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## THERAPIES

### HEADING: Hemato-oncopharmacology

## Dermatological adverse drug reactions of anticancer drugs: international data of pharmacovigilance: VigiBase<sup>®</sup>

**Mathilde Strumia<sup>a</sup>, Marie-Loup Perrin<sup>a</sup>, Emilie Patras de Compaigno<sup>a</sup>, Cécile Conte<sup>a,b,c,d,e</sup>,  
François Montastruc<sup>a,b,c,d,e</sup>, Maryse Lapeyre-Mestre<sup>a,b,c,d,e</sup>, Vincent Sibaud<sup>f</sup>, Fabien  
Despas<sup>a,b,c,d,e,\*</sup>**

<sup>a</sup> *Service de pharmacologie médicale et clinique, CHU de Toulouse, 31000 Toulouse, France*

<sup>b</sup> *UMR1027, Inserm, université Paul Sabatier, 31000 Toulouse, France*

<sup>c</sup> *Service de pharmacologie médicale et clinique, faculté de médecine, université Paul Sabatier,  
31000 Toulouse, France*

<sup>d</sup> *Centre Midi-Pyrénées de pharmacovigilance, de pharmacoépidémiologie et d'informations sur le  
médicament, centre hospitalier universitaire de Toulouse, 31000 Toulouse, France*

<sup>e</sup> *INSERM CIC 1436 Toulouse, centre d'investigation clinique de toulouse, centre hospitalier  
universitaire de Toulouse, 31000 Toulouse, France*

<sup>f</sup> *Oncodermatology, Institut Claudius Régaud and Institut universitaire du Cancer Toulouse  
Oncopole, 31059 Toulouse, France*

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**\*Corresponding author.** Laboratoire de pharmacologie médicale et clinique, faculté de médecine,  
université Paul Sabatier, 37, allées Jules Guesde, 31000 Toulouse, France.

*E-mail address:* [fabien.despas@univ-tlse3.fr](mailto:fabien.despas@univ-tlse3.fr) (F. Despas)

## **Summary**

In the 2000s, newer generations of drugs appeared on the market called drugs of targeted therapy (TT) drugs. The introduction of TT in oncology has profoundly changed the prognosis of many cancers but also introduced a wide variety of adverse drug reactions (ADR), including in particular dermatological adverse drug reactions (dADR). We investigated the evolutions of the notifications of dADRs of anticancer drugs since 2000s in international pharmacovigilance data. For this purpose, we separated non-targeted therapy and targeted therapy. During the period from 01/01/2000 to 31/12/2017, 1,226,252 ICSRs (8.7%) were related to anticancer drugs, among them concerning anticancer drugs, 192,108 cases (15.6%) contained at least one MedDRA term for “skin and subcutaneous tissue disorders” system organ classes. The dADRs of anticancer drugs are in constant increase on the period 2000 to 2017, from 0.91% to 1.90% of the total ADR of Vigibase®. The number of dADRs drugs in the non-targeted therapies class remained stable during this period, while the dADRs of targeted therapy drugs increased and exceeded those of non-targeted therapy in recent years. Using a disproportionality analysis, we found that targeted therapy drugs are associated with a higher risk of reporting dADRs of the type: dermatitis acneiform, hair color changes, acne, and hyperkeratosis and skin toxicity. While, non-targeted therapy drugs are associated with a higher risk of reporting dADRs of the type: skin hyperpigmentation, nail discoloration, dermatitis exfoliative, Hyperhidrosis and alopecia. TT drugs are used more and more for cancer indications and even beyond. This problematic of dADR will become more and more common and should benefit from specialized support with the organization of a coordinated network of professionals.

