Welcome

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SYNDROME ALLIANCE

GSAPR

Gorlin Syndrome Alliance Patient Registry

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SYNDROME ALLIANCE

- Gorlin Syndrome Alliance Patient Registry (GSAPR) is a platform for patients around the world to share information about their Gorlin syndrome experiences.
- Its purpose is to build an international resource to be used by scientists in future research.
- Most comprehensive registry for Gorlin syndrome patient data in one secure location.
- The GSAPR is more than a versatile online system that securely collects and stores data for medical research - it is a dynamic participant-driven resource that can empower and unite the Gorlin syndrome community through shared knowledge.
- The GSA will ensure that data privacy and confidentiality are strictly maintained.
- Participation in the GSAPR is free and voluntary, and participants may withdraw at any time.
- It's simply a series of mini-surveys asking about your life and medical history of Gorlin syndrome.
- You can answer the surveys in one sitting or do a little at a time and come back to where you left off.
- And, as a bonus, when you completely finish your initial enrollment, you are eligible for a $75 Amazon gift card.

gorlinsyndrome.org/gsa-patient-registry

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GSA Webinar
"Beyond the Creams & Cutting"
Systemic Treatments for BCCs
Thursday, February 24, 2022

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GSA Medical and Scientific Advisory Committee Member
Practicing Dermatologist, California

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Industry Relationships

Ervin Epstein, M.D.

DISCLOSURES

Distant Past [re HH/BCCs]:
Genentech/Novartis/Amgen/Infinity

CURRENT:
PellePharm - CoFounder/Director/Stockholder/Consultant

I WILL discuss off label use

Systemic Treatments for BCC's: When & Why

FDA Approved

- **What for: Primary or Recurrent BCCs**
- **Why: BCCs that are Advanced = "Too Big for Surgery"**

OR

- **Metastatic = Has moved internally, beyond the skin**

Not FDA Approved

and in the real world of adults with Gorlin syndrome, the ***why it is used*** is different:

- **Why: High Number of BCCs "Too Many to Treat" with surgery or drugs applied to the skin**

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Systemic Treatments vs. BCCs

FDA Approved

1.) Hedgehog Signaling Pathway Inhibitors

- ***These medications target the skin cancer cells (BCCs) themselves.***
- ***ONLY used for BCCs.***
- ***Small molecules that can be taken in pill form by mouth.***

Signaling pathways = Cell's environmental monitors/Nervous system
c.f. Your hand on a hot stove

BCCs in Gorlin syndrome develop because patients have mutations aka typos in DNA. The DNA that is affected is a tumor suppressor gene, so the typo allows BCCs to grow.

In GS, cells continue to multiply rather than fulfilling their typical destiny which is to multiply only as needed to produce the skin's normal top layer and normal hair.

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Systemic Treatments vs. BCCs

FDA Approved - Continued

2.) Immune Checkpoint Inhibitors

These mediations act on immune cells and unleash the immune system allowing it to attack tumor cells. These drugs do not directly act on the tumor cells. Instead, they act on cells that can kill the tumor cells. They can be used on a variety of different types of cancer. These drugs are big molecules [proteins] that are destroyed by the stomach and therefore must be given intravenously.

What does the immune system do?

- **Protects the body from bad things. For example: bacteria, viruses, fungi, foreign material, unrecognized foreign tissue (such as transplanted organs (kidney,…))**
- **Cells with mutations, i.e. CANCER CELLS are protected by tricks/defenses of the tumor cells themselves**

Systemic Treatments for BCCs: Mechanisms

Cellular Targets

1. Hedgehog Inhibitors

Hedgehog inhibitors target the tumor cells themselves.

Site of action - Inside the cells.

Small molecules replace mutant gene function.

2. Immune Checkpoint Inhibitors

Tumors hide from the immune system by putting up barriers. Immune checkpoint inhibitors take down the barriers allowing the immune system to attack the tumor.

Sites of action – Outside the cells

Systemic Treatments vs. BCCs

FDA Approved Drugs

Hedgehog signaling pathway inhibitors

Odomzo & Erivedge: FDA Approved as “first line treatment for advanced BCCs”

Efficacy

- vs. advanced BCCs 50-90% (depends on definition)
- vs. too many to treat (GS) – close to 100%
- Efficacy tends to end when treatment stops

Adverse effects: Mechanisms

- Hedgehog signaling inhibition in normal cells: Hair/Taste loss
- Less certain mechanisms: Muscle cramps, GI changes, etc.

Duration: Limited by intolerance and in aBCCs by resistance.
Most BCCs recur when hedgehog inhibitor treatment stops.

Difference Between Odomzo and Erivedge

- No head-to-head trial ever done.
- They are like apples.
  Some people prefer the Granny Smith variety, others like Cortland but, they are all apples.
- Cure rates are low, but they make a difference.
- If you do not tolerate one, it is ok to switch / try the other.
- Experiences with each vary from person to person.

Side Effects: Erivedge vs. Odomzo

No direct comparison studies have been done.
This table was created using the articles noted below.

Adverse events from Erivedge vs Odomzo								
	ERIVEDGE				ODOMZO			
	G1	G2	G3	G4	G1	G2	G3	G4
Muscle Spasm	53.00%	16.00%	2.00%	0.00%	44.00%	8.00%	3.00%	0.00%
Dysguesia (change of taste of food)	57.00%	13.00%	0.00%	0.00%	32.00%	13.00%	0.00%	0.00%
Alopecia (hair loss)	48.00%	10.00%	0.00%	0.00%	37.00%	13.00%	0.00%	0.00%
Diarrhea	19.00%	4.00%	1.00%	1.00%	27.00%	4.00%	1.00%	0.00%
Nausea	16.00%	3.00%	0.00%	0.00%	27.00%	11.00%	1.00%	0.00%
Fatigue	12.00%	7.00%	1.00%	0.00%	20.00%	11.00%	1.00%	0.00%
Weight Loss	10.00%	6.00%	0.00%	0.00%	17.00%	9.00%	5.00%	0.00%

G 1 to G4 indicates grade of reaction, G1 being a less severe reaction progressing to G4, the most significant.

1. ODOMZO. Prescribing information. Sun Pharmaceutical Industries Inc; 2019.
2. Lear JT et al. *J Eur Acad Dermatol Venereol*. 2017. doi:10.1111/jdv.14542.
3. Dummer R et al. *Br J Dermatol.*2020;182(6):1369-1378. doi:10.1111/bjd.18552.
4. 4. Dummer R et al. *J Eur Acad Dermatol Venereol.* 2020;34(9):1944-1956. doi:https://doi.org/10.1111/jdv.16230
5. Chang AL, Solomon JA, Hainsworth JD, et al.Expanded access study of patients with advanced basal cell carcinoma treated with the Hedgehog pathway inhibitor, vismodegib. J Am Acad Dermatol.2014;70(1):60–9.

Systemic Treatments of BCCs

Oral Hedgehog inhibitors really work.
FDA approved as "first line" systemic therapy for treatment of advanced BCCs.

Immune checkpoint inhibitors really work.
FDA approved as "2nd line" therapy.

This means that
a) other treatment methods must have been tried,
b) the advanced BCC(s) is resistant to HH inhibitor(s), or
c) patient unable to tolerate other form(s) of treatment.

Neither is specifically FDA approved for Gorlin syndrome,
AND
surgery remains the treatment of choice for 99% of BCCs.