Clinical Trials in Uveal Melanomas

Zelia M. Correa, MD, PhD

Professor of Ophthalmology

Director of Ocular Oncology and Echography

Bascom Palmer Eye Institute, University of Miami

OCULAR ONCOLOGY PROGRAM

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Disclosure

- Castle Biosciences, Inc: investigator
- Ideaya Biosciences, Inc: investigator
- AURA Biosciences, Inc: investigator

Objectives

- Describe recent, ongoing and future clinical trials in ocular oncology
- Exemplify immediate clinical applications of these clinical trials
- Discuss how the findings of such trials will change the current management of intraocular tumors

Current clinical trials for primary posterior uveal melanoma

- Collaborative Ocular Oncology Group – study 2
- (Neo)adjuvant IDE196 in patients with localized uveal melanoma
- Belzupacap Sarotalocan (AU-011) for indeterminate melanocytic lesions or small choroidal melanoma
- Intravitreal Faricimab (6.0 mg) or Fluocinolone Acetonide (0.19 mg) vs Observation for Prevention of Visual Acuity Loss due to Radiation Retinopathy **(DRCR.net Protocol AL)**

COOG 2 study

- Prospective validation of the prognostic accuracy of GEP + PRAME expression in predicting the metastatic outcome of patients with uveal melanoma

- Analysis of independent variables and their prognostic value

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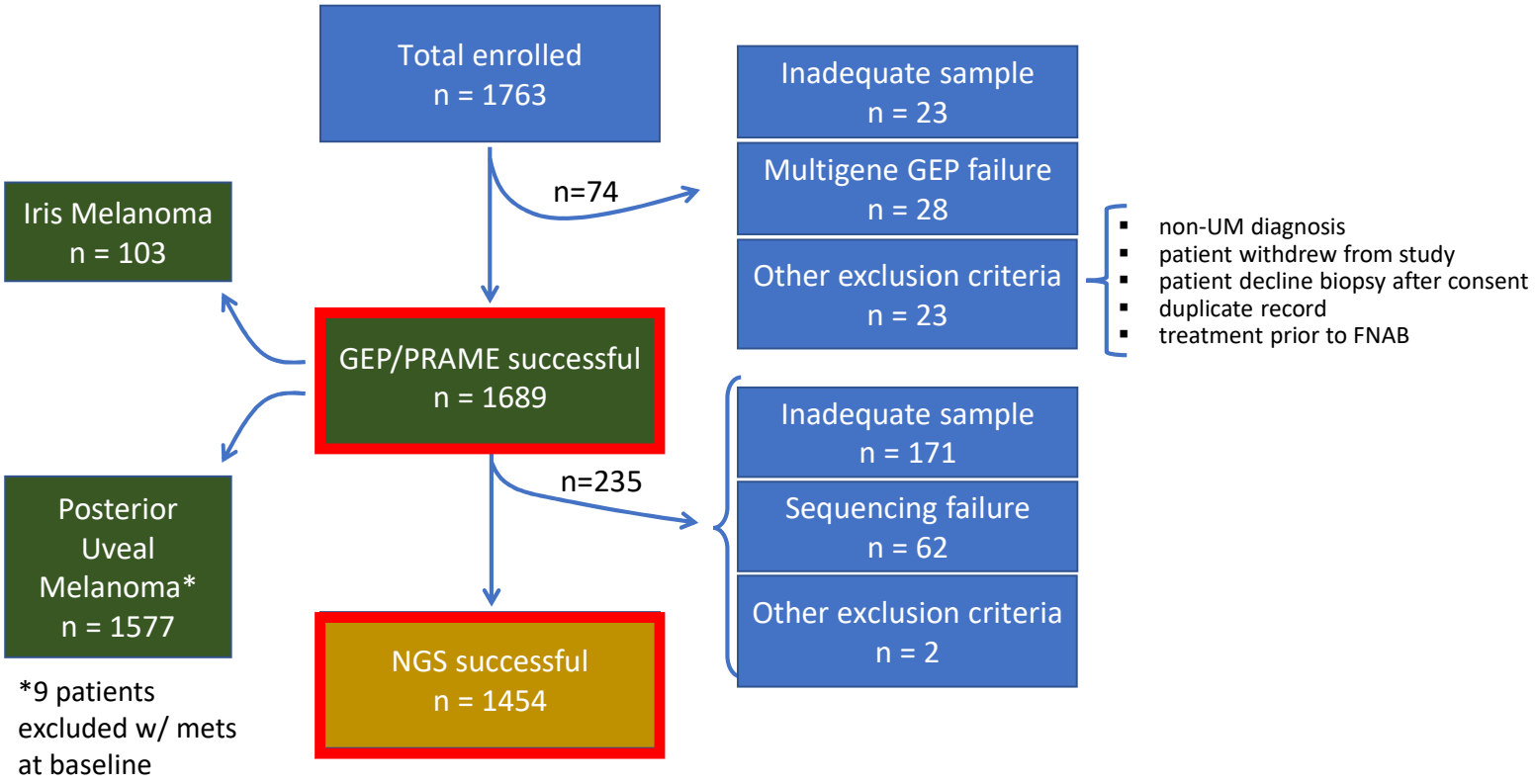
COOG
Collaborative Ocular Oncology Group
https://coog.life/