## **KEYWORDS**

Dermatological adverse drug reaction; anticancer drugs; Pharmacovigilance

## **Abbreviations**

ADR: adverse drug reaction

aRORs: adjusted RORs

CI: confidence interval

dADRs: dermatological adverse effects

EGFR: epidermal growth factor receptor

EMA: European Medicines Agency

ICSRs: individual case safety reports

NTT: non-targeted therapy

MedDRA: Medical Dictionary for Regulatory Activities

PKIs: protein kinase inhibitors

PT: preferred term

TT: targeted therapy

WHO: World Health Organisation

## Introduction

The first anti-cancer drugs were developed from mustard derivatives in the 1950s. These drugs called cytotoxic (or drugs "non-targeted therapy" (NTT)) have characteristic adverse drug reaction (ADR) by impacting especially all tissues with high cell proliferation capacity including dermatological adverse effects (dADRs). manyof patients exposed to these drugs were suffering from chemo-induced alopecia, severe skin reactions (erythema, pruritus), toxic erythema of chemotherapy, mucositis or nail changes. In the 2000s, newer generations of drugs appeared on the market called drugs of targeted therapy (TT) drugs, including protein kinase inhibitors (PKIs). The introduction of TT in oncology has profoundly changed the prognosis of many cancers. For example, imatinib drastically increased the 5-years overall survival rate from 40% to 77% among patients with chronic myeloid leukemia [1]. Despite this success, PKIs are also associated with severe adverse drug reactions [2–5], including very characteristic skin toxicities which clearly differ from those induced by chemotherapeutic agents. These drugs have had a very short development time and thus the ADR profiles are really only known after several years of commercialization. In addition, these drugs are usually administered chronically with side effects that may occur after a long exposure time. ADRs may lead to discontinuation of anticancer treatment and poor response to treatment. They can also affect the quality of life of exposed patients whose life expectancy has increased since the emergence of these new pharmacological classes. Thus, managing this adverse reaction to the drug can be a challenge for oncologists. Pharmacovigilance data can be used to identify the ADR profiles of drugs on the market and to compare the types of notifications according to the pharmacological classes or the notification periods. Thus, these real-life data allow a pragmatic approach to inform practitioners about the signs and risks of ADR in exposed patients.

In the present study, we investigated the evolutions of the notifications of dADRs of anticancer drugs since 2000s in international pharmacovigilance data. For this purpose, we separated non-targeted therapy and targeted therapy to analyze the specific type of dDARDs in each

group of drugs with a disproportionality analysis and to assess the risk for these drugs to induce dADRs.

## Methods

### Data sources

Pharmacovigilance database.

Vigibase® is the World Health Organisation's (WHO) safety report database, using data collected from 129 countries. It contains approximately 17 million individual case safety reports (ICSRs), which contain information on drugs suspected of causing ADRs. Drugs are coded using the WHO drug dictionary covering 150 000 medicines and vaccines. Vigibase® gathers ICSRs from national centers which contain information on patient age, gender, medical history, country, drugs taken, drug initiation and stop dates, indications for the drugs, adverse drug reactions (ADRs) and their seriousness and outcomes.

Dermatological adverse drug reactions (DADRs)

ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA). There are five levels in the MedDRA hierarchy, ranging from very specific to very general. The most general level of MedDRA gathers code groups into 27 system organ classes (SOCs) according to etiology, manifestation site and purpose. We identified DADRs in Vigibase® using the standardized MedDRA term "skin and subcutaneous tissue disorders".

Anticancer drugs

We included in our analysis the anticancer drug in the therapeutic classification "Antineoplastic agents". We separated the "targeted anticancer drugs" and the "non-targeted anticancer drug" according to the mechanism of action of the drug (Table 1).

### Analyses

## Descriptive analyses

We studied notifications of ADRs in the international VigiBase® database from 01/01/2000 to 31/12/2017, from an extraction of 28/01/2018. In our analysis we used information contained in the ICSRs: age, gender, country, comedication. Missing data were categorized as “unknown” in the analysis.

## Disproportionality analyses

Disproportionality analysis (also known as a case/non-case analysis) were performed for the DADRs. This method compares the proportion of specific ADR reported for a single drug, or a range of drugs, with the proportion of the same ADR for all other drugs or for a selected panel of control drugs. This indicator is easily reproducible and could be adjusted for potential confounders using logistic regression. Calculation of the ROR has been described elsewhere (ref.). In brief, if the proportion of “Y” ADRs in patients exposed to drug X (cases) is greater than the proportion of “Y” ADRs in patients not exposed to drug X (non-cases), this suggests an association between the specific drug and the reaction and is a potential safety alert. In the present study, disproportionality was calculated using the adjusted RORs (aROR). We compared the proportion of each dADR in the “targeted therapy” and proportion of the same dADR in the “non-targeted therapy”. All RORs were calculated with their 95% confidence interval (CIs).

## Results

### Pharmacovigilance data

Extraction from Vigibase® during the study period from 01/01/2000 to 31/12/2017 resulted in a total of 14,140,280 ICSRs for all drugs, among them 1,226,252 ICSRs (8.7%) were related to anticancer drugs. Among these ICSRs concerning anticancer drugs, 192,108 cases (15.6%) contained at least one MedDRA term for “skin and subcutaneous tissue disorders” system organ classes. The baseline characteristics of the patients included in the analysis are depicted in Table 1. Patients treated with anti-cancer drugs and with a dermatologic adverse drug reaction have the

following characteristics: 56.3% of these ICSRs were relating to woman, the modal age class was [45-64] years. The United States was the first country which reported the most of ICSRs of dADRs (34.4%) before South Korea (13.8%) and France (7.3%).

During the study period, the majority of dADR notifications are related to the drugs non-targeted therapy (57.6%).

