Clariﬁng the Current Understanding of Syndromic Basal Cell Carcinomas


TO THE EDITOR

Chiang et al. presented important data on the lower mutational load and increased genomic stability of basal cell nevus syndrome (BCNS)—basal cell carcinomas (BCCs) in contrast to sporadic BCCs in an original article titled “Genomic Stability in Syndromic Basal Cell Carcinoma” (Chiang et al., 2018).

Although they concluded that BCNS-BCCs show better therapeutic response than sporadic BCCs to Smoothed inhibitors (SIs) because of lower mutational load, it is important to note that some patients with BCNS do not carry PTCH1 mutations and therefore may not respond to SIs. In fact, we previously reported that 10–12% of genetically tested patients with BCNS failed to have chromosome 9/PTCH1 mutations despite meeting the clinical criteria for BCNS (Shih et al., 2018). Moreover, only 28.5% of 288 patients with BCNS received genetic testing for chromosome 9/PTCH1 mutations, though the types of mutations were not specified (Shih et al., 2018). We want to highlight the importance of genetic testing before initiating SI therapy, because patients with BCNS with germline mutations in non-PTCH1 genes, such as SUFU, are unlikely to respond to SIs (Smith et al., 2014; Bastuji-Garin et al., 2011; Bedane et al., 2011; Delaporte et al., 2011). Risk factors for brous pemphigoid in the elderly: a prospective case-control study. J Invest Dermatol 2011;131:637–43.


Abbreviations: BCC, basal cell carcinoma; BCNS, basal cell nevus syndrome; SI, Smoothed inhibitor

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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 illuminate 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; Demira; Eli Lilly and Company; Galden Research & Development, LLC; GlaxoSmithKline; HedgePath Pharmaceuticals, Inc; inVentive Health; Kythera; LEO Pharma, US; Mavis RX PharmaChoice; Merck & Co., Inc; Parexel; Pfizer, Inc; Polynoma, LLC; Regeneron; SymBio; 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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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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