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Alopecia in patients treated with molecularly targeted anticancer therapies

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Background: The introduction of molecularly targeted anticancer therapies presents new challenges, among which dermatologic adverse events are noteworthy. Alopecia in particular is frequently reported, but the true incidence is not known.

Patients and methods: We sought to ascertain the incidence and risk of developing alopecia during treatment with approved inhibitors of oncogenic pathways and molecules [anaplastic lymphoma kinase, breakpoint cluster region-abelson, B-rapidly accelerated fibrosarcoma, Bruton's tyrosine kinase, cytotoxic T-lymphocyte antigen-4, epidermal growth factor receptor, human epidermal growth factor receptor-2, Janus kinase, MAPK/ERK (extracellular signal-regulated kinase) Kinase, mammalian target of rapamycin, smoothened, vascular endothelial growth factor, vascular endothelial growth factor receptor, platelet derived growth factor receptor; proteasomes; CD20, CD30, CD52]. Electronic database (PubMed, Web of Science) and ASCO meeting abstract searches were conducted to identify clinical trials reporting alopecia. Meta-analysis was conducted utilizing fixed- or random-effects models.

Results: The calculated overall incidence of all-grade alopecia was 14.7% [95% confidence interval (CI) 12.6% to 17.2%]—lowest with bortezomib, 2.2% (95% CI 0.4% to 10.9%), and highest with vismodegib, 56.9% (95% CI 50.5% to 63.1%). There was an increased risk of all-grade alopecia [relative risk (RR), 7.9 (95% CI 6.2–10.09, $P \leq 0.01$)] compared with placebo, but when compared with chemotherapy, the risk was lower [RR, 0.32 (95% CI 0.2–0.55, $P \leq 0.01$)].

Conclusions: Targeted therapies are associated with an increased risk of alopecia.

Key words: alopecia, adverse events, antineoplastic agents, drug-induced alopecia, hair loss, targeted therapies

introduction

Significant advances in the field of cancer biology have spurred the development of several molecularly targeted anticancer therapies, which have shown impressive clinical benefit in terms of efficacy and survival rates. As a result, several agents have received marketing approval over the last decade for the treatment of various cancers. Unlike conventional cytotoxic chemotherapeutic agents, these drugs selectively target pro-oncogenic pathways/molecules crucial to tumor growth and survival. Although this action circumvents the severe adverse events (AEs) associated with conventional chemotherapies (e.g. myelosuppression, nausea, vomiting), a wide range of other AEs that affect nearly all organ systems continue to be increasingly recognized.

Among these, dermatologic manifestations are most noteworthy and include rashes, xerosis, pruritus, paronychia, mucositis, and hair disorders [1]. The latter comprise alopecia, textural changes, trichomegaly, and hair dyspigmentation, reported primarily with the epidermal growth factor receptor (EGFR) inhibitors [2, 3]. Although these alterations may not be dose-limiting or life-threatening, the impact on psychosocial well-being and body image, and the resulting anxiety and distress bear the potential to impair patients' health-related quality of life (HRQoL).

This aspect is well recognized in patients with chemotherapy-induced alopecia (CIA), which has an estimated overall incidence of 65% [4]. For example, women with breast cancer may find alopecia very traumatizing and distressing, and subsequently refuse treatment—some women describe the experience as more difficult than even losing a breast [5–7]. With similar

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studies and estimates lacking in patients receiving targeted therapies, the clinical scenario of alopecia remains poorly characterized in this setting. This is of significant concern because the therapeutic armamentarium and indications for use of these drugs are fast expanding, and patients are being treated for increasingly longer periods of time. Therefore, we performed a systematic review and meta-analysis of published clinical trials, to determine the incidence and risk of alopecia.

