

CLARITYPV: 薬物モニタリングとファーマコビジュランスのためのAIベースの予測分析と統合されたトランスレーショナルセーフティデータ

CLARITYPV: integrated translational safety data with AI-based predictive analytics for drug monitoring and pharmacovigilance

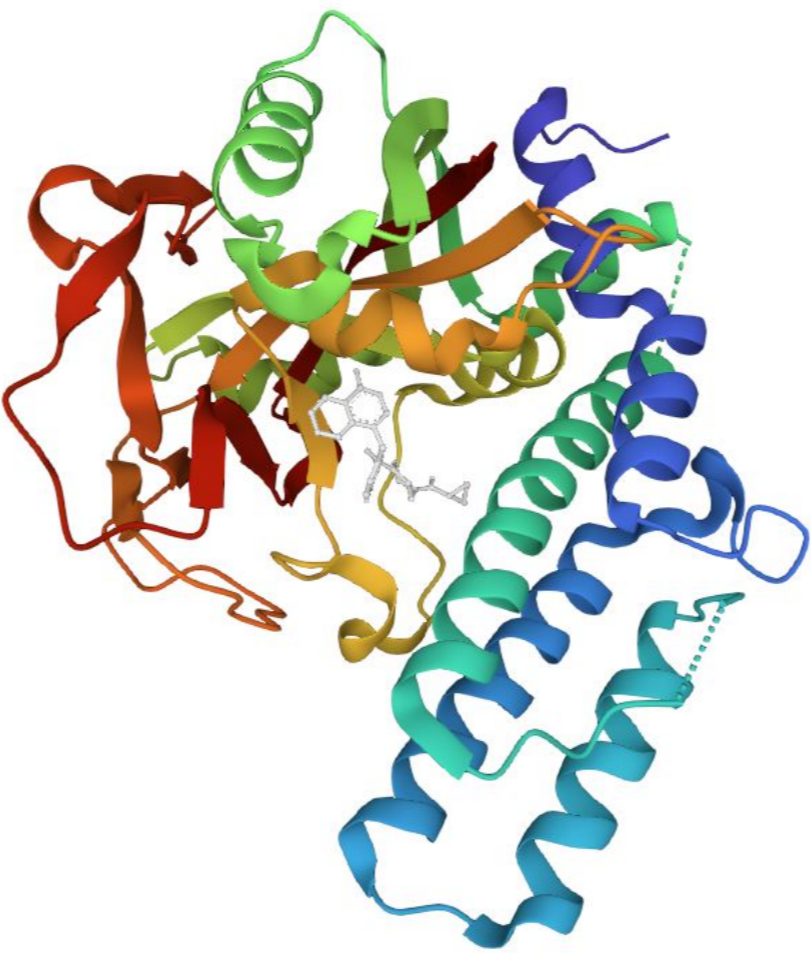
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We introduce CLARITYPV, a translational drug safety platform that integrates data from safety pharmacology, preclinical toxicology, clinical safety, and postmarketing reports for around 12,000 approved drug products and combinations, and almost 600 vaccines.

With CLARITYPV, drug researchers and surveyors involved in preclinical toxicology, clinical safety and/or pharmacovigilance are able to follow and analyze the entire safety lifetime of a drug product, both small molecules and biologics. The user can search and analyze integrated translational safety data, facilitate the collection of periodic safety update reports, anticipate postmarketing adverse drug reaction signals and use interactive visualization tools to easily navigate across data and signals. Also, CLARITYPV allows the user to carry out stratified analyses of safety events, to follow the safety evolution of drugs, to perform comparative safety analyses of drugs and drug classes, and to forecast the most likely safety signals of drug candidates entering clinical phases or new drugs entering the market using AI-based predictive methods and analytics. A use case of a drug and its drug class will be shown.

