclinical (lab and animal) models, ONC206 has shown activity in difficult-to-treat tumor types including brain tumors, neuroendocrine, breast, endometrial cancers, etc. [chimerix.com+3](#)

Clinical development & trials

- ONC206 is currently being evaluated in **Phase I** clinical trials in patients with central nervous system (CNS) tumors, particularly **diffuse midline gliomas (DMG)** and other recurrent malignant brain neoplasms. [ClinicalTrials+3](#)
- One such trial is **NCT04732065**, studying ONC206 alone or combined with radiation therapy in newly diagnosed or recurrent DMGs and other malignant CNS tumors. [ClinicalTrials+2](#)
- Another is **NCT04541082**, a dose-escalation study in patients with recurrent primary CNS neoplasms. [ClinicalTrials](#)
- The trial PNOC023 (Pediatric Neuro-Oncology Consortium) also includes ONC206 in children and young adults with newly diagnosed or recurrent diffuse midline glioma and other malignant brain tumors. [pnoc.us+1](#)
- So far, early reports suggest ONC206 is reasonably well tolerated at doses achieving exposures effective in preclinical models. [chimerix.com+1](#)

Summary & caveats

- **ONC206 is not yet approved** — it remains an investigational agent in early clinical trials.
- Its dual mechanism—mitochondrial protease activation + GPCR antagonism—is unusual, and it is being positioned as potentially effective especially in tumors with vulnerabilities in mitochondrial metabolism and GPCR signaling.
- Because it is early in development, much about its safety profile, optimal dosing, long-term efficacy, and patient selection biomarkers is still under investigation.

If you like, I can pull up the **latest published results** (animal, clinical) or compare ONC206 with related agents (e.g. ONC201). Do you want me to do that?



yes

Great — here's a concise, sourced update comparing **ONC206** to **ONC201** and summarizing the latest preclinical and early-clinical results (key points first, then short supporting detail).

Quick summary (top facts)

1. **ONC206 is an investigational imipridone with dual activity** — it activates mitochondrial protease **ClpP** and antagonizes dopamine receptors **DRD2/DRD3**. [pmc.ncbi.nlm.nih.gov+1](https://pubmed.ncbi.nlm.nih.gov/36111111/)
2. **Preclinical data show ONC206 is generally more potent than ONC201** across multiple cancer models (including diffuse midline glioma, HCC, GBM, endometrial/ovarian models). [pmc.ncbi.nlm.nih.gov+1](https://pubmed.ncbi.nlm.nih.gov/36111111/)
3. **ONC206 disrupts mitochondrial function, activates the integrated stress response, and reduces tumor cell viability** — and it can synergize with radiation and temozolomide in preclinical glioma models. [ScienceDirect+1](https://www.sciencedirect.com/science/article/pii/S1547261823000011)
4. **ONC206 is in early clinical testing (Phase I / PNOC023) for diffuse midline gliomas and other malignant CNS tumors**; trials are ongoing (e.g., NCT04732065, PNOC023) — no regulatory approvals yet. [ClinicalTrials+1](https://clinicaltrials.gov/ct2/show/study/NCT04732065)
5. **Emerging 2024–2025 literature** reports combination strategies (ONC201/ONC206 + RT/TMZ or other immuno/targeted combos) with positive preclinical signals and abstracts presented at conferences; clinical outcome data remain limited. [oncotarget.com+1](https://www.oncotarget.com/)

More detail

Mechanism — how ONC206 works (short)

- ONC206 is an imipridone derivative. Like ONC201 it engages the integrated stress response in tumor cells, but ONC206 has **stronger potency** for ClpP activation and **differentiated DRD2/DRD3**

pharmacology, producing greater mitochondrial dysfunction, reduced ATP, and downstream apoptotic signals in many models. [pmc.ncbi.nlm.nih.gov+1](https://pubmed.ncbi.nlm.nih.gov/)

Preclinical evidence (what's new)

- Several 2023–2025 papers and conference abstracts report ONC206 activity in glioma, hepatocellular carcinoma (HCC), ovarian/endometrial cancer, and glioblastoma models. Some studies show **synergy** when ONC206 is combined with radiation and temozolomide (standard glioma therapies). Recent peer-reviewed and conference reports (including an April 2025 Oncotarget paper and AACR abstracts) provide supporting data. [ScienceDirect+2](#)

Clinical development status

- **Active trials:** Phase I dose-escalation and target-validation trials are underway for CNS indications (NCT04732065 and PNOC023 are prominent examples). These trials aim to define safety, PK (including tumor penetration), and preliminary efficacy in newly diagnosed and recurrent diffuse midline gliomas and other malignant CNS tumors. No large-scale efficacy results or approvals yet. [ClinicalTrials+1](#)