patients and methods

data sources and search strategy

We accessed the United States Food and Drug Administration website [8], to identify systemic targeted anticancer agents approved for marketing in the United States (as of December 2013) (supplementary Table S1, available at *Annals of Oncology* online). We searched the PubMed and Thomson-Reuters' Web of Science databases using the drug's generic name (e.g. afatinib), the operator 'AND' and 'Phase II OR phase III', to identify human-only studies (1 January 1960–31 May 2014). Abstracts from the American Society of Clinical Oncology's annual and thematic meetings were also searched.

study selection and screening process

We included all phase II and III oncology trials utilizing a targeted agent and reporting clear safety data on 'alopecia' or 'hair loss' (Figure 1). We reviewed only the most updated full-text English versions and discarded duplicates. Phase I or I/II trials (involving multiple dosings and dose escalations) and combination trials with other agents/modalities were excluded.

data extraction and clinical end points

We extracted the name of the first author, year of publication, clinical trial design, enrollment number, treatment arms (experimental/control) and their sample sizes, number of patients with all-grade and grade 2 alopecia in each arm, the underlying cancer diagnosis, and the AE severity grading system used. In addition, the Clinicaltrials.gov website was searched utilizing the indexed 'NCT' number (if published in the manuscript) and any updated study results were ascertained [9].

The safety profile of each clinical trial was examined for the clinical end points. Over the years, the Common Terminology Criteria for Adverse Events (CTCAE) issued by the National Cancer Institute has evolved (versions 2.0, 3.0, 4.0) (supplementary Appendix S2, available at *Annals of Oncology* online) [10].

meta-analytic strategy

All statistical analyses were carried out using version 2 of the Comprehensive MetaAnalysis program (Biostat, Englewood, NJ) [11]. The total number of patients with all-grade alopecia was extracted from selected trials, as delineated above. For each clinical trial, the incidence of alopecia was calculated, and the 95% confidence interval (CI) derived. The relative risk (RR) of alopecia among patients assigned to the targeted agent was calculated and compared only with those assigned to control treatment in the same trial. Forest plots were constructed.

For the meta-analysis, both the fixed-effects model (weighted with inverse variance) and the random-effects model were considered [12]. For each meta-analysis, Cochran's Q statistic was first calculated to assess the heterogeneity of the included trials. For P value <0.1, the assumption of homogeneity was deemed invalid, and the random-effects model was used [13]. Otherwise, results from both the fixed-effects model and the random-effects model were evaluated, and if they were similar, only fixed-effects model results were reported. A two-tailed P value <0.05 was considered as statistically significant.

results

search results

We identified a total of 54 322 potentially relevant records, of which 119 clinical trials were retained for statistical analysis (phase II = 89; phase III = 30) (Figure 1). Of these, 113 trials investigated a targeted agent in solid organ malignancies and 6 trials involved hematologic malignancies. This discrepancy is because most agents have been tried and/or are approved in the treatment of solid tumors.

incidence of all-grade alopecia

Using the random-effects model, the calculated overall incidence of alopecia in our meta-analysis (heterogeneity: $Q = 1872$, $I^2 = 93$,

