

# Hedgehog Inhibitor Tips & Tricks

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## Disclosures

- Advisory Board, Speaker - Sun Pharma
- Advisory Board, Speaker - Regeneron

Sonidegib  
Vismodegib

# **Hedgehog Inhibitor Adverse Events**

- Muscle cramps
- Taste alterations (dysgeusia)
- Hair loss

Decrease the side effects of  
hedgehog inhibitors

by

Decrease dosing frequency

Change from everyday  
to 10-15 days per month

# JANUARY 2022

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
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2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23 30	24 31	25	26	27	28	29

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SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
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						<b>X1</b>
<b>X2</b>	<b>X3</b>	<b>X4</b>	<b>X5</b>	<b>6</b>	<b>7</b>	<b>8</b>
<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>	<b>13</b>	<b>14</b>	<b>15</b>
<b>16</b>	<b>17</b>	<b>18</b>	<b>19</b>	<b>20</b>	<b>21</b>	<b>22</b>
<b>23</b> 30	<b>24</b> 31	<b>25</b>	<b>26</b>	<b>27</b>	<b>28</b>	<b>29</b>

Fewer side effects  
with good efficacy

A hedgehog inhibitor dosed at 10 days per month is “optimal maintenance” for basal cell nevus syndrome (BCNS) patients

-Scott Dinehart

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						<del>X</del> 1
<del>X</del> 2	<del>X</del> 3	<del>X</del> 4	<del>X</del> 5	<del>X</del> 6	<del>X</del> 7	<del>X</del> 8
<del>X</del> 9	<del>X</del> 10	11	12	13	14	15
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**FOREVER**

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# Muscle Cramps

- Most common side effect: 60-70% of patients
- Start early and worsen with time
- Most common reason for discontinuation

# L-carnitine reduces muscle cramps in patients treated with hedgehog inhibitors

**SKIN**

## **FEATURED ARTICLE**



### **L-Carnitine Reduces Muscle Cramps in Patients Taking Vismodegib**

Matthew S. Dinehart BA M.Ed<sup>a</sup>, Stacy McMurray MD<sup>b</sup>, Scott M. Dinehart MD<sup>c</sup>,  
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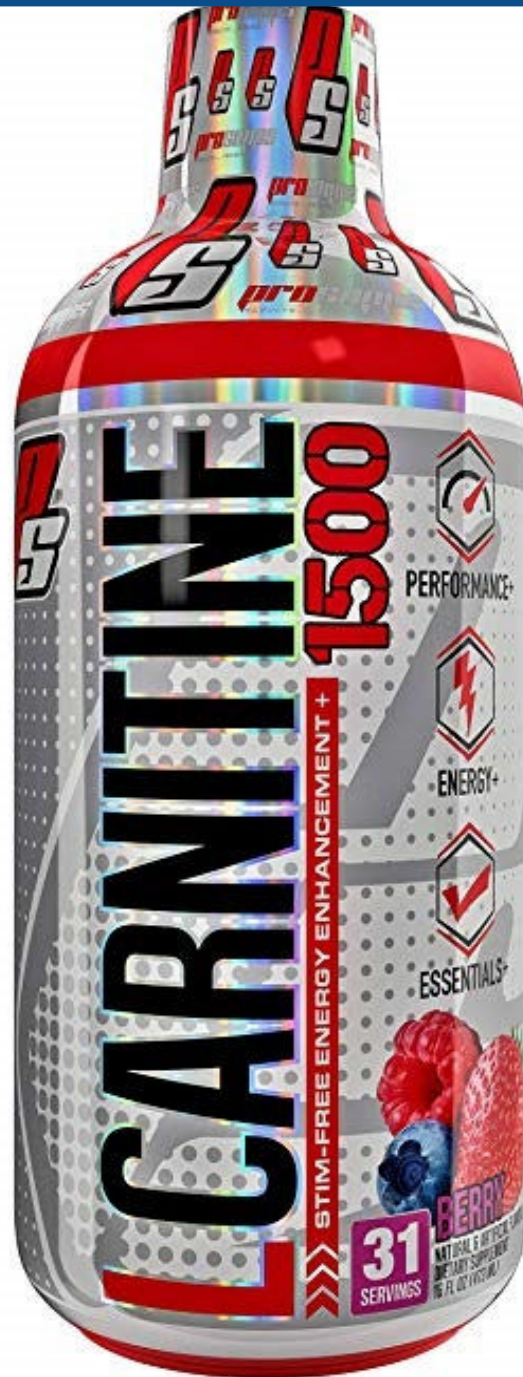
<sup>b</sup>Department of Dermatology, University of Tennessee Health Science Center, Memphis, TN