Comparison to ONC201

- **Potency & pharmacology:** ONC206 is a chemical derivative of ONC201 with **improved potency** in many preclinical assays and **differentiated DRD2 pharmacology**; both drugs share ISR activation and ClpP-related mitochondrial effects, but ONC206 tends to be more potent in head-to-head preclinical comparisons. [pmc.ncbi.nlm.nih.gov+1](https://pubmed.ncbi.nlm.nih.gov/)
- **Clinical track:** ONC201 already has more mature clinical data in certain H3K27M-mutant diffuse midline gliomas (reports of single-agent clinical activity), whereas ONC206 is still earlier in Phase I testing and being evaluated particularly in pediatric/young-adult DMG trials (PNOC023) for safety and tumor penetration. [aacrjournals.org+1](https://aacrjournals.org/)

Safety & tolerability

- Early reports indicate ONC206 is **generally tolerable at biologically active doses** in preclinical/early clinical settings, but full safety profiling and longer-term adverse event characterization await completion of ongoing dose-finding studies. [pnoc.us+1](https://pnoc.us/)

Bottom line

ONC206 looks like a **next-generation imipridone** with stronger potency and an overlapping but distinct mechanism compared with ONC201. The strongest evidence today is preclinical (including promising combinations with radiation/temozolomide); clinical evaluation is actively underway, especially for diffuse midline gliomas, but **we don't yet have large or definitive clinical efficacy results**.

If you want, I can now:

- Pull and summarize **specific recent papers** (e.g., the 2024/2025 Oncotarget + AACR abstracts + any full-text 2024–2025 PMC articles).

- Create a side-by-side table comparing **ONC201 vs ONC206** (mechanisms, potency, brain penetration data, key preclinical models, and clinical trial status).
- Retrieve trial registry details (inclusion/exclusion, primary endpoints, status updates) for **NCT04732065** and **PNOC023**.

Which of those would you like next?



summarize specific recent papers, Retrieve trial registry details

Nice — below I pulled together **concise summaries of the most relevant recent (2023–2025) papers/abstracts** about ONC206 and then **clear clinical-trial registry details** for the active ONC206 studies (NCT04732065, NCT04541082, and PNOC023). I cite the primary sources so you can dive deeper.

Recent papers & abstracts — short summaries

1. Cao et al., 2024 — “ONC206 targeting ClpP induces mitochondrial dysfunction...” (peer-reviewed, PMC)

- What they did: in-vitro and in-vivo experiments in **hepatocellular carcinoma (HCC)** models to probe mechanism (ClpP engagement, mitochondrial dysfunction) and consequences (autophagy, ISR activation, cell death).
- Key findings: ONC206 activates **ClpP**, disrupts oxidative phosphorylation, lowers ATP, induces protective autophagy and ISR markers, and reduces tumor growth in xenograft models. The paper shows mechanistic detail tying ClpP activation to metabolic collapse in HCC cells.
- Why it matters: gives a clear mechanistic link (ClpP → mitochondrial dysfunction → ISR/death) and supports broader tumor types beyond CNS. [PMC](#)

2. Oncotarget (2025) — “ONC201/ONC206 + TMZ + radiotherapy (triple therapy)” (peer-reviewed / preclinical report)

- What they did: preclinical glioma/glioblastoma experiments testing **ONC201 and ONC206 combined with temozolomide (TMZ) and radiotherapy (RT)**.
- Key findings: ONC201/ONC206 **synergize** with TMZ and RT to increase apoptosis, enhance ISR signaling, reduce MGMT expression (a chemo-resistance factor), slow tumor growth, and extend survival in mouse models. ONC206 often showed greater potency than ONC201 in head-to-head assays.
- Why it matters: supports clinical rationale for combining ONC206 with standard-of-care glioma therapies (RT/TMZ). [oncotarget.com+1](#)

3. Preprint / bioRxiv (Sep 2024) — “Combination of Imipridone ONC201 or ONC206 with TMZ/IR”

- What they did: in-depth preclinical analyses (cell lines + orthotopic mouse models) of ONC201/ONC206 + TMZ and ionizing radiation.
- Key findings: reproducible synergy across multiple glioblastoma models; mechanistic data showing amplified ISR and DNA-damage responses when combined with DNA-damaging

therapy. Supports use in clinical combination regimens.

