

DaVinci use in early phase ONC study

Innovative R tools in clinical practice

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Life forward

What is DaVinci?

An innovative solution at Boehringer Ingelheim to **provide Data Access** and **dynamic Visualization** for clinical insight.



Real time data access

Shorten to 2 days: from site to our user!



Data visualization and analysis

One stop data services provider!



Module extendable

More flexibilities at study level!

Timeline for application development in DaVinci

Dec 2021

EBAS (Exploratory biomarker data analysis) for exploratory biomarker data analysis. Typical outputs include heatmaps and subject-level/mean line plots.

Aug 2022

First **Modular DaVinci** was deployed online and then promoted to whole medicine team. It plays vital role in some deliverables like IB and SMC. PV physicians tend to find lab outliers and related patient profile on it.

Mar 2022

RENOVATE was onboard. STAT tends to monitor efficacy and DM would regularly do edit check for target legion and overall response in CQM.

Now

Platform integrated with DaVinci and TEAL is put into practice.

Content

1. **EBAS** : Exploratory Biomarker Analysis in Statistics
2. **RENOVATE**: RECIST (v1.1) based data moNitOring Visualization and Analytics Tool for Efficacy
3. **Modular DaVinci**: Data monitor with flexibilities
4. **Integrated with TEAL**

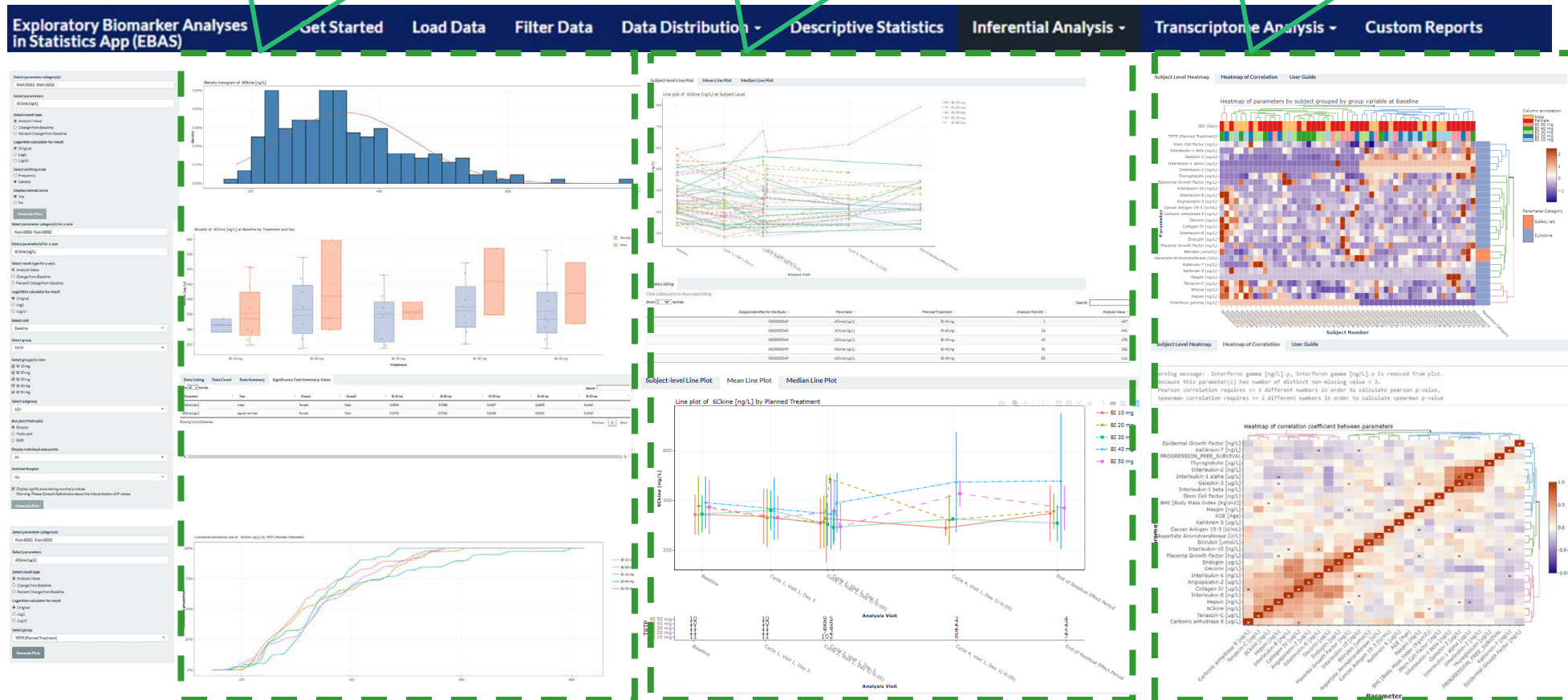