Ovarian cancer is one of the most common cancer in women worldwide. Early diagnosis is rare and although chemotherapy can be effective in the short term, the 5-year survival rate is only 20%. Impaired function of the homologous recombination pathway, a DNA repair mechanisms involving Breast Cancer type 1/2 susceptibility protein (BRCA), is associated with higher sensitivity to platinum-based chemotherapy. Under normal conditions, single-strand breaks (SSBs) in DNA are repaired by an error-free, poly(ADP-ribose) polymerase (PARP)-mediated mechanism [1].



Olaparib is used to treat BReast CAncer susceptibility protein (BRCA)-associated, platinum-sensitive ovarian cancer.

Olaparib inhibits poly(ADP-ribose) polymerase, thereby blocking the repair of single-strand DNA breaks [1,2].

Olaparib monotherapy is well tolerated, with adverse effects (AE) generally of mild-to-moderate severity.

The most commonly observed side effects (>10%) are **fatigue, nausea, vomiting, diarrhoea, dyspepsia, headache, altered taste, decreased appetite** and **dizziness**; and an **increase in serum creatinine**, and haematological toxicity (**anaemia, neutropenia, thrombocytopenia** and **lymphopenia**) have been reported.

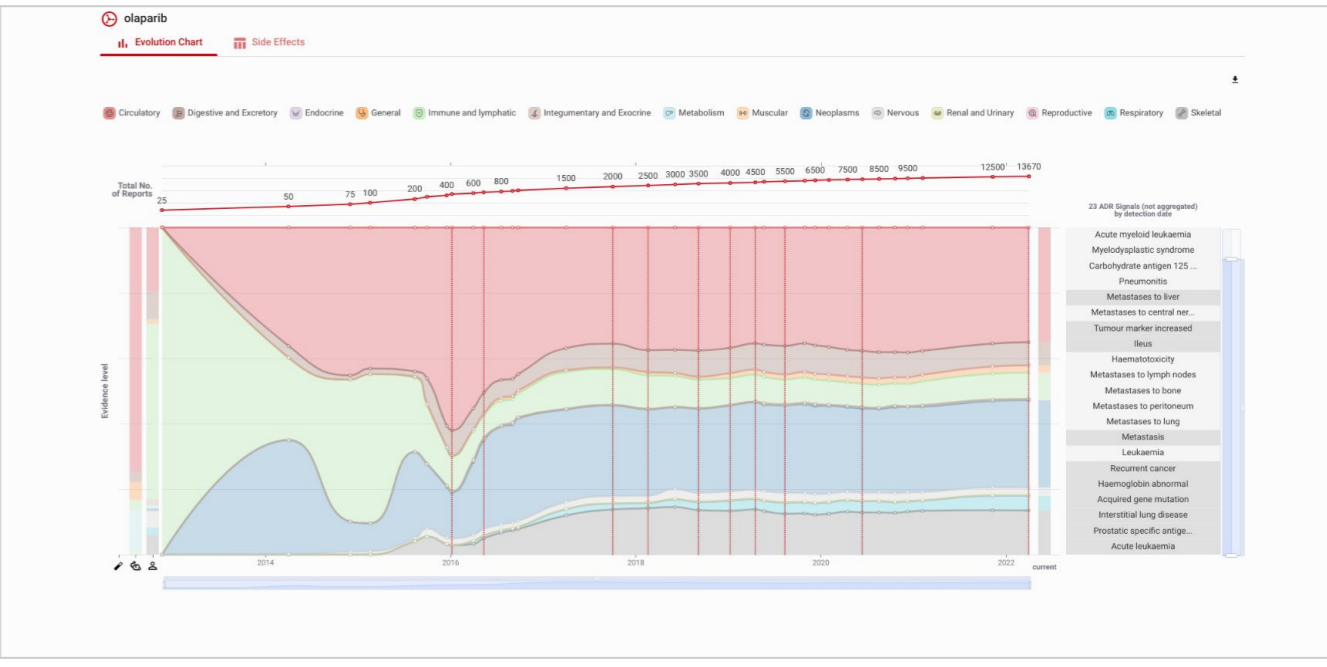
Uncommon serious AE included **myelodysplastic syndrome, acute myeloid leukaemia** and **pneumonitis** [1].