COOG 2.1



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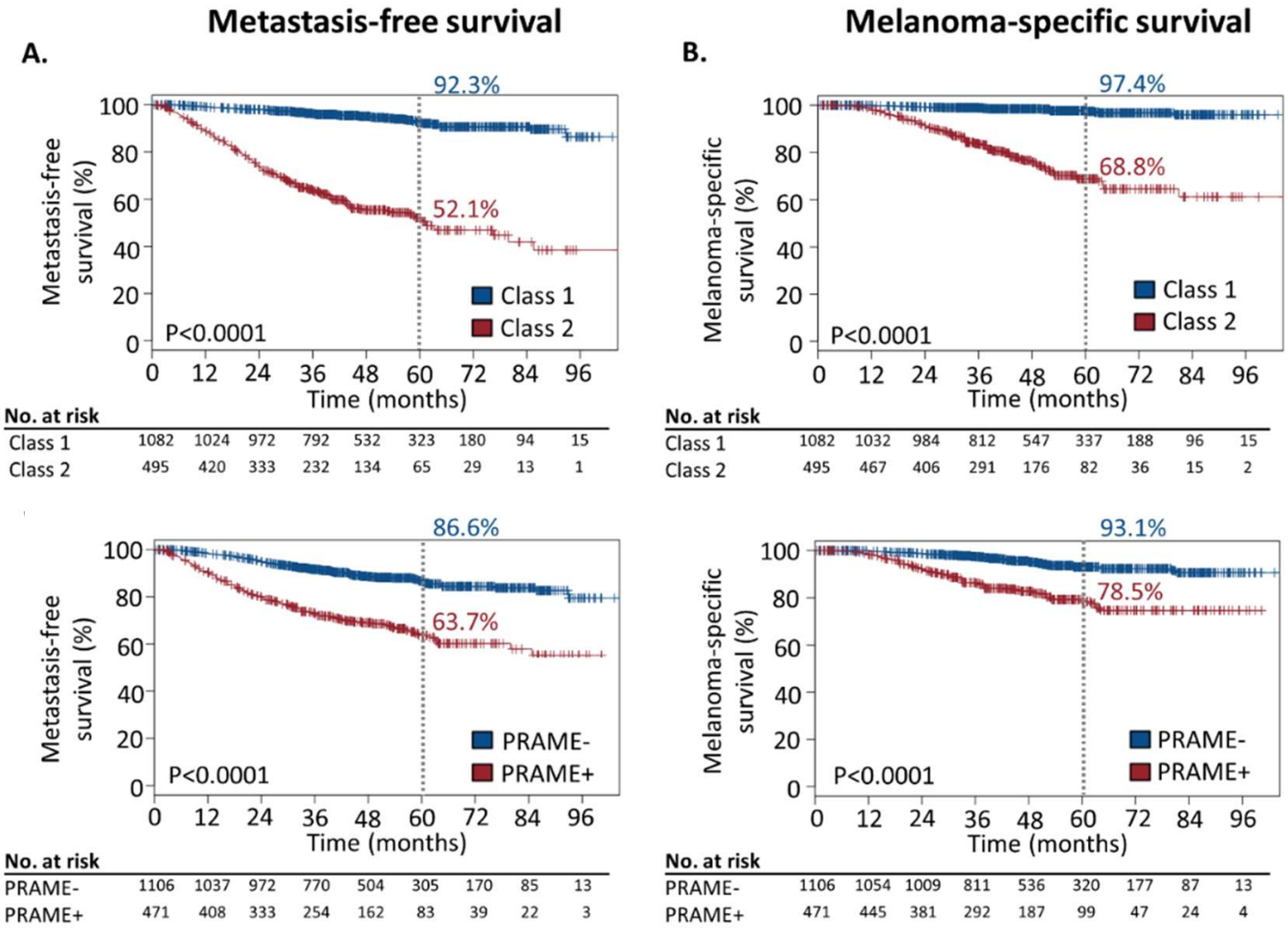
J Clin Oncol. 2024 Oct;42(28):3319-3329.