EBAS can generate instant outputs of biomarker

Frequency Histogram/Boxplots

Subject-level (Mean/Median) Line plots

Association Heatmap



Use Case #1

- Task: HOW MUCH BIOMARKER DATA ARE AVAILABLE?
- The team receives biomarker data in multiple batches as the trial is ongoing.
- After each batch, the team performs “interim” biomarker analyses.

Checking biomarker data availability

Plot Options Dendrogram Layout

Select parameter category(s)
Inhouse Myriad

Select parameters

- Angiopoietin-2 [ugEq/L]
- Granulocyte-Macrophage Colony-Stimulating Factor [ng/L]
- Interferon gamma [ng/L]
- Interferon gamma [ng/L] Interleukin-10 [ng/L]
- Interleukin-6 [ng/L]
- Macrophage Inflammatory Protein-1 alpha [ng/L]
- Monocyte Chemotactic Protein 1 [ng/L]

Select result type for parameters

- Analysis Value
- Change from Baseline
- Percent Change from Baseline

Logarithm calculator for result

- Original
- Log2
- Log10

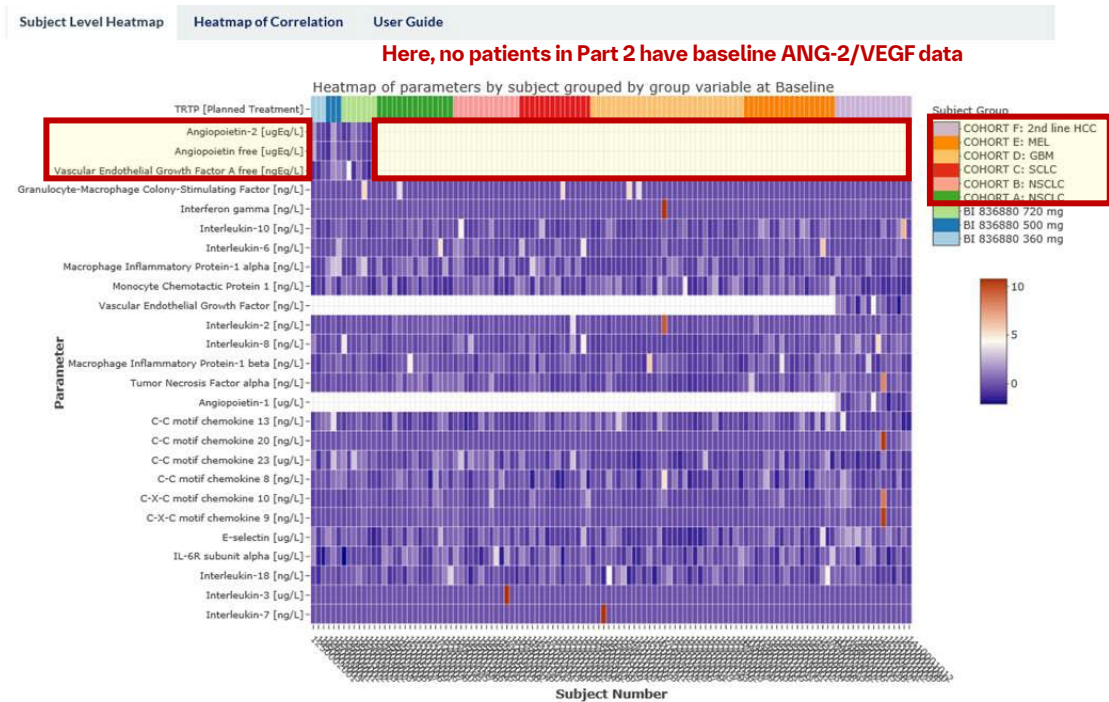
Select visit

Baseline

Select group variables

TRTP [Planned Treatment]

Select groups to view on plot



Use Case #2

- Task: ASSOCIATIONS BETWEEN BIOMARKER AND CLINICAL DATA?
- The trial team has several questions about possible associations between biomarkers and clinical response.
 - Can we potentially predict response based on baseline values? (e.g., Identify enriched populations?)
 - Is there a treatment effect on the biomarkers?
 - Is the change in biomarkers predictive of response?