The data and the set of analysis engines available in **CLARITYPV** can help to monitor **known** and **unknown** AEs to support **risk assessment** decisions, for the marketed drugs and for those drugs under development.

ANALYSIS

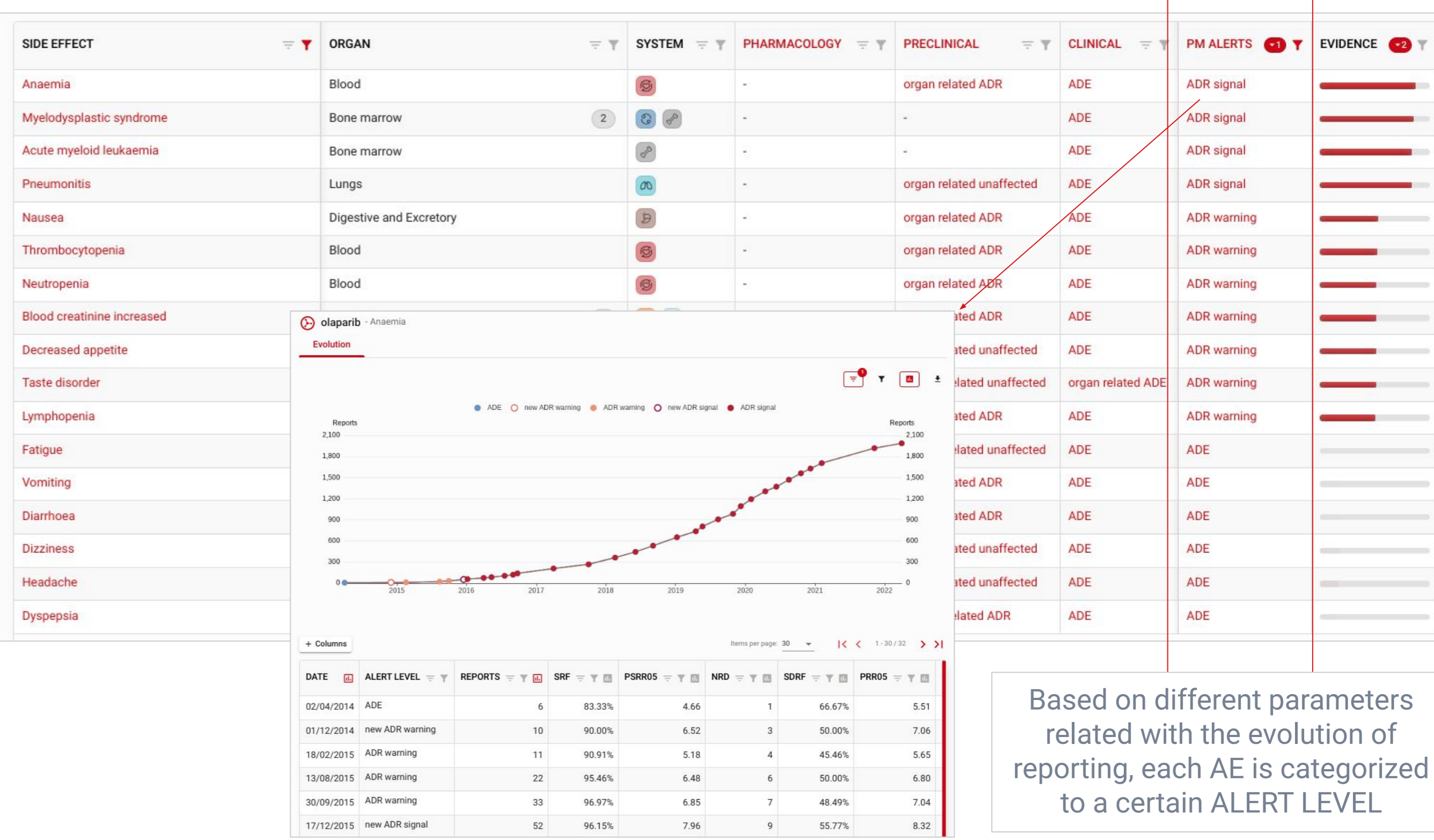
Translational Safety Analysis

To connect the events observed (**known AEs**) among the Drug Discovery Phases and the AEs reported (**known and unknown AEs**) in the Postmarketing period, the **Translational Safety picture** of **olaparib** presents the evolution of reporting, grouped by Organ System and shows the Organ System's Evidence level over the years.



KNOWN AEs

SIDE EFFECT
Enter side effect name
<input checked="" type="checkbox"/> Fatigue
<input checked="" type="checkbox"/> Nausea
<input checked="" type="checkbox"/> Vomiting
<input checked="" type="checkbox"/> Diarrhoea
<input checked="" type="checkbox"/> Dyspepsia
<input checked="" type="checkbox"/> Headache
<input checked="" type="checkbox"/> Taste disorder
<input checked="" type="checkbox"/> Decreased appetite
<input checked="" type="checkbox"/> Dizziness
<input checked="" type="checkbox"/> Blood creatinine increased
<input checked="" type="checkbox"/> Anaemia
<input checked="" type="checkbox"/> Neutropenia
<input checked="" type="checkbox"/> Thrombocytopenia
<input checked="" type="checkbox"/> Lymphopenia
<input checked="" type="checkbox"/> Myelodysplastic syndrome
<input checked="" type="checkbox"/> Acute myeloid leukaemia
<input checked="" type="checkbox"/> Pneumonitis



Based on different parameters related with the evolution of reporting, each AE is categorized to a certain ALERT LEVEL

Signal Analysis

Based on regular updates of spontaneous postmarketing reporting data processed from FAERS, Vigibase, and JADER databases, the **ADR Signals list** allows to identify disproportionality in reporting for each type of AE in reports where a drug is mentioned, and alerts pharmacovigilance professionals to monitor **unknown AE**.