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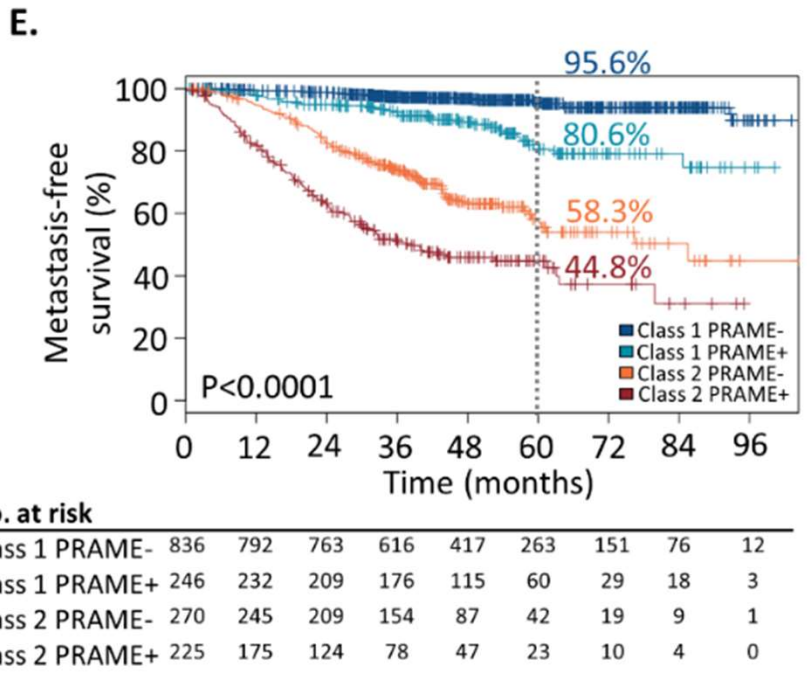
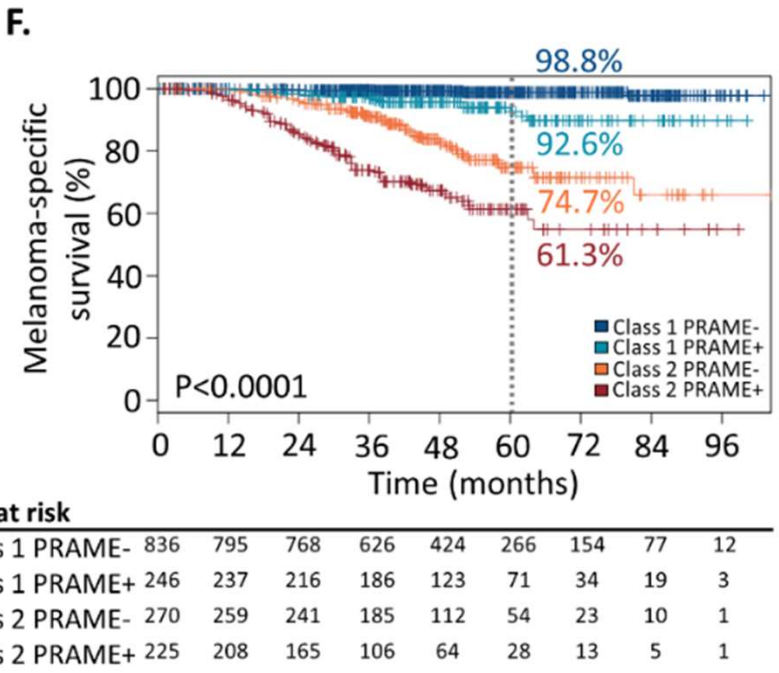
COOG 2.1

Metastasis-free survival



No. at risk									
Class 1 PRAME-	836	792	763	616	417	263	151	76	12
Class 1 PRAME+	246	232	209	176	115	60	29	18	3
Class 2 PRAME-	270	245	209	154	87	42	19	9	1
Class 2 PRAME+	225	175	124	78	47	23	10	4	0

Melanoma-specific survival



No. at risk									
Class 1 PRAME-	836	795	768	626	424	266	154	77	12
Class 1 PRAME+	246	237	216	186	123	71	34	19	3
Class 2 PRAME-	270	259	241	185	112	54	23	10	1
Class 2 PRAME+	225	208	165	106	64	28	13	5	1

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J Clin Oncol. 2024 Oct;42(28):3319-3329.

Cox proportional hazards

Variable	Univariate	Multivariate		
		GEP	GEP PRAME	GEP PRAME Diameter
GEP	+			
PRAME	+	+		
Age	+	-	-	-
Gender	-	-	-	-
Iris Color	-	-	-	-
Ciliary Body	+	+	-	-
Diameter	+	+	+	
Thickness	+	+	+	±

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COOG Collaborative Ocular Oncology Group

Univariate Cross Validation

Variables	Concordance Statistic
GEP + PRAME	.8189 ± .01
GEP + PRAME + LBD	.8551 ± .01

COOG2 validated PRAME as a significant risk modifier independent of and complementary to GEP