### **Evolution of dermatological adverse drug reaction (dADR)**

From 01/01/2000 to 31/12/2017, among all ICSRs in Vigibase® the relative proportion of dADRs reported with anticancer drugs increased from 0.91% to 1.90% (Fig. 1.). The relative proportion of dADRs reported with “no-targeted therapy” among all ICSRs in the Vigibase® remained stable over the study period. At the same time, the relative proportion of dADRs reported with “targeted therapy” among all ICSRs in Vigibase® was increased from 0.03% to 1.15%. In 2000, the vast majority of dADRs reported with anticancer drugs, was due to “no-targeted therapy” (97.8%). While since 2016, the trend has reversed and the majority of ICSR with dADR were in majority in relation with the drugs of TT.

Of all the dADRs of all drugs, the relative proportion of the dADRs reported with anticancer drugs increased from 5.65% to 11.96% during the period study (Fig. 2.). We observed the same evolution when we analyzed the relative proportion of drugs of NTT and TT among all ICRSs of DARDs: in 2000, the dADRs were due to the non-targeted therapy in majority. But from 2016 the targeted therapy was more frequently associated with dADRs than NTT.

Among all the adverse effects of anticancer drugs, the relative proportion of DARD reported with anticancer drugs remained stable from 18.61% to 15.91%. (Fig. 3). We can note that it is from the years 2016 that the curves cross and that the proportion of dADR in connection with a drug of targeted therapy becomes majority.

### **Comparison of NTT and TT dermatological adverse drug reactions**

During the study period, we analyzed the type of dADRs described in the ICSRs with their preferred term (PT) (Fig. 4). For the drugs of non-targeted therapy and targeted therapy, we found the most notified PT was “rash” (respectively 18.2% and 31.9%). In the top-10 of the “targeted”



therapy's dADRs some other terms were reported: pruritus, alopecia, erythema, urticaria, palmar-plantar erythrodysesthesia syndrome, hyperhidrosis, skin exfoliation and dry skin.

Some PTs have been reported more often with non-targeted therapy than with non-targeted therapy: for example, "skin, skin", "blister" or "acne".

### **Disproportionality analysis**

The disproportionality comparison of the dADRs profiles between drugs of the non-targeted therapy class and the targeted therapy class shows several differences. The aRORs, with their 95% CIs, are presented in a Fig. 5. The 5 types of ADRs where targeted therapy are most at risk are: "dermatitis acneiform" with an aROR of 14.14 (CI: 12.05-16.59), "hair colour changes" with an aROR of 12.44 (CI: 10.08-15.35), "acne" with an aROR of 7.18 (CI: 6.46-7.98), "Hyperkeratosis" with an aROR of 6.50 (CI: 5.49-7.69) and "skin toxicity" with an aROR of 3.58 (CI: 3.15-4.06). The 5 types of ADRs where non-targeted therapies are most at risk are: "skin hyperpigmentation" with an aROR of 0.17 (CI: 0.15-0.20), "nail discolouration" with an aROR of 0.19 (CI: 0.16-0.21), "dermatitis exfoliative" with an aROR of 0.31 (CI: 0.28-0.35), "Hyperhidrosis" with an aROR of 0.39 (CI: 0.37-0.41) and "alopecia" with an aROR of 0.43 (CI: 0.42-0.44).

### **Discussion**

Our study shows for the first time that among all the global notifications in Vigibase<sup>®</sup>, the dADRs of anticancer drugs are in constant increase on the period 2000 to 2017. The number of dADRs drugs in the non-targeted therapies class remained stable during this period, while the dADRs of targeted therapy drugs increased and exceeded those of non-targeted therapy in recent years. Using a disproportionality analysis, we found that targeted therapy drugs are associated with a higher risk of reporting dADRs of the type: dermatitis acneiform, hair color changes, acne, and hyperkeratosis and skin toxicity. While, non-targeted therapy drugs are associated with a higher risk of reporting dADRs of the type: skin hyperpigmentation, nail discoloration, dermatitis exfoliative, Hyperhidrosis and alopecia.

The increase in the number of dADRs reported over the study period is to be studied with the epidemiological data in this discipline. Indeed, the number of new cancer cases (excluding skin cancers other than melanoma) was estimated at 14 million in 2012 and it is estimated at 18 million