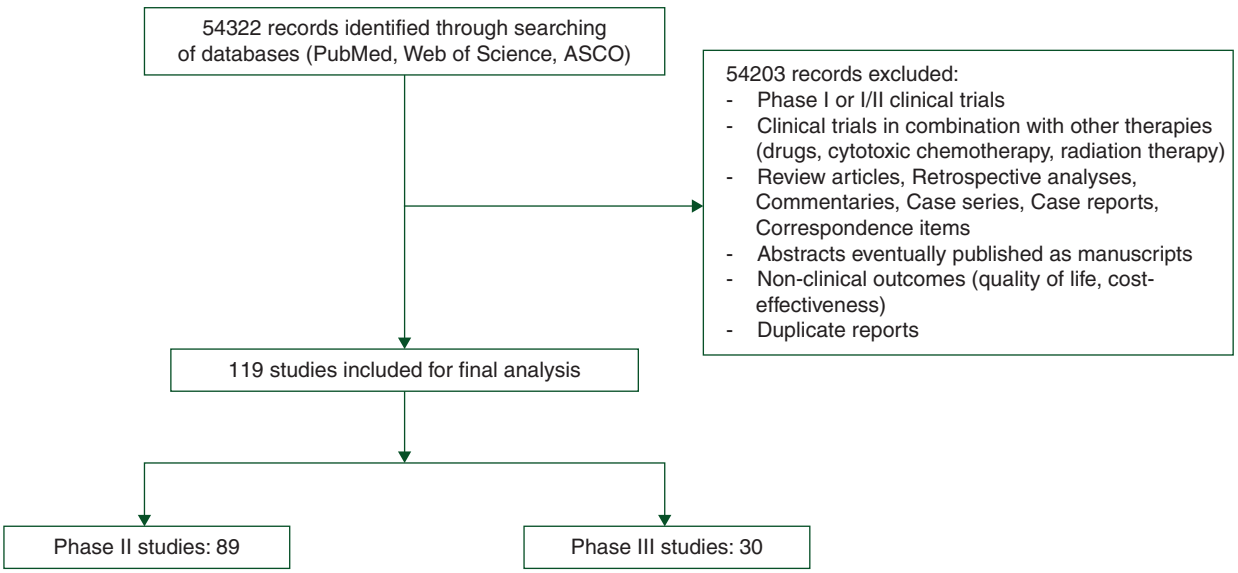

Figure 1. Flow diagram showing the selection process for studies included in the final analysis.

$P \leq 0.001$) was 14.7% (95% CI 12.6% to 17.2%), and was lowest for bortezomib, 2.2% (95% CI 0.4% to 10.9%) and highest for vismodegib, 56.9% (95% CI 50.6% to 63.1%) (Table 1; supplementary Table S1, available at *Annals of Oncology* online).

When individual trials of different drugs were analyzed, the incidence ranged between 0.25% and 80%. The lowest incidence was noted with erlotinib [0.25% (95% CI 0.02% to 3.9%)] in a phase III trial of non-small cell lung cancer patients [14], while the highest incidence was noted with sorafenib, 80% (95% CI 57.2% to 92.2%), in a phase II clinical trial ($n = 21$) involving patients with metastatic medullary thyroid cancer [15].

relative risk of developing alopecia: targeted therapies versus placebo

To calculate the risk of developing alopecia, we carried out a meta-analysis on all the available 15 randomized, controlled trials (RCTs) involving cabozantinib [16], pazopanib [17, 18], regorafenib [19, 20], sorafenib [21–27], sunitinib [28, 29], vismodegib [30], and a placebo. All-grade alopecia was noted in 677/3238 of patients treated with the targeted therapies, presenting an overall RR of 7.9 (95% CI 6.2–10.09) when compared with placebo (67/2373 patients); according to both the fixed- and random-effects models (Figure 2A). Statistical heterogeneity was not noted ($Q = 13.2$, $I^2 = 0$, $P = 0.5$).

Among individual drugs, the risk was lowest with sunitinib at 37.5 mg [RR 4.9 (95% CI 0.6–41.4, $P = 0.14$)] and highest with pazopanib 800 mg [RR 13.4 (95% CI 3.3–54.4, $P \leq 0.001$)] (Figure 2B).

relative risk of developing alopecia: targeted therapies versus chemotherapy

To calculate the risk of developing alopecia in patients receiving targeted therapies versus chemotherapy, we meta-analyzed 13 RCTs [14, 31–42]. Since we observed significant heterogeneity ($Q = 51.9$, $I^2 = 76.8$, $P \leq 0.01$) among these studies, a random-effects model was utilized to combine the effect of studies included (Figure 2C). All-grade alopecia was noted in 130/2140 of patients treated with the targeted therapies, presenting an overall RR of 0.32 (95% CI 0.2–0.55, $P \leq 0.001$) when compared with chemotherapy (337/1979 patients).

discussion

Our findings suggest that a majority of these drugs (~70%) are associated with alopecia, albeit to varying degrees. Inhibitors of the Sonic Hedgehog (Shh), vascular endothelial growth factor receptor (VEGFR), and mitogen-activated protein kinase (MAPK) signaling pathways are among the most commonly associated, with vismodegib exhibiting the highest incidence (56.9%). Overall, it appears that the risk of developing all-grade alopecia with targeted therapies is higher than with a placebo, but lower than with chemotherapy.