GEP + PRAME + LBD provides best prediction model

No value in including other clinical variables

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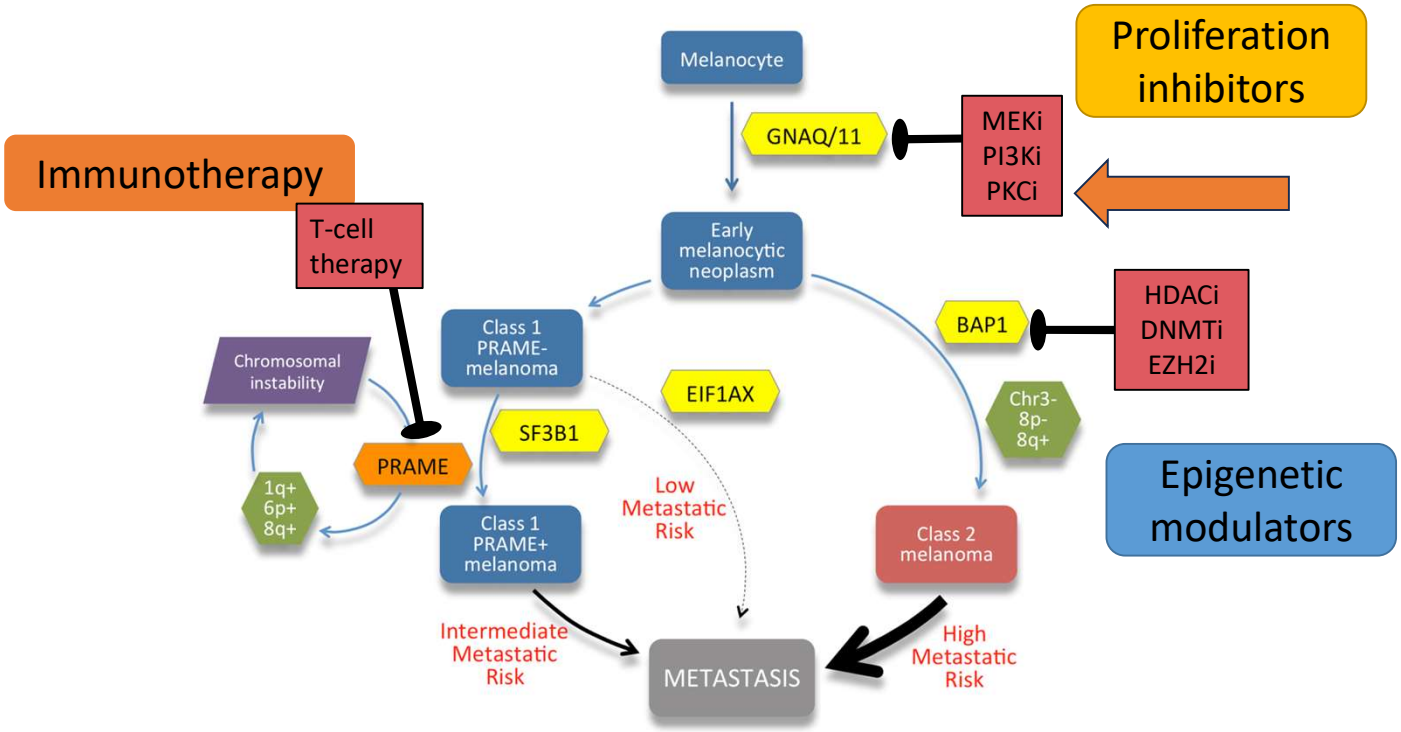
COOG Collaborative Ocular Oncology Group

Potential impact of COOG 2

- Incorporating prognostic testing to the management of uveal melanomas will optimize surveillance protocols
- UMAMs can be helpful for diagnosis confirmation and therapeutic guidance (precision medicine)
- It will allow risk stratification for early enrollment in clinical trials for adjuvant therapies
- It may have a long-term impact in patient survival due to early intervention

Precision Medicine in Uveal Melanoma



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Field MG, et al. *Clinical Cancer Research* (2016)

(Neo)adjuvant IDE196 in patients with localized uveal melanoma

- PRIMARY Objectives
  - assess safety, tolerability and response (tumor regression) of uveal melanomas to IDE196
- SECONDARY Objectives
  - Evaluate anti-tumor activity of IDE196 as neoadjuvant therapy
  - Assess visual acuity loss (or gain)
  - Evaluate rate of local disease recurrence
  - Evaluate the rate of distant metastasis

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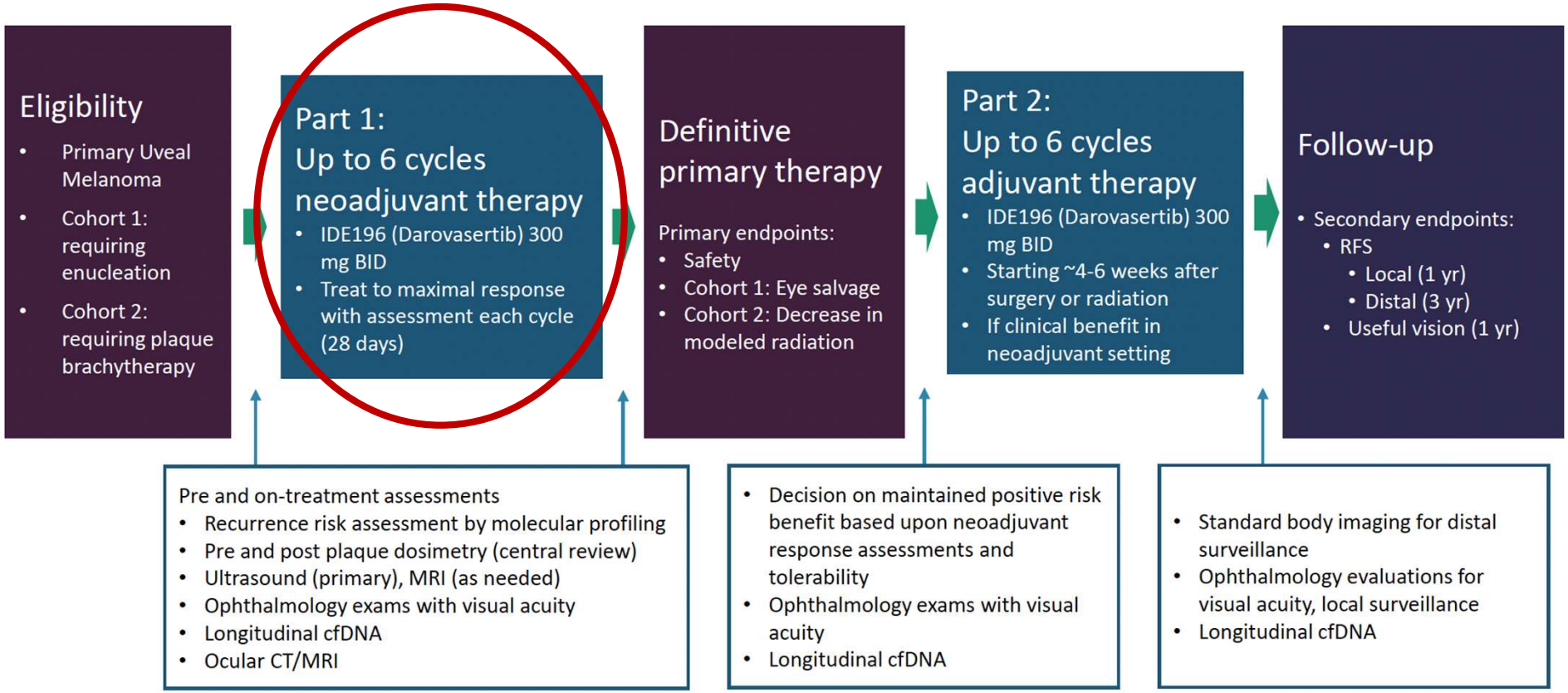
Front Pharmacol. 2023 Jul 28;14:1232787.