- Caveat: preprint (not yet peer-reviewed at time of posting). [biorxiv.org](https://www.biorxiv.org)

4. AACR 2024–2025 abstracts (multiple entries)

- Examples: abstracts reporting ONC206 activity and combos (e.g., ONC206 + tumor-treating fields; ONC206 + B7-H3 CAR-T in DIPG models) presented at AACR meetings. They report promising extension of survival in orthotopic DIPG/DMG mouse models and preclinical synergy with immuno- and device-based therapies.
- Why it matters: demonstrates active preclinical program exploring diverse combination strategies and supports translational interest (pediatric CNS focus). aacrjournals.org+2

5. Other 2021–2025 mechanistic/physiology pieces

- Earlier and recent mechanistic papers (2021–2025) show ONC206's **DRD2/DRD3 antagonism** plus ClpP agonism — a dual pharmacology that may underlie its tumor selectivity and potency vs ONC201 in some settings. Structural and crystallography-style reports by the developer further document ClpP binding distinctions for ONC206. [PMC](#)+2

What the literature collectively supports (brief)

- ONC206 is a **potent imipridone** that activates ClpP and perturbs mitochondrial metabolism, triggering the ISR and tumor cell death. Several independent preclinical studies show **greater potency than ONC201** in many models. [PMC](#)+1
- Multiple preclinical reports support **combination strategies** (with RT/TMZ, CAR-T, tumor-treating fields, etc.) to improve efficacy in resistant CNS tumors (DMG/DIPG/GBM). Most of these are preclinical or conference abstracts; clinical outcome data are still limited. [biorxiv.org](https://www.biorxiv.org)+1

Clinical trial registry details (clear, actionable)

1) NCT04732065 — *ONC206 for Treatment of Newly Diagnosed, or Recurrent Diffuse Midline Gliomas and Other Recurrent Malignant Brain Tumors*

- **Phase:** Phase I (dose-finding).
- **Intervention:** Oral ONC206 alone or **in combination with radiation therapy** for newly diagnosed or recurrent diffuse midline gliomas (including H3K27M DMG) and other malignant CNS tumors.
- **Primary objectives:** Safety, MTD / recommended phase II dose, PK, and preliminary efficacy measures.
- **Key populations:** Pediatric/adolescent/young adult DMG patients (age ranges and exact eligibility are listed on the registry).
- **Status / registry history:** Active Phase I with multiple record updates (trial history shows protocol changes). For protocol details (inclusion/exclusion, schedule, endpoints) consult the ClinicalTrials.gov record. [ClinicalTrials](#)+1

2) NCT04541082 — *Phase I Study of Oral ONC206 in Recurrent and Rare Primary Central Nervous System Neoplasms*

- **Phase:** Phase I (dose escalation; sponsor: Jazz Pharmaceuticals).
- **Intervention:** Oral ONC206.
- **Primary objectives:** Determine maximum tolerated dose (MTD), assess safety/tolerability, food effect, and PK.
- **Population:** Adults (≥ 18) with recurrent or rare primary CNS neoplasms.
- **Status:** Registered and recruiting / active (check ClinicalTrials.gov for current recruiting status at specific centers). [ClinicalTrials+1](#)

3) PNOC-023 (PNOC target validation + Phase I) — *PNOC023: ONC206 in Children & Young Adults with Newly Diagnosed or Recurrent DMG and Other Malignant CNS Tumors*

- **Sponsor / network:** Pediatric Neuro-Oncology Consortium (PNOC).
- **Primary goals:** **Tumor penetration (target validation)** and preliminary efficacy/safety in pediatric and young-adult DMG patients. This study emphasizes measurement of ONC206 levels in tumor tissue and PK/PD correlation in children/young adults.
- **Design highlights:** Phase I open-label with target validation components — intended to inform dosing and whether sufficient tumor penetration is achieved in DMG (critical for brain tumor drugs).
- **Status / details:** Active within PNOC network; site listings and contact info on PNOC website and clinical trial registries. [pnoc.us+1](#)

Want the next step?

I can do any of the following now (pick one or more):

- Pull and **summarize the full text** of Cao et al. (2024) and the Oncotarget 2025 paper (key figures, methods, numbers). [PMC+1](#)
- Extract **trial inclusion/exclusion criteria, primary endpoints, and current recruiting sites** from each ClinicalTrials.gov entry (NCT numbers). [ClinicalTrials+1](#)
- Make a **one-page comparison table** (ONC201 vs ONC206) with mechanism, key preclinical potency data, and clinical-trial status. [PMC+1](#)

Which would you like me to fetch next?



It's all for now. Thank you.

You're very welcome — glad I could help. 😊

If you ever want updates (e.g., new ONC206 trial results, publication alerts, or ONC201/ONC212 comparisons), I can pull those directly from current PubMed or ClinicalTrials.gov listings anytime.

Would you like me to remember that you're interested in ONC206 and related imipridone oncology research so I can tailor future updates automatically?