In our study, the incidence of alopecia was 14.7%, which is lower than the rates seen with CIA (65%) [4]. This may be attributed to the targeted action of these agents and molecular prescreening to select patient population, which is in contrast to cytotoxic chemotherapy where rapidly proliferating cells (both normal and tumoral) are inhibited indiscriminately and patients are not prescreened for determining treatment eligibility. Likewise, in our analysis, the overall risk of developing alopecia was also threefold lower than with chemotherapy. Besides, it appears that the event itself may be dose-dependent, as evinced in a limited number of sunitinib trials (37.5 mg: RR, 4.94 versus 50 mg: RR, 7.0) (Figure 2B). Notwithstanding, alopecia is not considered a dose-limiting AE in clinical oncology practice.

The mechanisms underlying this event remain poorly understood. These drugs are designed to selectively target various oncogenic molecules/pathways (e.g. SMO, VEGFR, MAPK) critical to the growth and survival of tumors. Intriguingly, alopecia may be noted with the blocking of a variety of such (distinct) targets and with different drugs (Tables 1 and 2). The incidence tends to vary even among drugs acting on the same primary molecular target [e.g. vascular endothelial growth factor receptor: sorafenib (29%) versus sunitinib (6.9%)]. However, it must be acknowledged that each of these drugs often target multiple other pathways [e.g. Raf, fibroblast growth factor receptor (FGFR), PDGFR, c-MET, c-KIT], and besides, the spectrum of inhibition and receptor affinity might vary. This suggests that various pathogenic mechanisms may be involved.

The role of the Shh and EGFR pathways in hair follicle biology and epidermal homeostasis is well established. Murine studies have shown that Shh pathway inhibition in the skin can lead to (reversible) alopecia and arrest of hair growth in the telogen phase [43], which explains the occurrence of alopecia with vismodegib. Inhibition of the EGFR, located in the outer root sheath of hair follicle [44] and crucial to anagen–catagen transition [45], can lead to follicular disintegration accompanied by inflammation [46, 47]. The large number of case reports describing folliculitis and folliculitis decalvans attest to these findings. On the other hand, studies in mice have shown that fibroblast growth factor (FGF) signaling may stimulate anagen hair growth [48]. The anagen inner root sheath and telogen bulge of hair follicles (FGF) and the hair follicle matrix cells (FGFR) appear to be active regions. Also, PDGF signaling has been found to play an important role in the induction and maintenance of the anagen phase in hair follicles [49]. Hence, the primary target inhibited, type of the drug (e.g. mAb, tyrosine kinase inhibitor), variations in the target spectrum of inhibition, molecular cross-talk between pathways, and finally, the inherent role of these molecules in hair follicle biology may all play important roles in the pathogenesis of alopecia. This is in contrast to conventional chemotherapy where the mechanism is predominantly nonselective cytotoxicity [50].

The onset and pattern of alopecia are not recorded by oncologists, with published case reports/series and personal experience (SW, KJB, MEL) offering some insights. The alopecia may be a frontal (androgenetic-like), diffuse, or patchy, with some slowing of hair growth. It is generally nonscarring [51, 52], and may be accompanied by pruritus. In some cases, scarring alopecia/folliculitis decalvans with pain and associated infection may develop, especially with erlotinib [53, 54]. The onset after initiation of treatment may range from a couple of weeks to months, with resolution 1–6 months after drug discontinuation; the quality of hair and rate of regrowth, however, may be affected [55]. Jaber et al. reported widespread alopecia (scalp, eyebrows, face, pubic region, and trunk) with ipilimumab, which mimicked alopecia areata both clinically and histologically [56]. Other abnormalities include but are not limited to trichomegaly,

