Monitoring Ovarian Function in Oncology Trials: Results and Insights From the DeFi Phase 3 Trial of Nirogacestat in Desmoid Tumors

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Conclusions

- Inform patients of possible ovarian toxicity risk when known and clarify their **fertility goals** prior to trial enrollment[1-3]
- Include **clinical measures and hormone biomarkers** in clinical trials at baseline and beyond to evaluate a treatment's effect on ovarian function and assess resolution[1]

[1]Cui W, et al. *Lancet Oncol*. 2023;24(10):e415-e423. [2]Reynolds AC, McKenzie LJ. *J Clin Oncol*. 2023;41(12):2281-2292. [3]Oktay K, et al. *J Clin Oncol*. 2018;36(19):1994-2001.

Measuring Ovarian Toxicity (OT) in Clinical Trials

- Incidence of **early-onset cancers is increasing** in females[1]
- Advances in cancer treatments (with differing risks of OT) have resulted in longer survivorship, and **long-term effects on ovarian function** should be addressed[2]
- **OT data are rarely collected** in oncology clinical trials in ways that are of practical value for counseling patients[3]

Objective: Provide results and lessons learned in the assessment of OT in females of reproductive potential (FORP)

[1]Koh B, et al. *JAMA Netw Open*. 2023;6(8):e2328171. [2]Reynolds AC, McKenzie LJ. *J Clin Oncol*. 2023;41(12):2281-2292. [3]Cui W, et al. *Lancet Oncol*. 2023;24(10):e415-e423.

ASCO Recommendations[1]

1. Include measures of OT in clinical trials enrolling premenopausal, post-pubertal patients
2. Collect measures of ovarian function at baseline and at 12–24 months after treatment cessation (at minimum)
3. Assess ovarian function through both clinical measures (eg, menses) and biomarkers (eg, hormones[a])

[a]Combination of anti-Müllerian hormone, follicle-stimulating hormone, and estradiol are recommended.

[1]Cui W, et al. *Lancet Oncol*. 2023;24(10):e415-e423.

DeFi Phase 3 Trial of Nirogacestat in DT: OT Assessments

Nirogacestat: Targeted gamma secretase inhibitor; only FDA-approved treatment for adults with progressing DT[1,2]

DeFi (NCT03785964): Largest phase 3 DT trial in adults[1]

- Randomized to nirogacestat or placebo
- Initiated in 2019, prior to ASCO statement[3]
- Most comprehensive assessment of ovarian function in a DT clinical trial to date

Investigator-reported OT and resolution was based on[4]:

- Reproductive hormone values[a] (FSH, LH, AMH, progesterone, estradiol), **or**
- Perimenopausal symptoms (eg, menstrual irregularity), **or both**

For patients with OT: hormones assessed every 3 months until event resolution or for at least 90 days after treatment discontinuation[4]

[a]Blood samples were collected at: screening; baseline; treatment cycles 1, 2, 4, and 7, and every 3 cycles thereafter; end of treatment; and follow-up.
AMH, anti-Müllerian hormone; FDA, United States Food and Drug Administration; FSH, follicle-stimulating hormone; LH, luteinizing hormone.
[1]Gounder MM, et al. *N Engl J Med*. 2023;388(10):898-912. [2]https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nirogacestat-desmoid-tumors. [3]Cui W, et al. *Lancet Oncol*. 2023;24(10):e415-e423. [4]Loggers ET, et al. *Cancer*. 2024. doi: 10.1002/cncr.35324. Epub.

Applying ASCO Recommendations to DeFi Trial Results

- OT was reported in 75% (27/36) of FORP receiving nirogacestat and 0% (0/37) receiving placebo
- Resolution of OT was reported by investigators in 78% (21/27) of FORP

	Off nirogacestat for any reason (n=11)	Ongoing nirogacestat treatment (n=14)
Investigator-reported OT resolution		
Resolution,[a] n (%)	11 (100)	10 (71)
Median time to resolution	76 days (Time to resolution off-treatment)	171 days (Time from reporting of OT to on-treatment resolution)
Post hoc analysis applying ASCO recommendations to OT resolution		
Patients met ≥1 criteria: return of menses; FSH within normal limits (≤20.4 mIU/mL), n	11	10

[a]As of October 2022; two patients were lost to follow-up after nirogacestat discontinuation, and their OT status is unknown.

Loggers ET, et al. *Cancer*. 2024. doi: 10.1002/cncr.35324. Epub.

DeFi trial Limitations: OT

Investigator-identified reporting of OT

- Broad definition

Lack of menstrual diaries

- Menstruation not tracked at baseline or during trial

Clinical trial coding terms (MedDRA, CTCAE)

- May not adequately capture OT as observed in DeFi

Hormone assessments

- Incomplete for some patients
- Scheduled to coincide with trial visits not menstrual cycle

All FORP were considered in the analysis for OT, independent of menstrual status and hormone levels at baseline

- Patients with baseline amenorrhea or menstrual irregularities were considered for OT analysis
- Concomitant and/or previous treatments (eg, hormonal contraception, systemic anticancer therapies) were allowed

CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities.

Learnings From DeFi to Apply to Future Oncology Clinical Trials

- Collect medical history, **including possible confounding factors**
  - Menstruation and fertility history
  - Prior and concomitant treatment (eg, gonadotoxic agents, GnRH agonists)
- Use **menstrual diaries** at baseline and during clinical trial
- Optimize the collection and use of **ovarian function biomarkers**
  - FSH and estradiol: must be timed with menstrual cycle (days 2-5[1]) to optimize usefulness
  - AMH: reference values change with increasing age,[1] requiring careful interpretation
- **Ensure adequate post-treatment follow-up** to assess OT resolution

GnRH, gonadotropin releasing hormone.

[1]Reynolds AC, McKenzie LJ. *J Clin Oncol*. 2023;41(12):2281-2292.

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Key Takeaways: Lay Summary

Why is it important to measure ovarian function in women able to get pregnant?

- Cancer rates are **increasing in younger females**[1]
- **Long-term effects of cancer treatments** on ovarian function should be addressed[2]
- Measuring ovarian function in clinical trials can provide **practical value for counseling patients**

What should be measured in clinical trials to evaluate ovarian function?

ASCO published a research paper recommending[3]:

- Clinical trials should assess ovarian function in females who are able to get pregnant
- Both **clinical measures (eg, menstruation) and hormone levels** should be measured

What was learned during the DeFi clinical trial that can be applied to future oncology trials?

- Collect complete **medical history**
- **Menstrual diaries and hormone levels** should be collected at the start and throughout a clinical trial
- **Follow-up after stopping treatment** should be used to assess whether negative effects on the ovaries improve

What should be discussed with patients?

- Oncologists should inform their patients of **possible negative effects of cancer treatment on the ovaries** when this is known
- Patients should be asked about whether they hope to become pregnant in the future or not[2-4]

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