Directly analyzing biomarker and clinical data

The screenshot shows the EBAS software interface. On the left, the 'Plot Options' panel is visible, with the 'Layout' tab selected. The 'Layout' tab is highlighted with a red box. Below it, various options are configured: 'Select parameter category(s) for y-axis' is set to 'Inhouse cytokine', 'Myriad cytokine'; 'Select parameter(s) for y-axis' is 'Angiotensin-2 [ugEq/L]'; 'Select result type for y-axis' is 'Analysis Value'; 'Logarithm calculator for result' is 'Original'; 'Select group' is 'TRTP [Planned Treatment]'; 'Select groups to view' includes 'COHORT A: NSCLC', 'COHORT B: NSCLC', 'COHORT C: SCLC', and 'COHORT E: MEL'; 'Select subgroup' is 'BORC [Best Overall Response Confirmed]'; 'Select subgroups to view' includes 'SD', 'PR', and 'PD'; 'Select group by page' is 'AVISIT [Analysis Visit]'. On the right, a box plot shows 'Angiotensin-2 [ugEq/L]' on the y-axis (0 to 14) across four cohorts: COHORT A: NSCLC, COHORT B: NSCLC, COHORT C: SCLC, and COHORT E: MEL. The plot is color-coded by Planned Treatment: PD (blue), PR (orange), and SD (green). A red box highlights the text 'Boxplots of baseline ANG-2 by BORC and cohort' in the plot area, with a red arrow pointing to it from the text 'Added a custom footnote using the "Layout" tab on the left side panel!'. Below the plot, the 'Data Listing' tab is active, showing a table of data entries.

Parameter Category	Parameter	Subject ID	Visit	Treatment	Borc	Analysis Value	Analysis Val
Inhouse cytokine	Angiotensin-2 [ugEq/L]		Baseline	COHORT A: NSCLC	PR	2.52	Within
Inhouse cytokine	Angiotensin-2 [ugEq/L]		Baseline	COHORT A: NSCLC	PR	8.01	Within
Inhouse cytokine	Angiotensin-2 [ugEq/L]		Baseline	COHORT A: NSCLC	PR	2.02	Within
Inhouse cytokine	Angiotensin-2 [ugEq/L]		Baseline	COHORT A: NSCLC	PR	1.61	Within

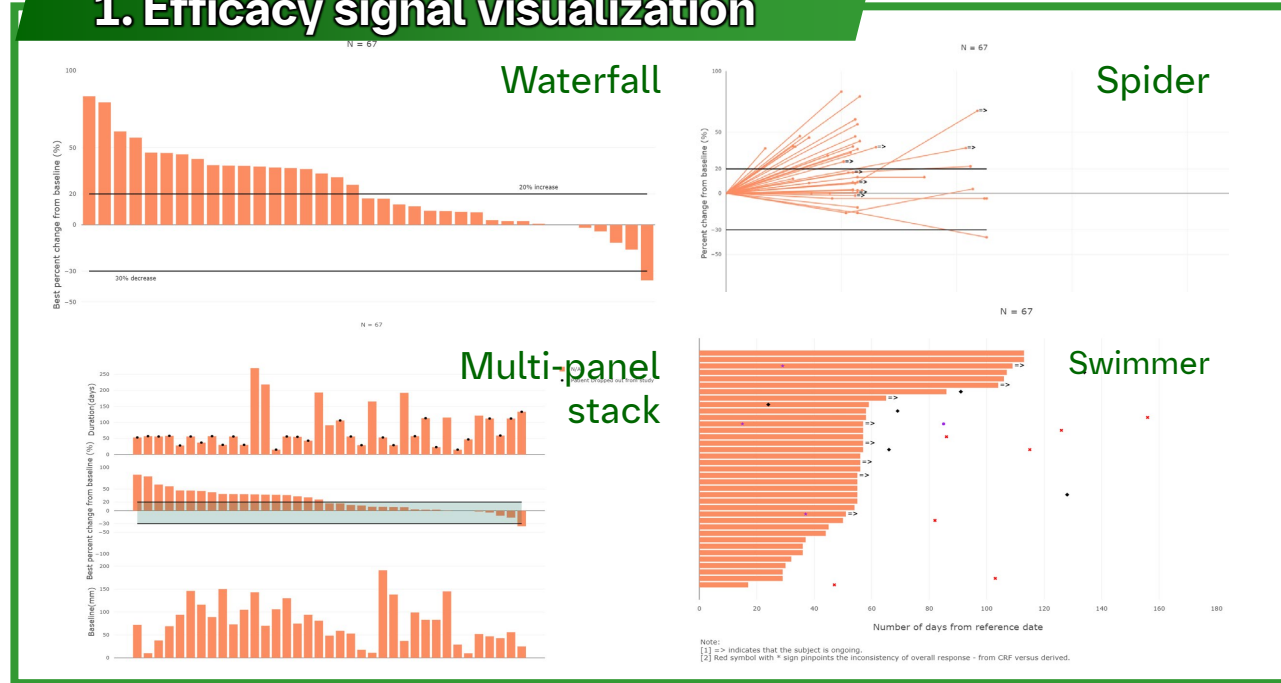
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RENOVATE can conduct efficacy signals monitor and edit check