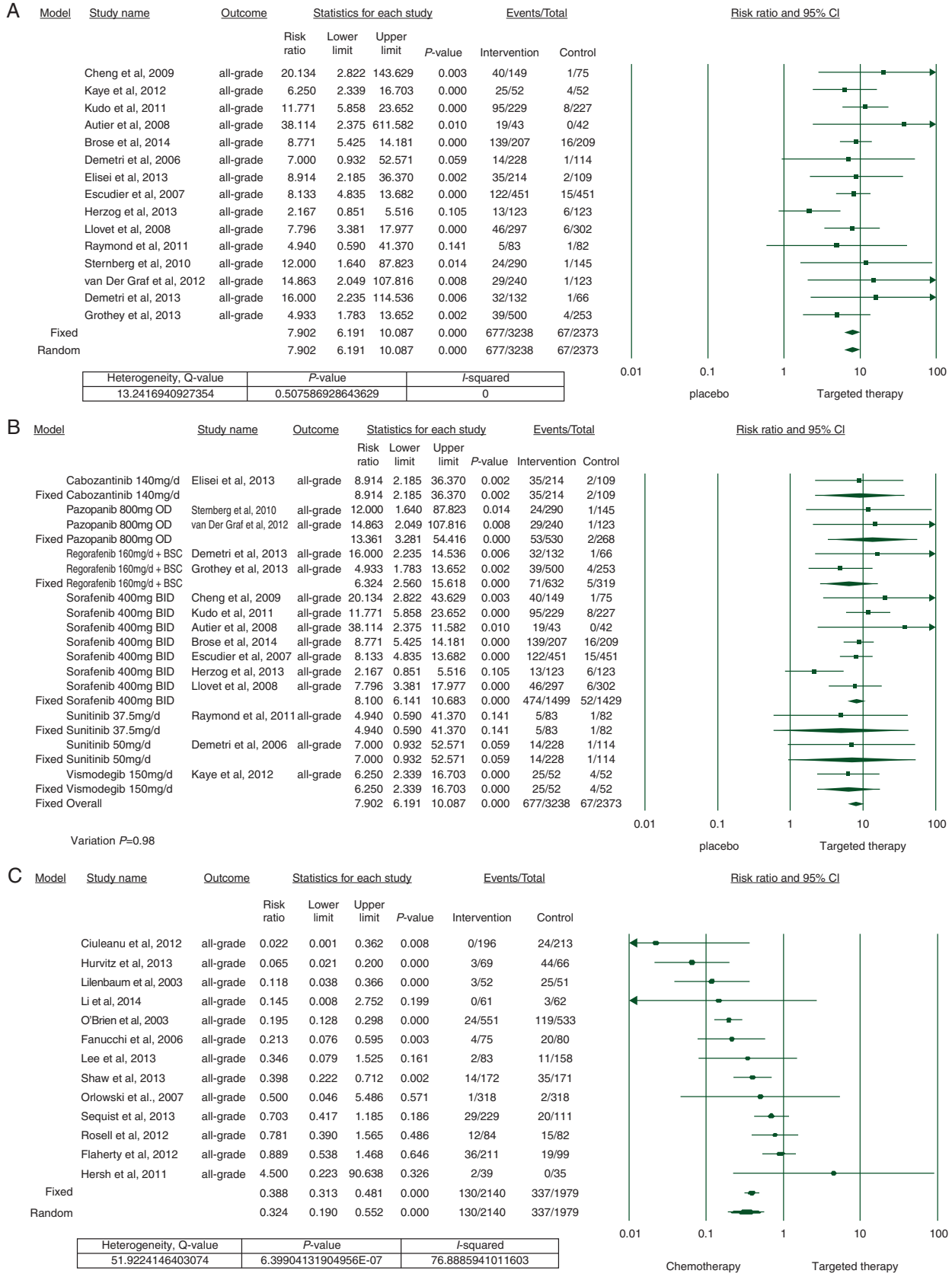

Figure 2. Forest plot corresponding to the main random-effects meta-analysis, including risk estimates quantifying the relationship between treatment with targeted agents and the development of all-grade alopecia: (A) targeted therapies versus placebo, (B) individual agent versus placebo, (C) targeted therapies versus chemotherapy. The size of the square box represents each risk estimate, and is proportional to the weight that the risk estimate contributed to the summary risk estimate (diamond symbol). Filled square box, risk estimate in each trial; horizontal lines, 95% CI; filled diamond, summary risk estimate.