<sup>c</sup>Arkansas Dermatology, Little Rock, AR

<sup>d</sup>Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY

# L-Carnitine

- Naturally occurring amino acid
- 1000-2000 mg orally
- Start L-carnitine 2 weeks prior to starting HHI



L-Carnitine  
1500 mg q hs

## LETTER TO THE EDITOR

**48% reduction in median muscle spasm frequency with L-Carnitine**

**Placebo increased muscle spasm by 54%**

**-137% between L-Carnitine and placebo**

**Levocarnitine for vismodegib-associated muscle spasms: a pilot randomized, double-blind, placebo-controlled, investigator-initiated trial**

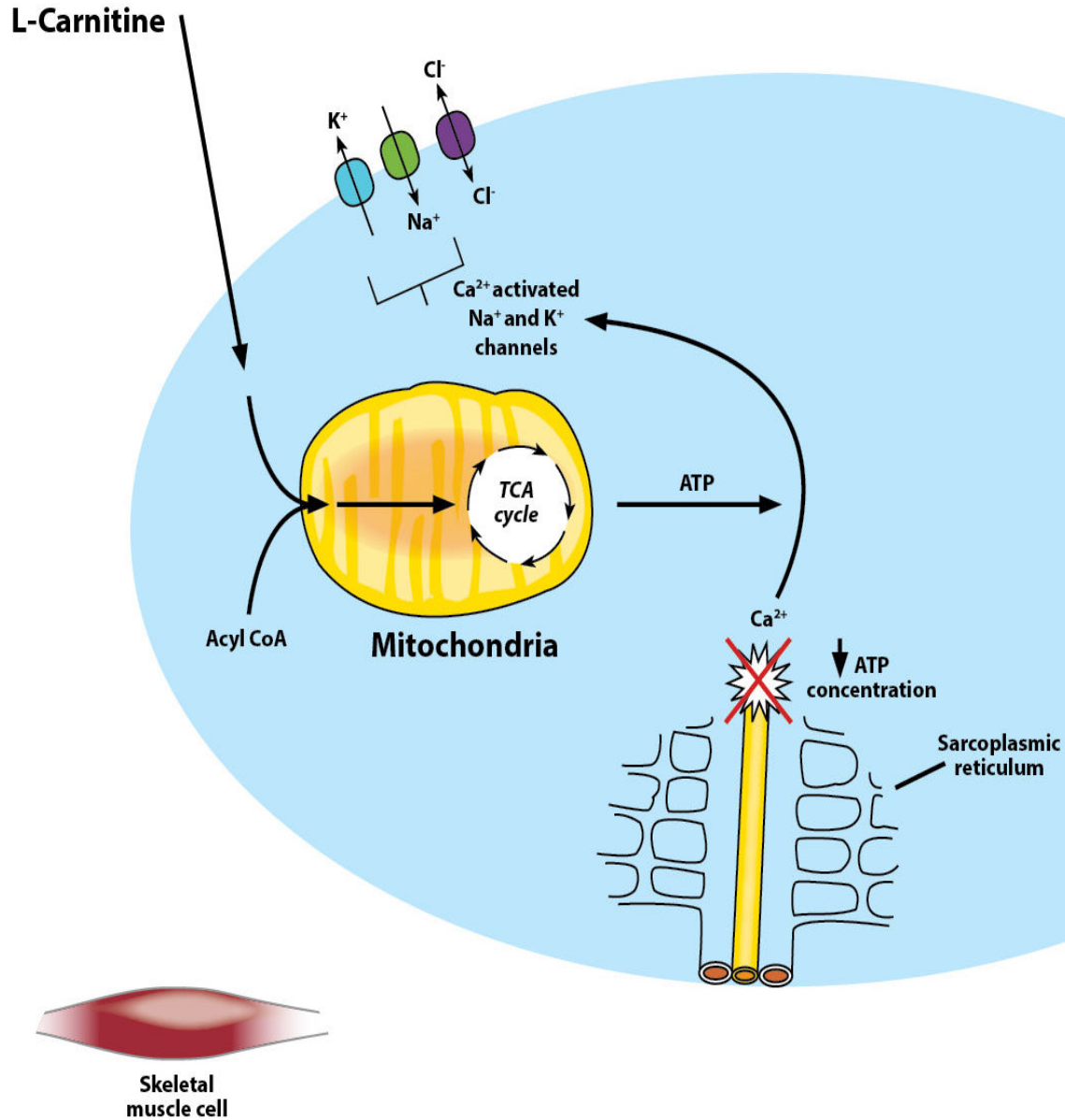
*Editor*

Smoothed inhibitors (SIs) are a new, targeted therapy for the treatment of advanced basal cell carcinoma (BCC), but their usage is significantly limited by the most common side-effect, muscle spasms.<sup>1</sup> Muscle spasms affect up to 80% of users and are the most common reason for drug discontinuation despite tumour response.<sup>1</sup> Currently, no placebo-controlled trials exist

initiation were enrolled. Enrollees underwent a 4-week treatment period, a 4-week washout period (>5 half-lives of LC) and then 'crossed-over' into a second 4-week treatment period. Computer-based randomization allocated participants to receive LC (495 mg twice daily by mouth) for the first treatment period and identical appearing placebo capsules for the second treatment period or vice versa.