in 2018 [6]. Moreover over the period 2000 to 2014, even if there are differences from one country to another, there has been a general increase in the survival of patients with a cancer diagnosis [7]. This overall increase in survival suggests that in real life conditions patients are exposed to more anticancer treatments and for longer periods of time. The number of new drugs is very important in oncology, for example over the period 2009-2013; the European Medicines Agency (EMA) has approved 48 cancer drugs for 68 indications [8]. For these reasons, we chose to work from relative data. Indeed, we chose to analyze the ADR reporting data and compare the proportions of the types of adverse events to limit the effects of certain biases. Our analysis shows that the proportion of dADRs among the Vigibase<sup>®</sup> dataset nearly doubled over the analysis period. Descriptions of dADRs and proposed catch recommendations are now updated regularly [5,9–12]. Conventional cytotoxic chemotherapies and radiation cause ADRs such as alopecia, mucositis and radiation dermatitis, all of which have been relatively well documented [13]. It is true that the emergence of targeted therapy drugs including drugs interacting with the epidermal growth factor receptor (EGFR) pathway has increased the value of these types of ADR. Studies have shown that the onset of dADR may be associated with a significant decline in quality of life [14], with also significant impacts of patients' perception of their image [15,16]. In addition, with the modalities of oral administrations in ambulatory settings, the decrease in compliance with the onset of ADRs has already been demonstrated and cutaneous adverse effects are among those with one of the highest impact [17]. Therefore, sensitization of practitioners to dADRs and appropriate management of dADRs is essential to optimize management. Several published works describe the types of dermatological adverse events observed with these drugs and establish management recommendations [9,18–20]. However, the occurrence of dADR may be associated with a favorable response to treatment [21]. A more specific analysis of dADRs by pharmacologic subclasses would identify class effects but it is difficult to categorically separate these drugs because affinity profiles are often complex. This is the case for the medicament inhibitor of protein kinases [22,23]. Disproportionality analyzes using pharmacovigilance data from protein kinase inhibitors have identified the mechanisms involved in the occurrence of adverse effects such as heart failure [24], pleuropulmonary disorders [25] or pulmonary arterial hypertension [26]. By applying this approach, additional studies could better identify the mechanisms involved in the occurrence of dermatological adverse effects.

However, our study presents a number of limitations. Indeed, pharmacovigilance data are based on spontaneous notifications, while the very large amount of underreporting is well documented. Nevertheless, the deployment of data on a global scale makes it possible in part to

overcome these limits. In order to overcome these limitations, we chose to work in comparative evaluation in order to support changes in the proportion of dADR notifications over time.

### Disclosure of interest

Authors have no competing interest to declare

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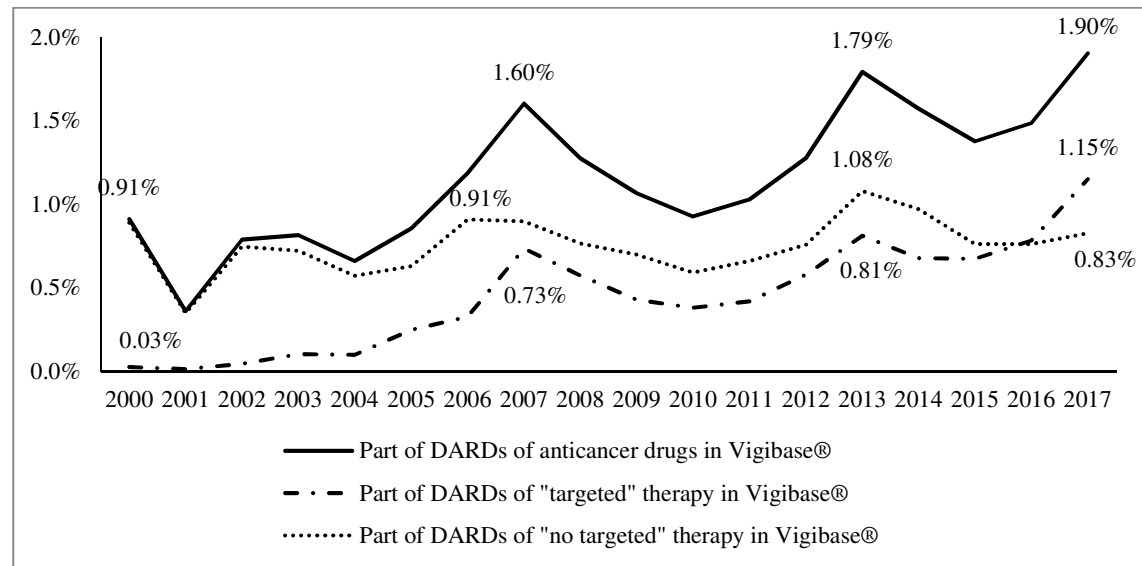
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**Table 1.** Baseline information reported in the individual case safety reports (ICSR) in Vigibase®