The ADR signals list of **olaparib** presents 23 ADR signals (including the **known AEs** and new ones, like **Interstitial lung disease** [3]), 62 ADR warnings and 4 new ADR warnings (mostly related with Circulatory and Digestive/Excretory systems) and 511 ADE.



Comparative Analysis



The comparison of the **olaparib**'s AEs versus its drug class **PARP inhibitors'** AEs shows a list of **common AEs** to be considered as **drug class effects**.

The Pairwise comparison between **olaparib** and each drug class member (e.g., rucaparib) shows a list of their **common** and **uncommon AEs**; and the Set comparison for a subset of **known AEs** shows that more recent approved drugs are getting reports on AEs reported for earlier approved ones.

olaparib (2014), rucaparib (2016), niraparib (2017), talazoparib (2018), veliparib (investigational)

References: [1]. Br J Clin Pharmacol. 2016; 81(1): 171–173., [2]. PDB DOI: 10.2210/pdb7KK4/pdb. [3]. Gan To Kagaku Ryoho. 2020;47(9):1351-1353.

The safety-related analyses of **olaparib** carried out through the **CLARITYPV** application show the list of AEs known from the drug discovery phases (64 preclinical, 191 clinical), and the large set of additional AEs that have been reported in various pharmacovigilance databases as part of this drug postmarketing period.

The **Translational Safety picture** of **olaparib** shows that the Circulatory system (known from preclinical studies) and the Immune and Lymphatic systems (known from clinical studies) are the most affected due to this drug treatment, and the postmarketing reports confirm this drug safety concerns.

The **ADR Signals list** of **olaparib** highlights new AEs that can be categorized as ADR warnings and ADR signals, which are recommended to be monitored for further patient safety and to discover sets of events that precede more serious events.

The **Postmarketing Score comparison** between **olaparib** AE list and its drug class members AE shows a list of common and uncommon AEs which can be anticipated for other drugs in this class.