1. Efficacy signal visualization



2. Edict check



Dates related

- Time window
- assessment ranges
- chronological visit



Examination method

- CT scan / X-ray



Response related

- Response from CRF and the derived

3. Tumor assessment aggregation

A1	A3	A4	A5	A2
Total Respondents: 0	Total Respondents: 0	Total Respondents: 0	Total Respondents: 0	Total Respondents: 0
56001001: PD	6001002: PD	56001003: PD	001001: SD, SD, Ongoing	001003: PD
24001001: PD	4002002: PD	24002003: PD, PD, Ongoing	001006: SD, Ongoing	001004: SD, PD
24001002: SD, SD, SD, PD		24002004: SD, Ongoing	002005: SD, Ongoing	002001: PD

Showing 1 to 4 of 4 entries

Previous 1 Next

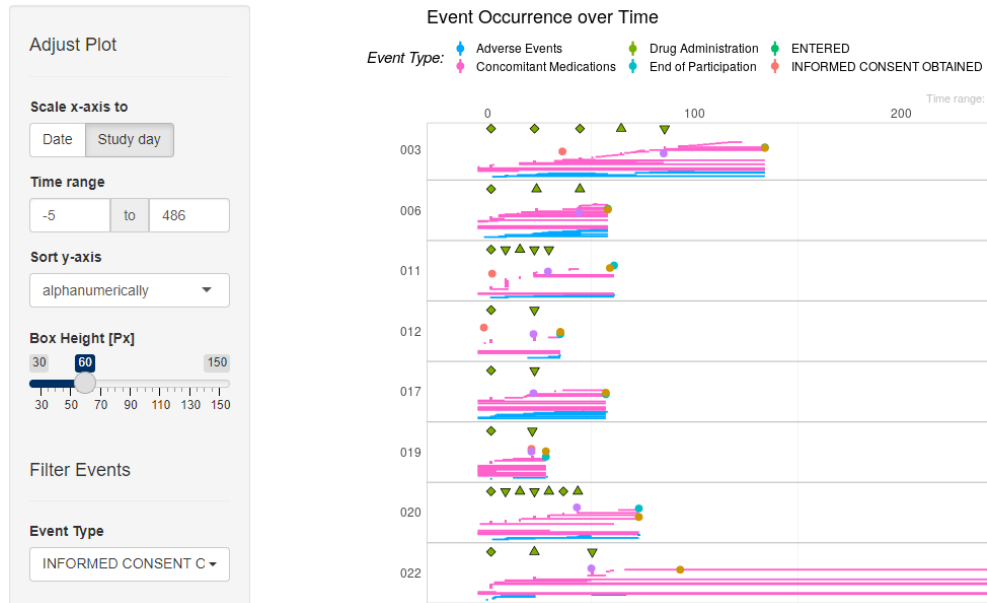
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DaVinci is a platform integrating diverse modules (1/3)

1. Clinical timeline



Any 'event' of interest track

2. SDTM listing

Clinical Timelines Patient Profile AE Hierarchy Table Vital Signs Listing Adverse Events Listing Concom.