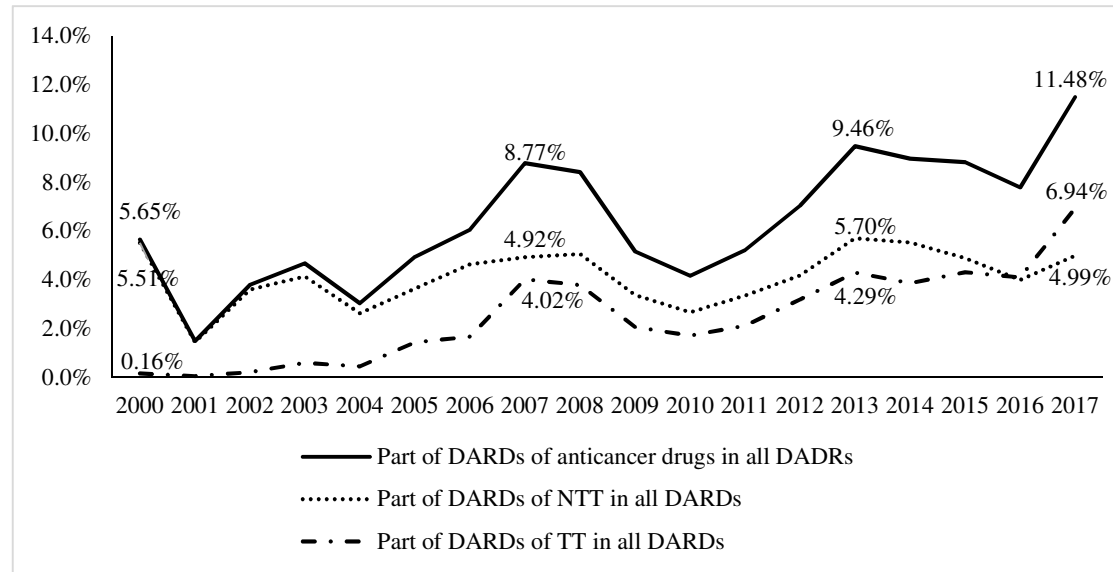
		<b>ICSRs</b> (n = 14,140,280)	<b>ICSR with DADRs</b> (n = 2,563,627)	<b>Anticancer ICSR</b> (n=1,226,252)	<b>Anticancer ICSR with DADR</b> (n = 192,108)
<b>Gender</b>					
Female		8,028,027 (56.8)	1,509,069 (58.9)	612,833 (50.0)	108,115 (56.3)
Male		5,318,820 (37.6)	981,005 (38.3)	522,730 (42.6)	76,095 (39.6)
Unknown		793,433 (5.6)	73,553 (2.9)	90,689 (7.4)	7,898 (4.1)
<b>Age</b>					
[0-2[		376,575 (2.7)	104,414 (4.1)	3,505 (0.3)	625 (0.3)
[2-12[		489,077 (3.5)	152,917 (6.0)	18,666 (1.5)	3,484 (1.8)
[12-17[		320,605 (2.3)	77,471 (3.0)	13,132 (1.1)	2,213 (1.2)
[18-45[		2,691,991 (19.0)	644,443 (25.1)	122,882 (10.0)	23,554 (12.3)
[45-65[		3,459,946 (24.5)	701,862 (27.4)	386,320 (31.5)	69,576 (36.2)
[65-75[		1,626,185 (11.5)	283,343 (11.1)	227,013 (18.5)	34,643 (18.0)
≥ 75		1,340,404 (9.5)	198,397 (7.7)	131,094 (10.7)	18,250 (9.5)
Unknown		3,835,497 (27.1)	400,603 (15.6)	323,640 (26.4)	39,763 (20.7)
<b>Country</b>					
USA		6,970,897 (49.3)	829,739 (32.4)	459,516 (37.5)	65,371 (34.0)
South of Korea		1,061,414 (7.5)	249,757 (9.7)	140,293 (11.4)	26,587 (13.8)
China		734,941 (5.2)	180,432 (7.0)	44,036 (3.6)	3,646 (1.9)

France	528,764 (3.7)	130,773 (5.1)	54,897 (4.5)	14,020 (7.3)
Germany	461,908 (3.3)	62,723 (2.4)	75,256 (6.1)	7,623 (4.0)
Canada	445,986 (3.2)	66,358 (2.6)	38,082 (3.1)	6,028 (3.1)
United Kingdom	442,351 (3.1)	69,496 (2.7)	35,168 (2.9)	4,173 (2.2)
Italia	374,170 (2.6)	99,415 (3.9)	59,615 (4.9)	13,600 (7.1)
Thailand	324,952 (2.3)	240,326 (9.4)	3,103 (0.3)	1,348 (0.7)
Japan	299,654 (2.1)	32,371 (1.3)	78,621 (6.4)	5,302 (2.8)
India	283,564 (2.0)	74,385 (2.9)	52,687 (4.3)	11,350 (5.9)
Spain	244,668 (1.7)	50,059 (2.0)	22,853 (1.9)	3,697 (1.9)
Singapore	169,589 (1.2)	92,484 (3.6)	7,091 (0.6)	3,226 (1.7)
Others	1,797,422 (12.7)	385,309 (15.0)	154,854 (12.6)	26,137 (13.6)
<b>Medication</b>				
Anticancer drug	1,226,252 (8.7)	192,108 (7.5)	1,226,252 (100)	192,108 (100)
non-targeted therapye NTT	744,201 (5.3)	110,605 (4.3)	744,201 (60.7)	110,605 (57.6)
targeted therapy TT	558,980 (4.0)	89,798 (3.5)	558,980 (45.6)	89,798 (46.7)