Based on public data and/or by integrating proprietary data, **CLARITYPV** can change the way to:

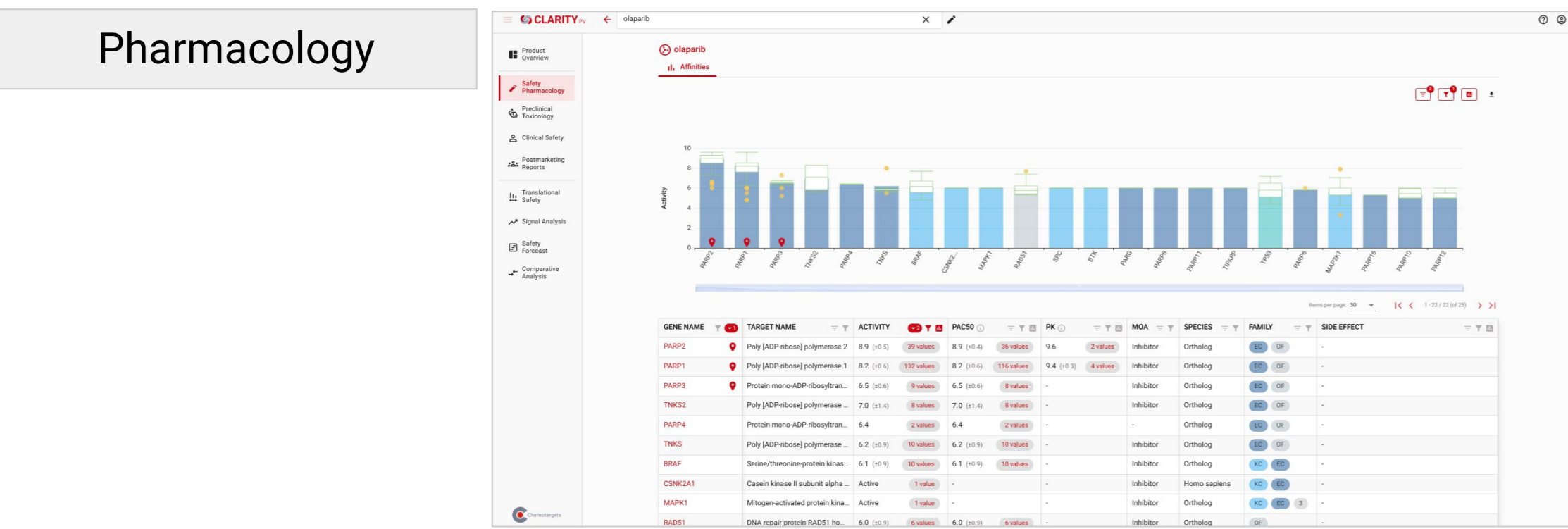
- Monitor and anticipate Adverse Drug Reactions in marketed products
- Support treatment-related decisions
- Guide the development of safer medicines