IDEAYA BIOSCIENCES

(Neo)adjuvant IDE196 (Darovasertib) in Primary Uveal Melanoma

Phase 2 study of neoadjuvant then adjuvant monotherapy treatment



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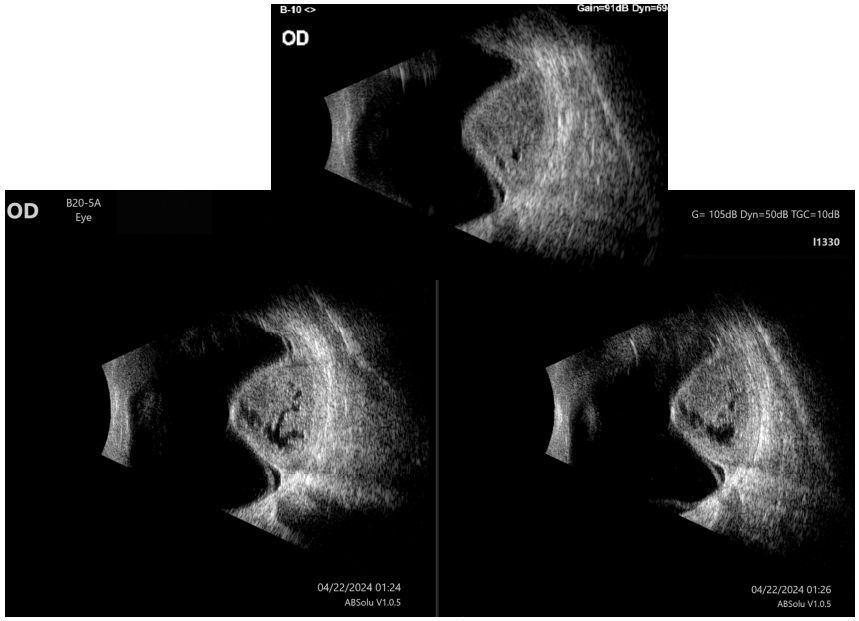
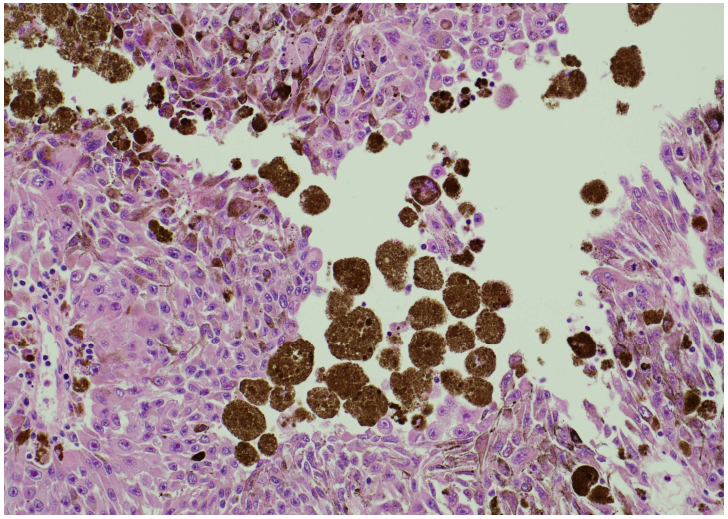
Our experience

- 5 patients screened
- 3 enrolled
- First patient was removed due to uncontrolled diarrhea
  - Large tumor w/ slight increase in thickness
  - Discussed the finding that may be due to tumor intumescence
- Second patient is showing early tumor changes
- Third patient will have first assessment next week