Primary outcome of median percentage change in muscle spasm frequency after LC compared to placebo treatment was assessed by Wilcoxon signed rank test, using Hodges–Lehmann estimator for effect size. Secondary outcomes included (i) median change in muscle spasm severity and (ii) median change in number of body location(s) affected by spasms. Outcome measures were self-reported using validated survey items<sup>6</sup> at monthly study visits, with results reconciled to daily diaries kept by par-

# Proposed Mechanism



Paradoxical activation of the noncanonical SMO/Ca<sup>2+</sup>/AMPK axis and inhibition of the canonical SMO signaling pathway by HHI, which results in Ca<sup>2+</sup> influx into muscle cells and consequent muscle contraction.



# **Hedgehog Inhibitor Adverse Events**

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- Taste alterations (dysgeusia)
- Hair loss

Miracle fruit can reduce  
dysgeusia in patients  
who take hedgehog  
inhibitors (HHI)



# Miracle Fruit

- Berry from a West African plant (***Synsepalum dulcificum***)
- Glycoprotein molecule (**miraculin**) binds to the tongue's taste buds, causing sour foods to taste sweet
- Counteracts the metallic taste in mouth seen in chemotherapy





10x Large Miracle Frooties

Simply turns sour  
into sweet

miracle fruit tablets  
NET WEIGHT: 6g (0.21 OZ)

**Nutrition Facts:** Serving size: 600mg, Servings: 10. Amount Per Serving: Calories 1, Fat 0g (0% DV), Cholest. 0g (0% DV), Sodium 1mg (0% DV), Total Carb. 0.3g (0% DV), Fiber 0 (0% DV), Sugars 0g (0% DV), Protein 80mg, Magnesium 1mg, Vitamin A 0%, Vitamin C 0%, Calcium 0%, Iron 0%. Percent Daily Values (DV) are based on a 2,000 calorie diet.