Table 1. Incidence of alopecia with approved targeted agents in monotherapy[a]

#	Class of targeted therapy	Targeted agent	All-grade alopecia (95% CI)	Rank by incidence
1	SMO inhibitor	**Vismodegib**	56.9% (50.6% to 63.1%)	**1**
2	VEGFR inhibitor(s)	**Sorafenib**	29% (23.9% to 34.7%)	**2**
3		**Regorafenib**	23.5% (9.7% to 46.7%)	**4**
4		Cabozantinib	16.4% (12.0% to 21.9%)	6
5		Pazopanib	12.3% (9.0% to 16.6%)	10
6		Axitinib	7.5% (4.4% to 12.7%)	17
7		Sunitinib	6.9% (4.9% to 9.6%)	18
8	EGFR/VEGFR inhibitor	Vandetanib	NR	NA
9	BRAF inhibitor(s)	**Vemurafenib**	23.7% (9.6% to 47.5%)	**3**
10		**Dabrafenib**	18.9% (10.5% to 31.5%)	**5**
11	Bcr-abl inhibitor(s)	Nilotinib	15.9% (12.4% to 20.1%)	7
12		Dasatinib	7.8% (3.0% to 19.1%)	16
13		Imatinib	6.6% (3.9% to 10.9%)	19
14		Bosutinib	NR	NA
15		Ponatinib	NR	NA
16	Anti-CD30 mAb	Brentuximab	14.0% (9.9% to 19.4%)	8
17	MEK inhibitor	Trametinib	13.3% (6.2% to 26.4%)	9
18	EGFR inhibitor(s)	Afatinib	11.9% (9.1% to 15.4%)	11
19		Cetuximab	8.9% (2.2% to 29.7%)	13
20		Erlotinib	8.9% (5.4% to 14.4%)	13
21		Panitumumab	NR	NA
22	VEGF inhibitor	Bevacizumab	10% (3.3% to 26.8%)	12
23	ALK inhibitor	Crizotinib	8.1% (4.9% to 13.2%)	15
24	mTOR inhibitor(s)	Everolimus	5.3% (1.9% to 13.2%)	20
25		Temsirolimus	5.2% (0.9% to 25.9%)	22
26	Anti-CD52 mAb	Alemtuzumab	5.3% (0.7% to 29.4%)	20
27	CTLA-4 inhibitor	Ipilimumab	5.1% (1.3% to 18.3%)	23
28	HER2 inhibitor(s)	Ado-trastuzumab emtansine	4.3% (1.4% to 12.6%)	24
29		Trastuzumab	NR	NA
30	Proteasome inhibitor(s)	Bortezomib	2.2% (0.4% to 10.9%)	25
31		Carfilzomib	NR	NA
32	BTK inhibitor	Ibrutinib	NR	NA
33	JAK inhibitor	Ruxolitinib	NR	NA
34	Anti-CD20 mAbs	Ofatumumab	NR	NA
35		Rituximab	NR	NA

The top five agents with the highest incidence of alopecia appear in bold.

[a]The full bibliography for this table is provided in supplementary Appendix S1, available at *Annals of Oncology* online.