Courtesy Dr. JW Harbour

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Potential impact of IDE196

- Possibly improve globe salvage and possibly limit vision loss associated with radiation treatment
- Could change systemic outcomes by targeting GNA11 systemically
- Its downstream effect could potentially improve patient survival

Belzupacap Sarotalocan (AU-011) for indeterminate melanocytic lesions or small choroidal melanoma

- Phase 3 randomized trial of belzupacap sarotalocan (AU-011) treatment versus sham in patients with primary indeterminate melanocytic lesions or small choroidal melanomas

- Belzupacap sarotalocan (bel-sar, AU-011), the SCS Microinjector (Clearside Biomedical, Inc.) and two ophthalmic lasers (Modulight, Inc. ML6710i and Quantel Medical Vitra 689)

- Seeking FDA approval

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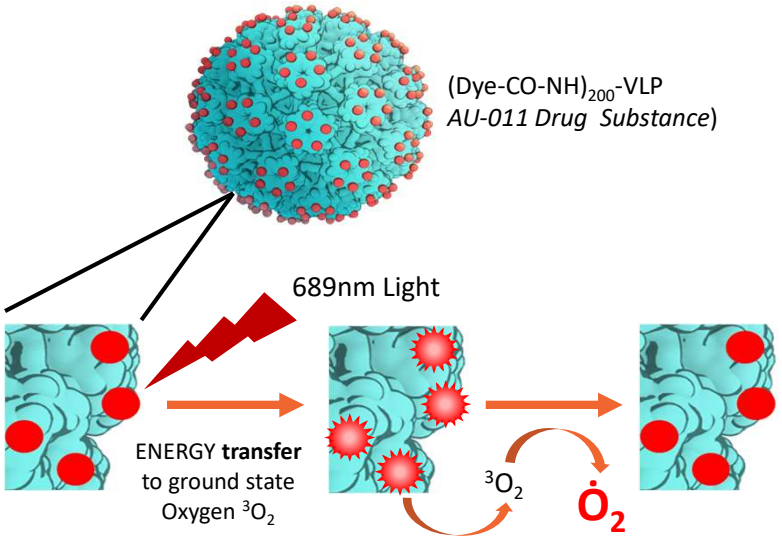
AU-011 is a Highly Tumor Targeted with Dual Specificity First-in-Class Therapy

Overview of Mechanism of Action

- Dual Specificity:
  - Selective tumor binding & activation with NIR light
- Activation of drug results in downstream events:
  - Release of singlet oxygen close to the tumor cell mbn
  - Induction of necrotic factors (pyroptosis)
  - Disruption of membrane integrity
- Additional pro-immunogenic anti-tumor response

Key Benefits

- Selective binding to tumors
- High potency given number of dye molecules delivered via VLP
- Can be activated multiple times with NIR
- No bystander toxicity: unbound AU-011 is not toxic to other cells, even after NIR activation



AU-011 claims their results in tumor control occur through acute cellular necrosis with concurrent immune activation

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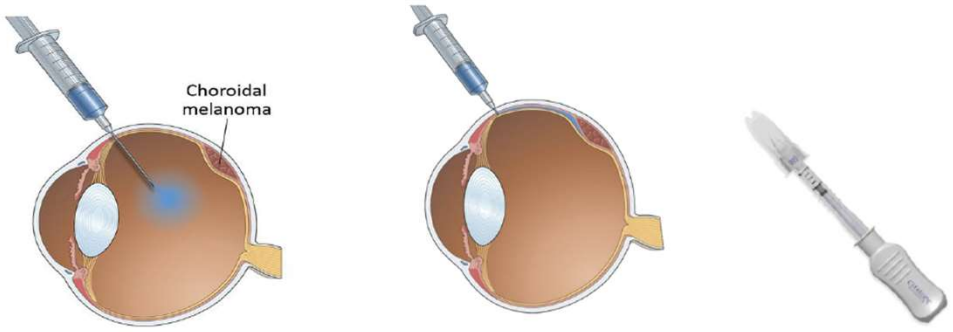
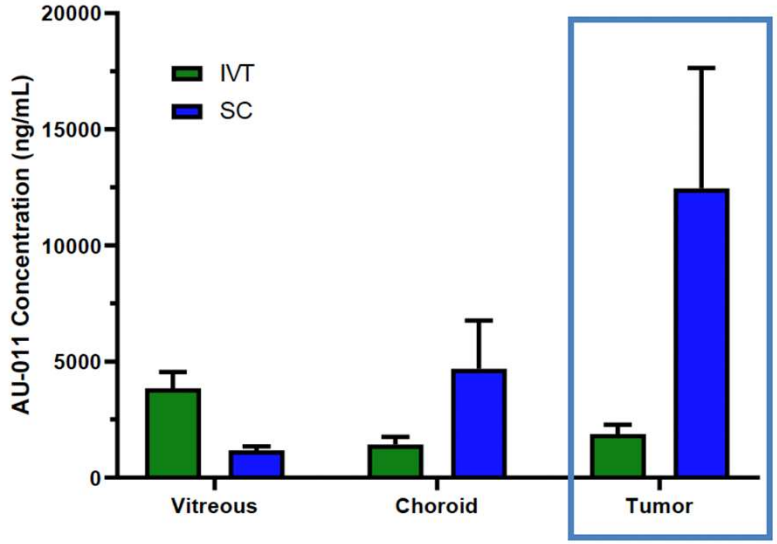
Suprachoroidal injection optimizes drug delivery to the posterior segment