CLARITYPV



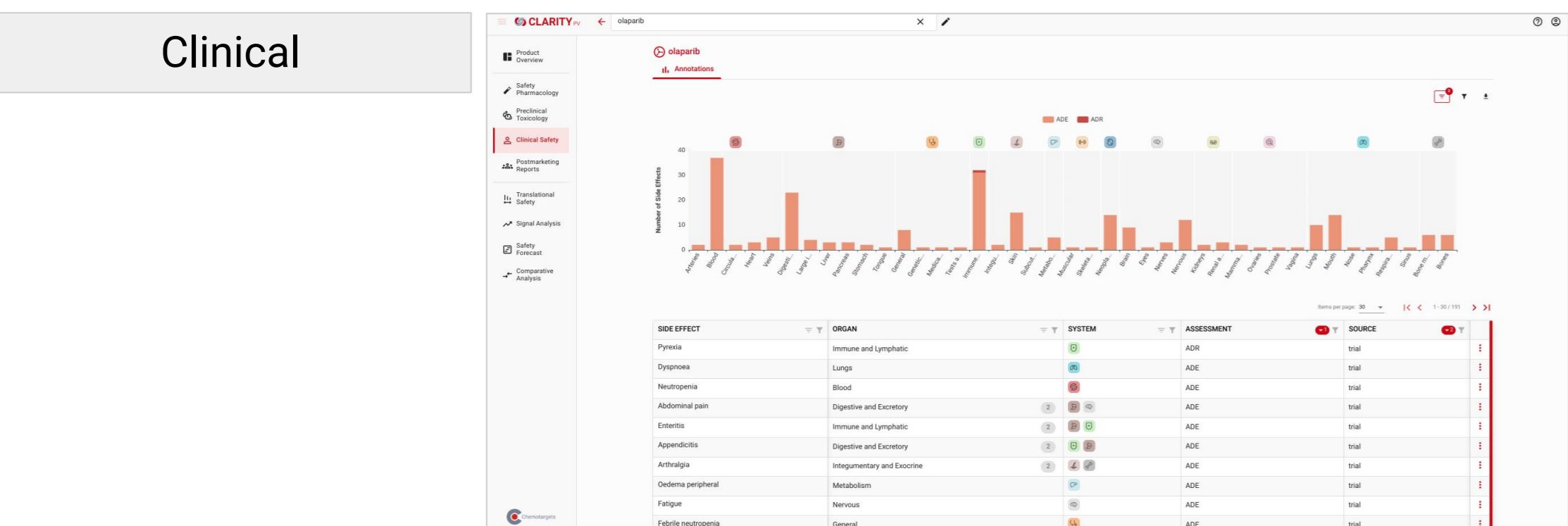
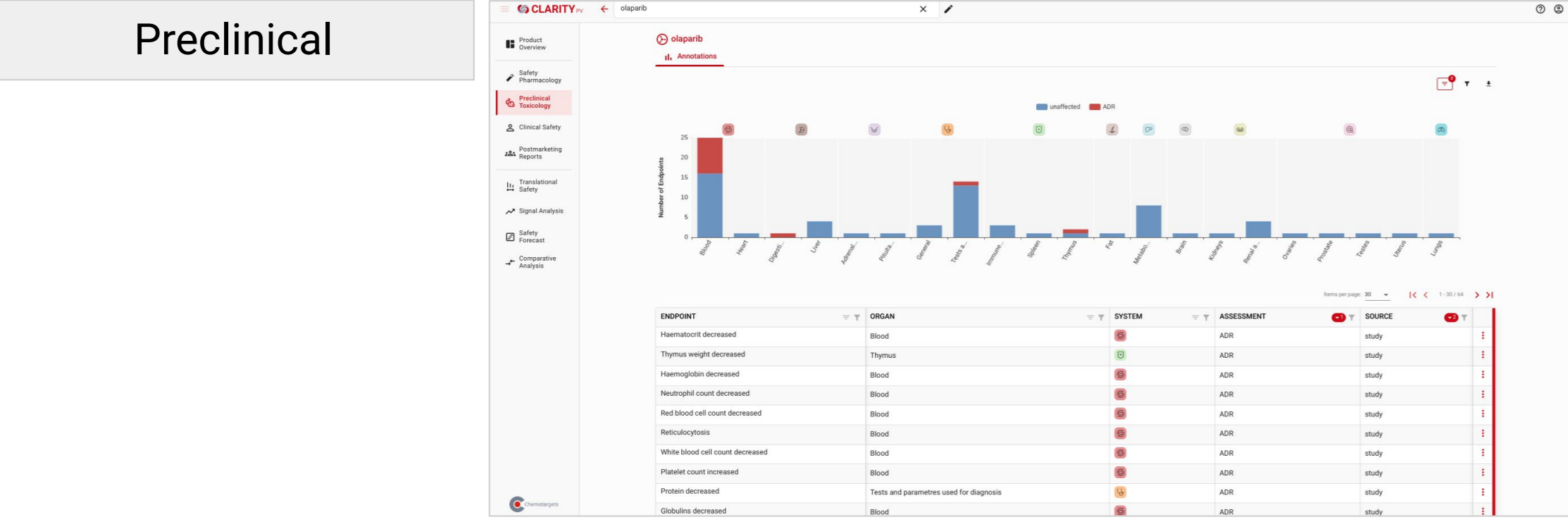
DATA and DATABASES