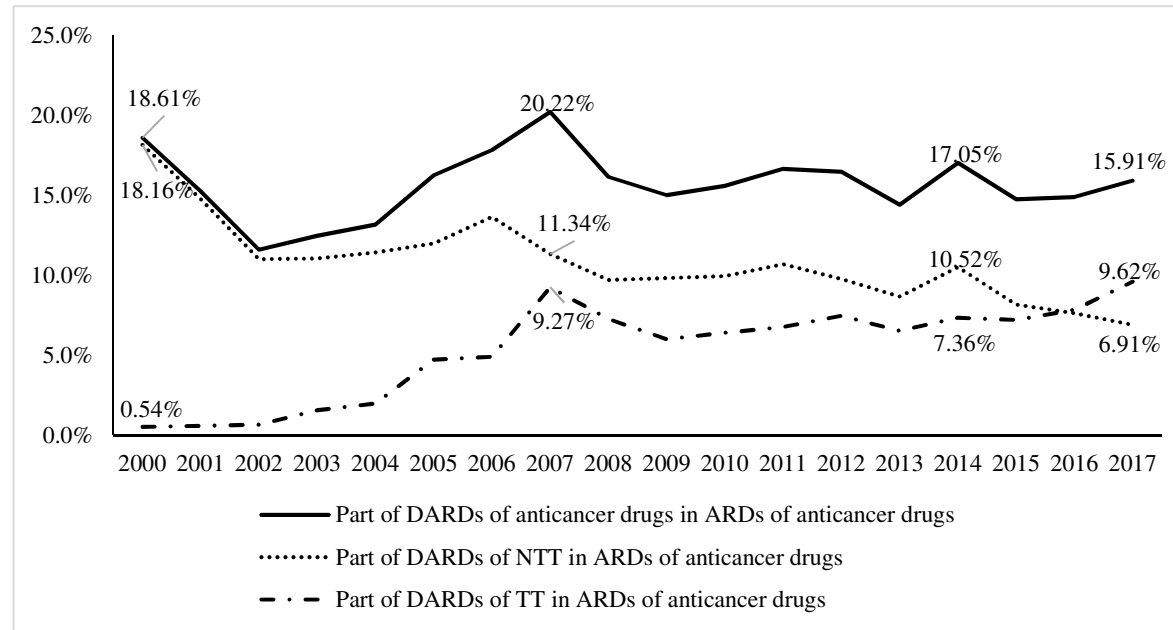


**Figure 1.** Part of dermatological adverse drug reactions (DARDs) of anticancer drugs / non-targeted therapy: NTT / targeted therapy: TT in Vigibase®