NA, not applicable; NR, not reported; SMO, smoothened; VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; BRAF, B-rapidly accelerated fibrosarcoma; Bcr-abl, breakpoint cluster region-abelson; MEK, MAPK/ERK (extracellular signal-regulated kinase) Kinase; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; ALK, anaplastic lymphoma kinase; mTOR, mammalian target of rapamycin; CTLA-4, cytotoxic T-lymphocyte antigen-4; HER2, human epidermal growth factor receptor; BTK, Bruton's tyrosine kinase; JAK, Janus kinase.

textural abnormalities (fine, brittle and curly hair), dyspigmentation (brown to orange/red, hypo- to depigmentation), and facial hypertrichosis [57]. The histopathology and a management algorithm for alopecia being used in the author's practice (M.E.L.) are discussed (supplementary Appendix S3, available at *Annals of Oncology* online).

Our study has some limitations. First, the reporting of safety data is inconsistent in clinical trials [58, 59]. Second, the data available/extracted represent only the summary results. Third, trials report AEs encountered at a certain frequency (e.g. >10%); any AEs below these cutoffs therefore would not have been captured. We attempted to minimize this issue by additionally searching the ClinicalTrials.gov website. Fourth, oncologists' expertise in diagnosing alopecia may vary (interobserver bias). In addition, telogen effluvium is common in patients stressed with the diagnosis of cancer and the prospect of receiving anticancer therapy. The actual incidence in general population and cancer patients is not known; however, some degree of alopecia occurs in up to 40% of females and 70% of men aged above 60 years [60–62]. Lastly, the CTCAE definitions include only grades 1 and 2 for alopecia—the data for the latter were not reported in some trials, while others erroneously reported grade 3 alopecia, thus precluding the estimation of high-grade alopecia. In summary, our findings may be an underestimation of the true incidence and severity.

Table 2. Alopecia with approved targeted agents in monotherapy

Agents that USUALLY cause alopecia (incidence >15%)	Agents that INFREQUENTLY cause alopecia (incidence 5%–15%)	Agents that RARELY cause alopecia (incidence <5%, or NR)
Vismodegib	Brentuximab	Ado-trastuzumab emtansine
Sorafenib	Trametinib	Bortezomib
Vemurafenib	Pazopanib	
Regorafenib	Afatinib	
Dabrafenib	Bevacizumab	Vandetanib (NR)
Cabozantinib	Cetuximab, erlotinib	Bosutinib (NR)
Nilotinib	Crizotinib	Ponatinib (NR)
	Dasatinib	Panitumumab (NR)
	Axitinib	Trastuzumab (NR)
	Sunitinib	Carfilzomib (NR)
	Imatinib	Ibrutinib (NR)
	Everolimus, alemtuzumab	Ruxolitinib (NR)
	Temsirolimus	Ofatumumab (NR)
	Ipilimumab	Rituximab (NR)

NR, not reported.

conclusion

With the expanding indications for targeted agents (including off-label use), there is an urgent need for prospective studies and investigation into the mechanistic basis of this distressing condition (alopecia) and design of evidence-based management strategies. This is also crucial to direct supportive care efforts, ensure consistent dosing, treatment compliance, and maintain patients' HRQoL.

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disclosure

VRB, KM, CE, LG, TP, PAG, and KJB have no conflicts of interest to declare; SW has a speaking arrangement with Novartis, Bayer-Onyx, Pfizer, and Mediavation. MEL has a speaking, consultant or advisory role with Advancell, Amgen, AstraZeneca, Augmentium, Aveo, Bayer, Berg Pharma, Biopharm Communications, Boehringer Ingelheim, Brickell Biotech, Bristol-Myers Squibb, Clinical Assistance Programs, Clinical Care Options, EMD Serono, Envision Communications, Foamix, Galderma, Genentech, GlaxoSmithKline, Helsinn, Institute for Medical Education and Research, Integro-MC, Lindi Skin, Medscape, Medtrend International, Merck, Nerre Therapeutics, Novartis, Novocure, Oncology Specialty Group, OSI Pharmaceuticals, Permanyer, Physicians Education Resource, Pierre Fabre, Pfizer, Reata Pharmaceuticals, Roche, Sandoz, Sanofi Aventis, and Threshold Pharmaceuticals. The contents of this manuscript have not been presented earlier, and are not under consideration for publication elsewhere.

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