Based on Literature and Patents annotations, **obtain evidence to clarify a drug's MoA and the connection with its Adverse Events (AEs)**.

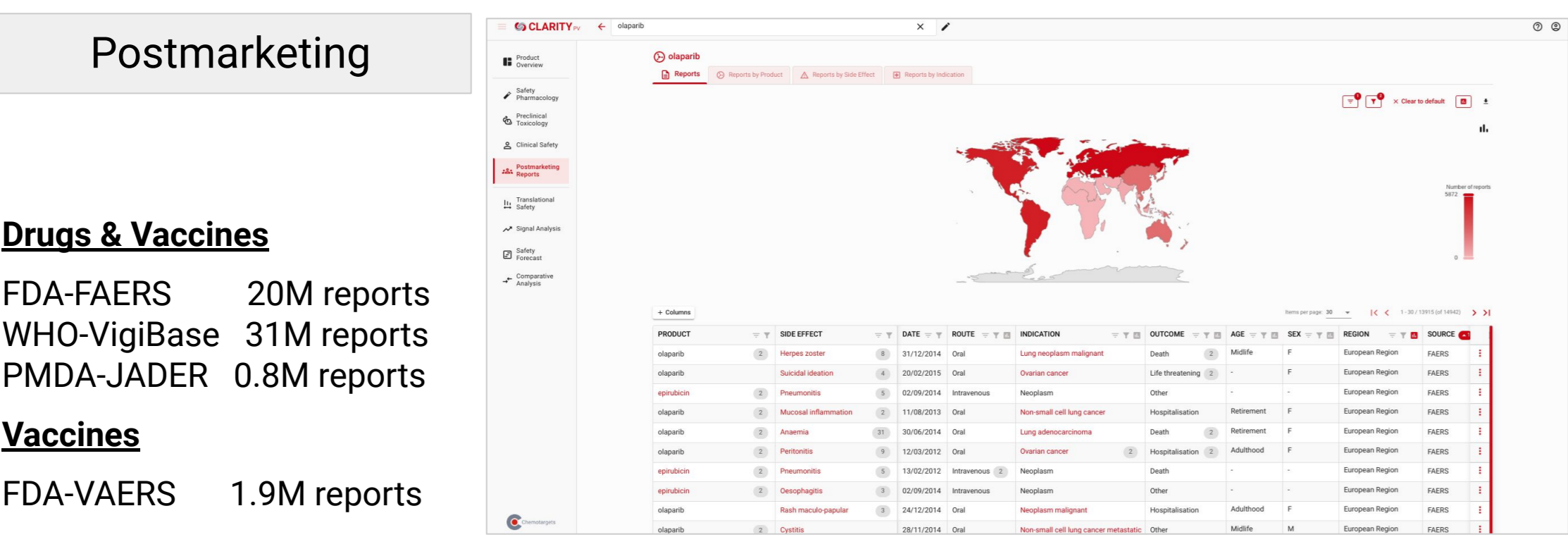


For each Organ System, find translational data and identify potential Adverse Drug Reactions (ADRs) to be monitored.

Anticipate the need for monitoring of unknown AEs for a drug, based on its drug class trends, during the preclinical and clinical studies.



Monitor demographic trends and known AEs (and related) to support risk assessment decisions at drug or drug class level.



Drugs & Vaccines
FDA-FAERS 20M reports
WHO-VigiBase 31M reports
PMDA-JADER 0.8M reports
Vaccines
FDA-VAERS 1.9M reports