**Ingredients:** Dried Miracle Fruit Pulp, Potato Starch  
**Net Weight:** 600mg per serving, 0.21 OZ (6g)



# Engage the patient's social/family safety net



# Expand your use of HHI

- smaller tumors
- poor surgical candidates
- neoadjuvant to surgery

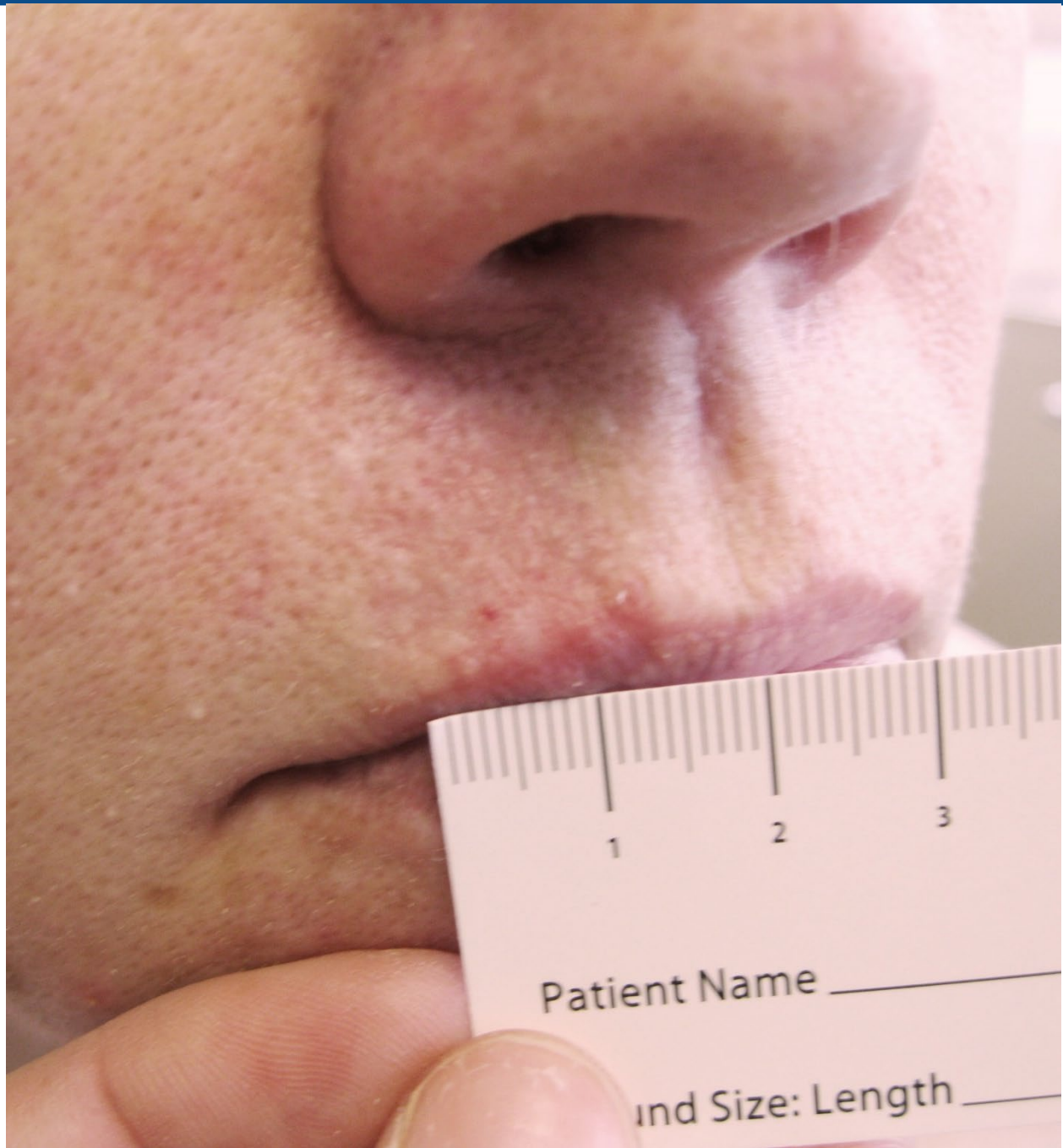
If HHIs work well in giant tumors imagine  
how well they work for smaller ones

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# **An investigator-initiated open-label clinical trial of vismodegib as a neoadjuvant to surgery for high-risk basal cell carcinoma**

Mina Sarah Ally, BSc, MBBS,<sup>a</sup> Sumaira Aasi, MD,<sup>a</sup> Ashley Wysong, MD, MS,<sup>a,d</sup> Claudia Teng,<sup>a</sup>  
Eric Anderson, BSE,<sup>b</sup> Irene Bailey-Healy,<sup>a</sup> Anthony Oro, MD, PhD,<sup>a</sup> Jinah Kim, MD, PhD,<sup>a,c</sup>  
Anne Lynn Chang, MD,<sup>a</sup> and Jean Yuh Tang, MD, PhD<sup>a</sup>

*Stanford and La Jolla, California*







When you see good results but a small persistent amount of tumor is left, treat the area with imiquimod (even if the tumor is not superficial)

Sonidegib  
Vismodegib

# Hedgehog Inhibitor Tips

- Alternative Dosing Frequency
- L-carnitine for cramps
- Expand who you consider to be candidates for HHI therapy

Thank you!

Aaron S. Farberg, MD, FAAD

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