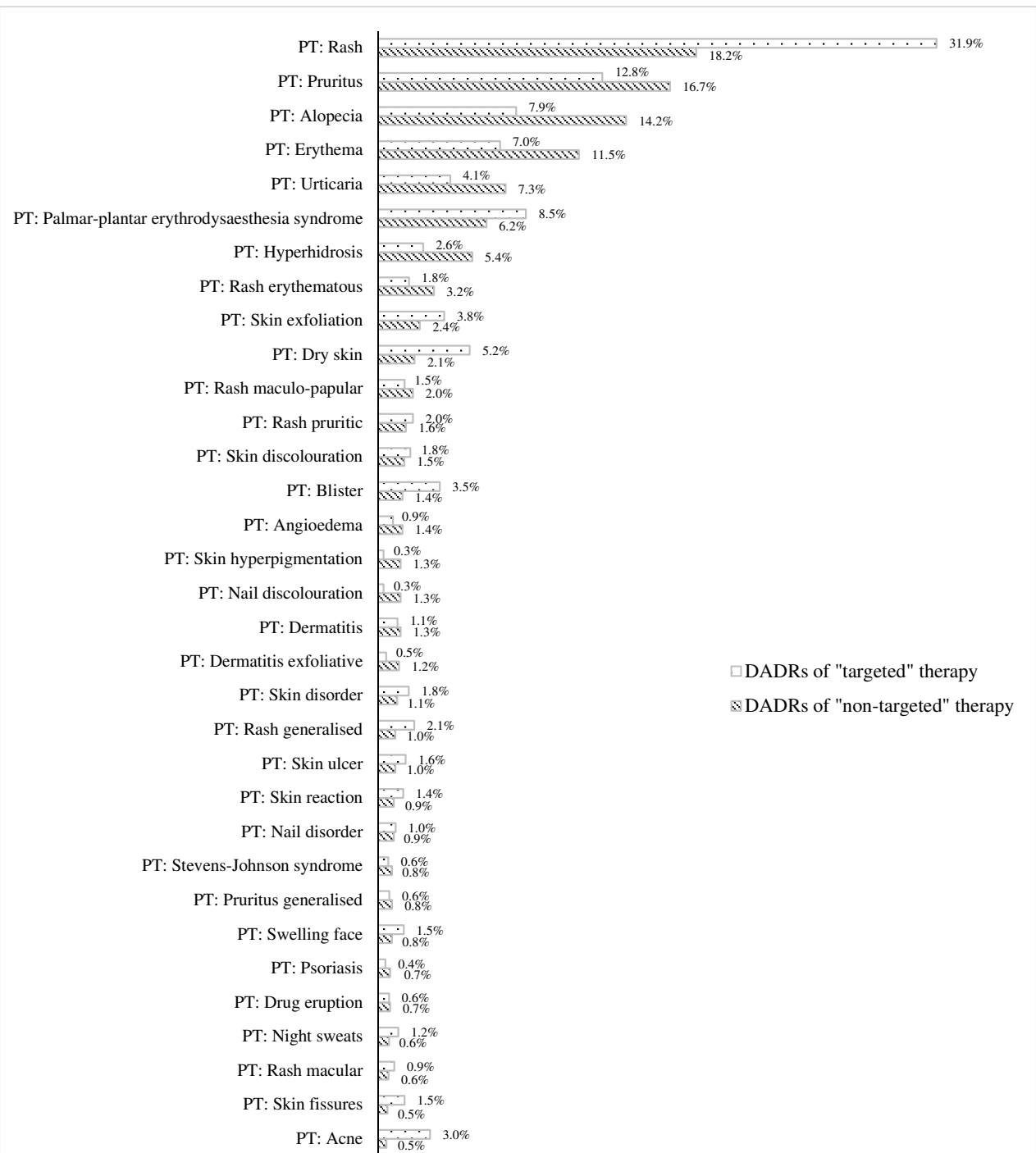




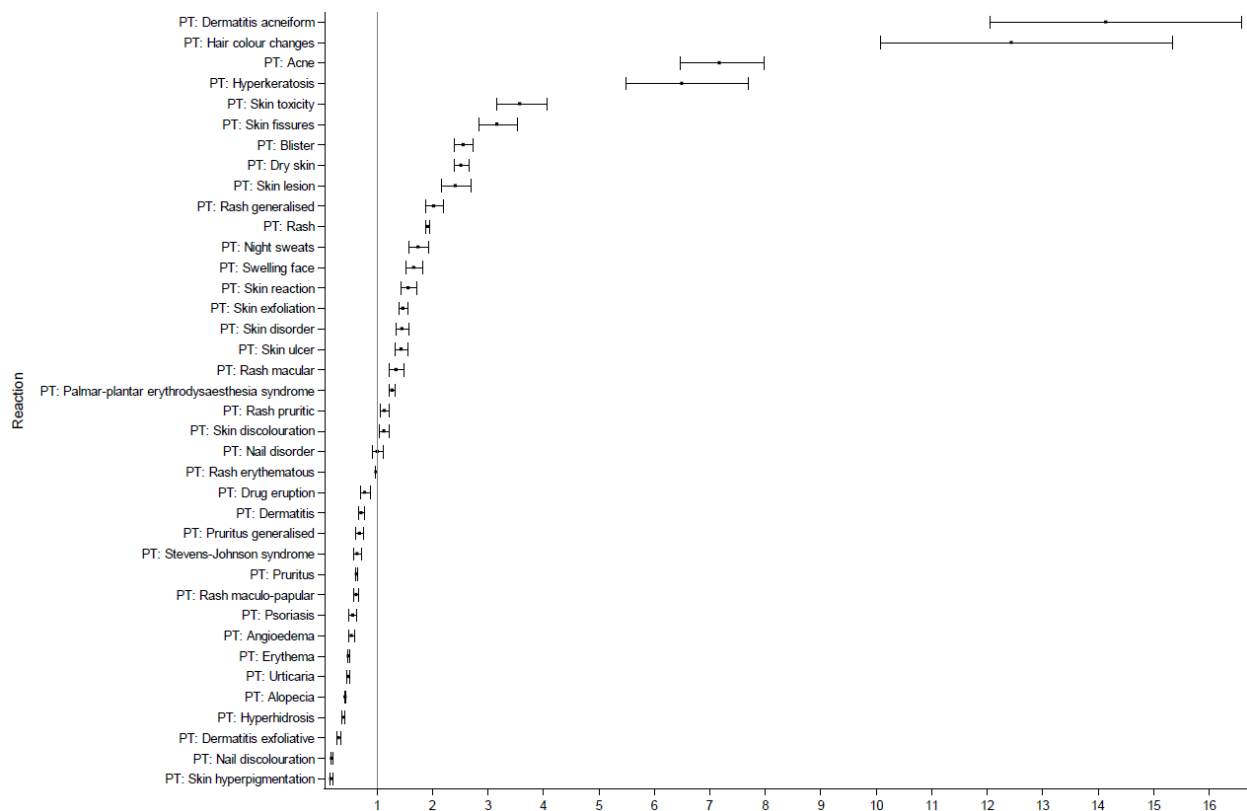
**Figure 2.** Part of dermatological adverse drug reactions (DARDs) of anticancer drugs / non-targeted therapy: NTT / targeted therapy: TT in all DARDs