- **Optimize therapeutic index**
  - 5x higher tumor exposure with SC versus IVT observed in pre-clinical model
  - Lower levels in the vitreous translates into lower risk of Intraocular Inflammation and vitreous floaters
- **Optimize treatment parameters**
  - Shorter time to laser activation
- **May increase potential patient population**
  - Medium choroidal tumors
  - Choroidal Metastases

Ocular Exposure After IVT or SC Injection[1]



PK studies in rabbit tumor model demonstrate higher tumor bioavailability with SC administration

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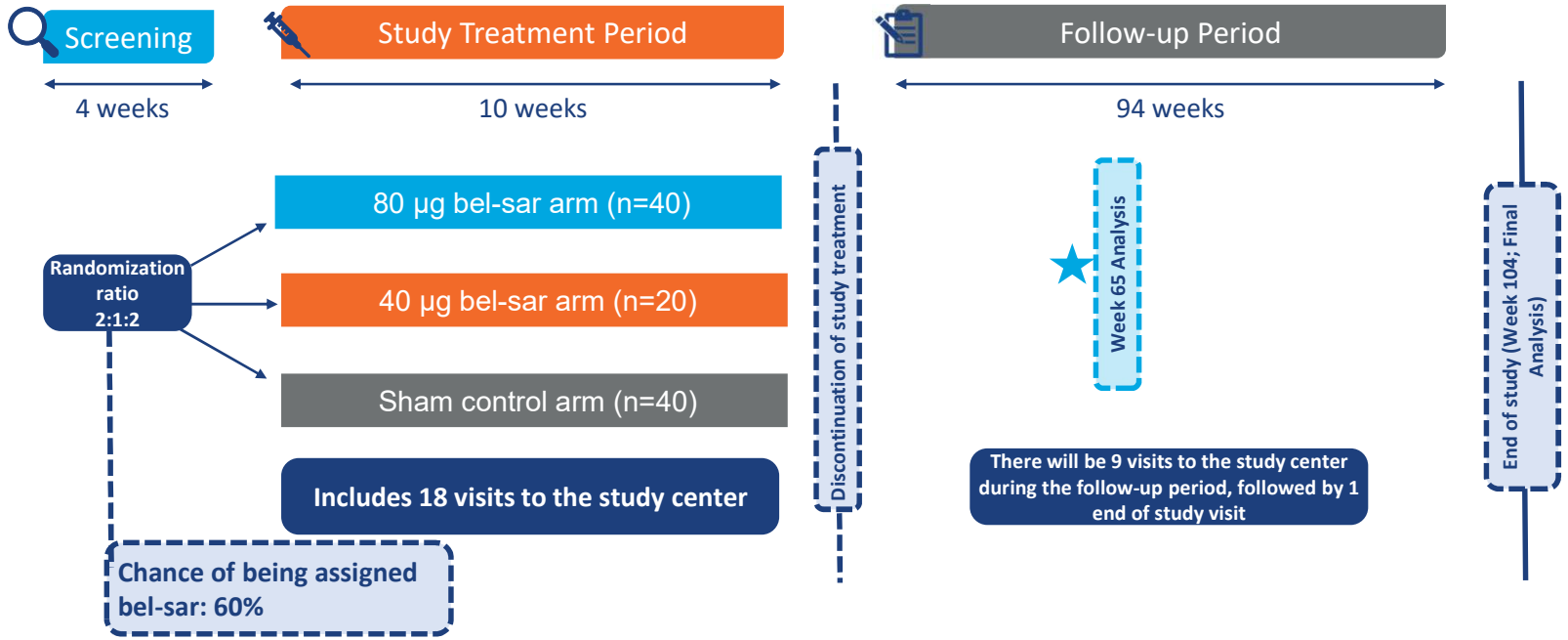
Savinainen, et al. *IOVS* 62.8 (2021): 2861-2861

Phase 3 - study schema



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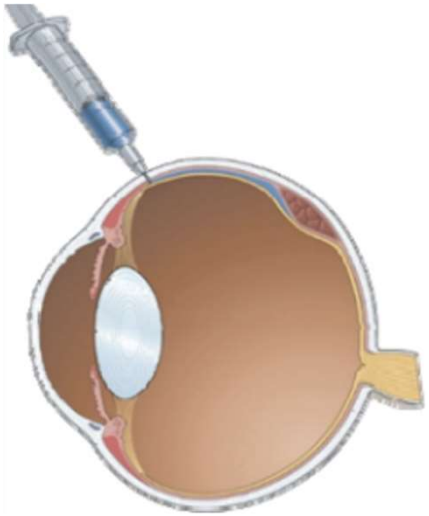
Inclusion Criteria

