in each of the patients may provide additional insight into the genetic variability of different tumors to guide treatment options for BCC tumors that harbor differing somatic mutations. Comparing multiple BCNS-BCCs taken from the same patient may provide a deeper understanding of tumor-specific resistance to SI therapy, as different lesions from the same individual can respond differently to treatment. Additionally, comparisons of sequencing data on BCNS-BCCs over time may provide useful information on the evolution of SI therapy resistance in these tumors and illustrate what pathways and mutations are involved most frequently in developing resistance. Finally, targeted sequencing of genes reported to be found more frequently in sporadic BCCs may provide further evidence on the genomic stability of BCNS-BCCs. Chiang et al. contributed necessary data that augments the growing understanding of BCC development. Our inputs and suggestions for future studies may enhance for physicians, patients, and pharmaceutical companies the understanding and therapeutic implications of this complex disease.

CONFLICT OF INTEREST
JAS has received honoraria for participating on the advisory boards of Samumed, LLC; Sun Pharmaceutical Industries Ltd.; Mayne Pharmaceutical Company; HedgePath Pharmaceuticals; and Asparian Pharmaceuticals. He has participated as a Principal Investigator for AbbVie; Allergan, Inc; BoehringerIngelheim; Cutanea Life Sciences; Dermira; Eli Lilly and Company; Galdemra Research & Development, LLC; GlaxoSmithKline; HedgePath Pharmaceuticals, Inc; inVentive Health; Kythera; LEO Pharma, US; Mavis RX PharmaChoice; Merck & Co., Inc; Parexol; Pfizer, Inc; Polynoma, LLC; Regeneron; Symboio; and UCB. All funds which JAS receives as an investigator for clinical trials are paid to his employer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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REFERENCES


Response to Shih et al.

TO THE EDITOR

Most individuals with basal cell nevus syndrome (BCNS) have germline mutations affecting *PTCH1*, and basal cell carcinomas (BCCs) that develop in these individuals are highly responsive to Smoothened inhibitors. However, BCCs that develop in a minority of patients with BCNS with underlying *SUFU* mutations may be less responsive to Smoothened inhibitors because inactivation of *SUFU* is downstream of *SMO*. Development of next-generation Hedgehog (HH) antagonists that target components downstream of *SMO* are under development for efficacy in Smoothened inhibitor–resistant BCCs and may have efficacy in BCCs with *SUFU* mutations.

We agree with Shih et al. (2019) that further research into more BCCs from the same individual could improve characterization of BCNS. Comparing sequencing data from two BCCs each from four individuals, we found that only 3–18% of acquired mutated genes were shared between pairs, suggesting that acquired tumor mutations evolve independently despite common genetic background.

Further research comparing BCCs in patients with BCNS over time would also help the understanding of tumor evolution and mechanisms of escape from Smoothened inhibition specifically in BCNS-BCCs, which have low frequency of resistance and may have different pathways of resistance when compared with sporadic BCCs. In summary, Shih et al. contribute insightful commentary on future studies that can improve the understanding of mutations and therapies in BCNS.

Shih et al. make several interesting points regarding future research on BCNS (Shih et al., 2019). Detectable germline mutations or deletions affecting the *PTCH1* locus are found in 67% of individuals with BCNS (Smith et al., 2014). BCCs that develop in these individuals are highly responsive to Smoothened antagonists, although the response is not durable (Tang et al., 2012; Tang et al., 2016). However, approximately 5% of patients with BCNS harbor deleterious *SUFU* mutations. In comparison to *PTCH1*-mutated patients with BCNS, *SUFU*-mutated patients with BCNS lack odontogenic jaw keratocysts and have an increased risk of ovarian fibromas and medulloblastoma (Smith et al., 2014). BCCs that

Abbreviations: BCC, basal cell carcinoma; BCNS, basal cell nevus syndrome; HH, Hedgehog

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develop in patients with BCNS with underlying SUFU mutations may be less responsive to Smoothened inhibitors because aberrant activation of the HH pathway in BCCs from SUFU-mutated individuals with BCNS predominantly occurs because of genetic inactivation of SUFU, which is downstream of SMO (Schulman et al., 2016).

Development of next-generation HH antagonists that target HH signaling components downstream of SMO are under development for BCCs and other HH-activated tumors. These drugs may have efficacy for Smoothened inhibitor–resistant BCCs. We and others have demonstrated that most BCCs escape suppression by Smoothened inhibitors by acquiring genetic alterations at the level of SMO (Atwood et al., 2015). Drugs that target the HH signaling pathway downstream of SMO have potential to bypass this resistance mechanism. These drugs may also have efficacy in treated BCCs with SUFU mutations (Atwood et al., 2014). As loss of SUFU upregulates GLI transcriptional activity, antagonists targeting GLI transcription factors such as GANT58 and GANT61 are potential therapies that may have promise for patients with BCNS with germline SUFU mutations (Atwood et al., 2014). Similarly, combination therapy targeting histone deacetylase, which binds to GLI1 regulatory regions, and atypical protein kinase C Κ, which acts in conjunction with histone deacetylase 1 in forming a positive feedback loop on GLI, can be investigated as other potential therapies for downstream HH suppression in BCCs (Mirza et al., 2017).

Shih et al. also propose further research studies needed to identify oncogenic drivers of tumor evolution in patients with BCNS. The authors cite that the five samples (BCNS6, BCNS8, BCNS10, BCNS14, and BCNS15) did not express oncogenic mutations (Chiang et al., 2018). In fact, three samples (BCNS8, BCNS10, and BCNS14) had PTCH1 mutations, and one (BCNS10) had an ARID1A mutation. ARID1A is a gene associated with increased cell proliferation and loss of differentiation that was recently noted as highly mutated in basosquamous carcinomas and BCCs (Chiang et al., 2019). Thus, only two of these tumors had no known oncogenic BCC drivers. We agree that further studies to identify additional new driver gene mutations in BCC could be of benefit in these tumors.

The authors also suggest that further research into more BCCs from the same individual could be done to understand variation in tumors in patients with BCNS. Indeed, we also obtained sequencing data from two BCCs each from four individuals with BCNS: BCNS7 and BCNS8, BCNS9 and BCNS10, BCNS13 and BCNS14, and BCNS15 and BCNS16. Interestingly, only 3–18% of acquired mutated genes were shared between these pairs. Although these are small sample sizes, this suggests that acquired tumor mutations evolve independently despite a common genetic background.

Further research comparing sequence data of BCCs in patients with BCNS over time would also be useful in analyzing tumor evolution and mechanisms of escape from Smoothened inhibition (Shih et al., 2019). Several Smoothened inhibitor resistance pathways have been elucidated and include mutation in SMO ligand-binding pocket or carboxyl terminus, activation of GLI downstream from SMO, and activation of the phosphoinositide 3-kinase/ mTOR signaling pathway that activates S6K1, which prevents SUFU inhibition of GLI (Atwood et al., 2014; Sharpe et al., 2015). However, given the difference in frequency of resistance in sporadic and BCNS-BCCs, BCNS-BCCs that develop resistance may have different pathways of resistance that can be identified in comparison with sporadic BCCs.

In summary, Shih et al. contribute insightful commentary on future studies that can improve the understanding of mutations and therapies in patients with BCNS.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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REFERENCES


Mirza AN, Fry MA, Urman NM, Atwood SX, Rofley J, Ott GR, et al. Combined inhibition of atypical PKC and histone deacetylase 1 is cooperative in basal cell carcinoma treatment. JCI Insight 2017;2.