**Figure 3.** Part of dermatological adverse drug reactions (DARDs) of anticancer drugs / non-targeted therapy: NTT / targeted therapy: TT of anticancer drugs.



**Figure 4.** Dermatological adverse drug reactions of "non-targeted" and "targeted" therapy during the study period (2000 to 2017)



**Figure 5.** Disproportionality analysis between targeted anticancer drugs and non-targeted anticancer drugs from 2000 to 2017.

## Supplemental data

**Table S1.** System organ class (SOC) reactions of “non-targeted therapies”.

Reaction	n	%
SOC: General disorders and administration site conditions	190 268	25.6
SOC: Gastrointestinal disorders	168 725	22.7
SOC: Blood and lymphatic system disorders	146 157	19.6
SOC: Skin and subcutaneous tissue disorders	110 632	14.9
SOC: Nervous system disorders	94 546	12.7
SOC: Respiratory, thoracic and mediastinal disorders	84 939	11.4
SOC: Investigations	84 124	11.3
SOC: Infections and infestations	74 749	10.0
SOC: Vascular disorders	51 333	6.9
SOC: Musculoskeletal and connective tissue disorders	49 646	6.7
SOC: Metabolism and nutrition disorders	47 956	6.4
SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)	44 252	5.9
SOC: Injury, poisoning and procedural complications	37 792	5.1
SOC: Cardiac disorders	36 671	4.9
SOC: Renal and urinary disorders	26 263	3.5
SOC: Immune system disorders	23 960	3.2
SOC: Psychiatric disorders	23 765	3.2
SOC: Hepatobiliary disorders	20 736	2.8
SOC: Eye disorders	14 105	1.9
SOC: Reproductive system and breast disorders	6 956	0.9
SOC: Surgical and medical procedures	6 400	0.9
SOC: Ear and labyrinth disorders	5 760	0.8

SOC: Product issues	2 758	0.4
SOC: Social circumstances	2 413	0.3
SOC: Congenital, familial and genetic disorders	2 370	0.3
SOC: Endocrine disorders	2 036	0.3
SOC: Pregnancy, puerperium and perinatal conditions	1 602	0.2

Table S2 : SOC reactions of "targeted therapies"

<b>Reaction</b>	<b>n</b>	<b>%</b>
SOC: General disorders and administration site conditions	196 482	35.1
SOC: Gastrointestinal disorders	129 257	23.1
SOC: Skin and subcutaneous tissue disorders	89 838	16.1
SOC: Investigations	80 709	14.4
SOC: Respiratory, thoracic and mediastinal disorders	77 006	13.8
SOC: Nervous system disorders	72 993	13.1
SOC: Infections and infestations	71 003	12.7
SOC: Blood and lymphatic system disorders	55 602	9.9
SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)	54 588	9.8
SOC: Injury, poisoning and procedural complications	49 186	8.8
SOC: Musculoskeletal and connective tissue disorders	43 268	7.7
SOC: Metabolism and nutrition disorders	42 189	7.5
SOC: Vascular disorders	37 056	6.6
SOC: Cardiac disorders	31 769	5.7
SOC: Renal and urinary disorders	23 089	4.1
SOC: Eye disorders	20 409	3.6
SOC: Psychiatric disorders	19 524	3.5
SOC: Hepatobiliary disorders	15 944	2.9
SOC: Immune system disorders	11 352	2.0
SOC: Surgical and medical procedures	8 659	1.5
SOC: Endocrine disorders	5 125	0.9
SOC: Reproductive system and breast disorders	4 082	0.7
SOC: Ear and labyrinth disorders	3 838	0.7
SOC: Social circumstances	1 825	0.3
SOC: Congenital, familial and genetic disorders	1 487	0.3
SOC: Product issues	1 308	0.2