- Treatment naïve
- Post-equatorial tumor

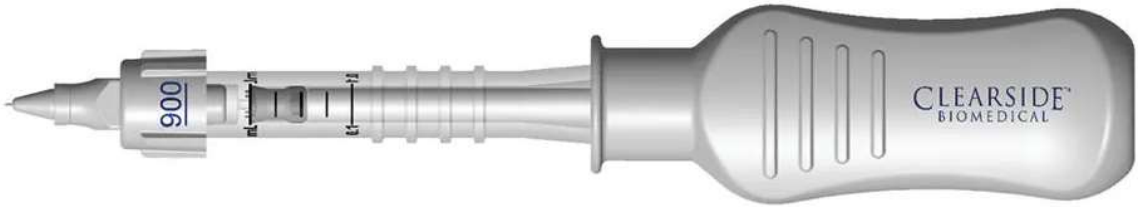


- Increase thickness ≥ 0.4 mm based on inter-site measurements or ≥0.3mm based on intra-site measurements within 2 yrs

- Thickness growth rate ≥0.2mm/yr and >1.5mm/yr based on all site measurements within 2 yrs of screening

- Tumor thickness ≥0.5 mm and ≤2.5 mm on B-scan and LBD ≤10.0 mm on fundus photos or UWF color imaging

Clearside injector



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https://clearsidebio.com/clearside-videos/

Potential impact of protocol Au-011

- Early treatment of small posterior tumors showing progression over short period of time
- Expected low risk for vision loss
- Possibility of radiation treatment if treatment fails

- Question
  - Are we testing the efficacy of treatment for small melanomas or large nevi?

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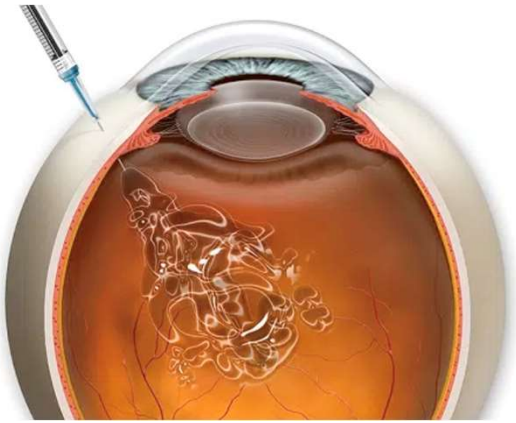
Intravitreal Faricimab (6.0 mg) or Fluocinolone Acetonide (0.19 mg) vs Observation for Prevention of Visual Acuity Loss due to Radiation Retinopathy **(Protocol AL)**

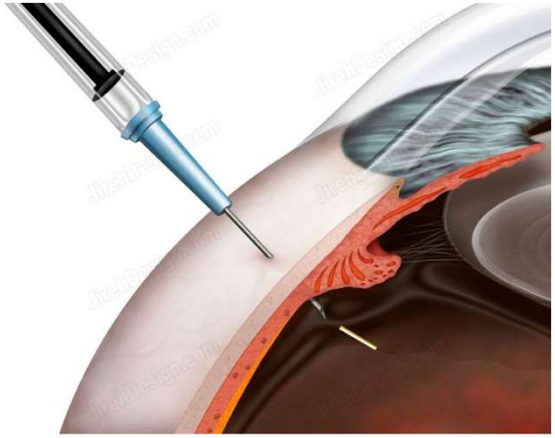
- Primary
  - compare long-term vision outcomes in radiated eyes that receive repeated faricimab or fluocinolone intravitreal implants with those observed initially and treated only if macular edema (ME) develops.

- Secondary
  - determine if repeated treatment with IVit faricimab or fluocinolone versus observation can prevent or alter the course of ME from Rad Ret.
  - evaluate the natural history of Rad Ret with multimodal imaging including widefield color fundus photos, FA, and OCTA.

Faricimab or Fluocinolone vs Observation for Prevention of Vision Loss due to Radiation Retinopathy

- Phase 3 Randomized Clinical Trial
- Patients are assigned to either intravitreal Faricimab (Vabysmo®), Fluocinolone (Illuvien®), or observation
  - **Faricimab** injections at randomization and every three months
  - **Fluocinolone** implant injection at randomization and at the 24-month visit
  - **Observation** defers initial treatment, but Faricimab and Fluocinolone treatment will be given only if macular edema develops





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https://public.jaeb.org/drcrnet/stdy/598

Clinical examination (Protocol AL)

- Visual acuity (both eyes) - BCVA (no ETDRS needed)
- Slit lamp examination
- IOP measurements
- OCT and OCT-A
- Fundus photos
- Fluorescein angiography

- office visit every 3 months for 3 years
- Faricimab injections q3months
- Fluocinolone q24months – IOP check 4 weeks after

Potential impact of protocol AL

- Insight into the benefit of “preventive” medication to avoid or minimize radiation retinopathy
- Determine the success of treatment for radiation retinopathy
- Determine the frequency of treatment depending on the drug used – anti-VEGF or steroid

Conclusions

- After over a century of unchanged outcomes of patients with uveal melanoma, we are seeing a new era of clinical trials and emerging new treatments

- These clinical trials will likely change how patients with uveal melanoma are managed

- This is the first step to improve survival of patients with uveal melanoma

zcorrea@med.miami.edu

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