Click to see inputs -

Reset Rows Order

	STUDYID [Study Identifier]	AETERM [Reported Term for the Adverse Event]	AEDECOD [Dictionary-Derived Term]	
	<input type="text" value="All"/>	<input type="text" value="All"/>	<input type="text" value="All"/>	
1	1438-0001	HYPOALBUMINAEMIA	Hypoalbuminaemia	
2	1438-0001	RASH MACULOPAPULAR	Rash maculo-papular	
3	1438-0001	NON CARDIAC CHEST PAIN	Non-cardiac chest pain	
4	1438-0001	BACK PAIN INTERMITTENT	Back pain	
5	1438-0001	WHITE BLOOD CELL COUNT DECREASE	White blood cell count decreased	
	AESER [Serious Event]	AEOUT [Outcome of Adverse Event]	AEREL [Causality]	AETOXGR [Standard Grade]
	<input type="text" value="All"/>	<input type="text" value="All"/>	<input type="text" value="All"/>	<input type="text" value="All"/>
	N	RECOVERED/RESOLVED	N	1
	N	NOT RECOVERED/NOT RESOLVED	N	1
	N	RECOVERED/RESOLVED	N	1
	N	NOT RECOVERED/NOT RESOLVED	N	1

Raw data checking

DaVinci is a platform integrating diverse modules (2/3)

3. Patient profile - listing

Select Patient ID: 1438-0001-127601003

Patient Information
 Description of Planned Arm : BI 764532 0.03 ug/kg, Q3S
 Asian Race : NA
 Date/Time of First Study Treatment : 2020-10-07T11:00
 Study Site Identifier : 1438-0001-DEU1
 Sex : M
 Date/Time of Last Study Treatment : 2020-12-30T13:13
 Race : WHITE
 Date/Time of Informed Consent : 2020-07-30
 Date/Time of End of Participation : 2021-02-17

Data Table
 Select Domain: Adverse Events, Concomitant Meds, Vital Sign, Subject Visit
 Select Extra Columns: USUBJID, AETERM, AEDECOD, AEOBODI
 Reset Columns Order

Uniqg Sbjct Identif	Term for Adverse Event	Dictionary-Derived Term	Body System or Organ Class	Primary System Organ Class	Severity/Intensity	Serious Event	Action Taken with Study Treatment	Causality	Outcome of Adverse Event	Concomitant or Additional Trtmt Given	Epoch	Start Date/Time of Adverse Event	End Date/Time of Adverse Event
1 143L 12760	...JUMNNAEMIA	Hypoalbuminaemia	Metabolism and nutrition disorders	Metabolism and nutrition disorders		N	DOSE NOT CHANGED	N	RECOVERED/RESOLVED	N	TREATMENT	2020-10-08T00:00	2020-10-14T23:59
2 1438-0001-127601003	RASH MACULOPAPULAR	Rash maculo-papular	Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders		N	DOSE NOT CHANGED	N	NOT RECOVERED/NOT RESOLVED	Y	TREATMENT	2020-10-14T00:00	

User-friendly labels attached

4. Patient profile - graphical display

Graphical Display
 Please Select Parameter for Lab plot : Nothing selected
 Please Select Parameter for Vital Sign Plot : Nothing selected

* No Parameter for Lab plot Selected / Selected Parameter for Lab plot Have No Data.
 * No Parameter for Vital Sign Plot Selected / Selected Parameter for Vital Sign Plot Have No Data.

VS, AE & CM plots over time

DaVinci is a platform integrating diverse modules (3/3)

5. Adverse events hierarchy tree

Select Hierarchy Variables

Lowest Level Term ✕
Reported Term for the Adverse Event ✕

Select Group Variable

Causality ▼

Grouped		N		Y	
Lowest Level Term	Reported Term for the Adverse Event	N(55)	%	N(49)	%
▼ Cytokine Release Syndrome (5)		0	0 %	30	61.2244897959184 %
	Cytokine Release Syndrome	0	0 %	29	59.1836734693878 %
	Cytokine Release Syndrome Gr1	0	0 %	1	2.04081632653061 %
	Cytokaine Release Syndrome	0	0 %	1	2.04081632653061 %
	[Irr (Infusion-Related Reaction) /JCr (Cytokine Release Syndrome)	0	0 %	1	2.04081632653061 %
▶ Asthenia (3)		7	12.7272727272727 %	9	18.3673469387755 %
▶ Lymphocyte Count Decreased (3)		3	5.45454545454545 %	9	18.3673469387755 %

Flexible AE tables

6. Outlier explorer rho chart

Measure: Lymphocytes (10⁹/L) X-axis: VISIT Limits: Lower: 0 Upper: 17.2 Method: LLN-ULN Without Data Unscheduled

69 of 71 participant(s) shown (97.2%)

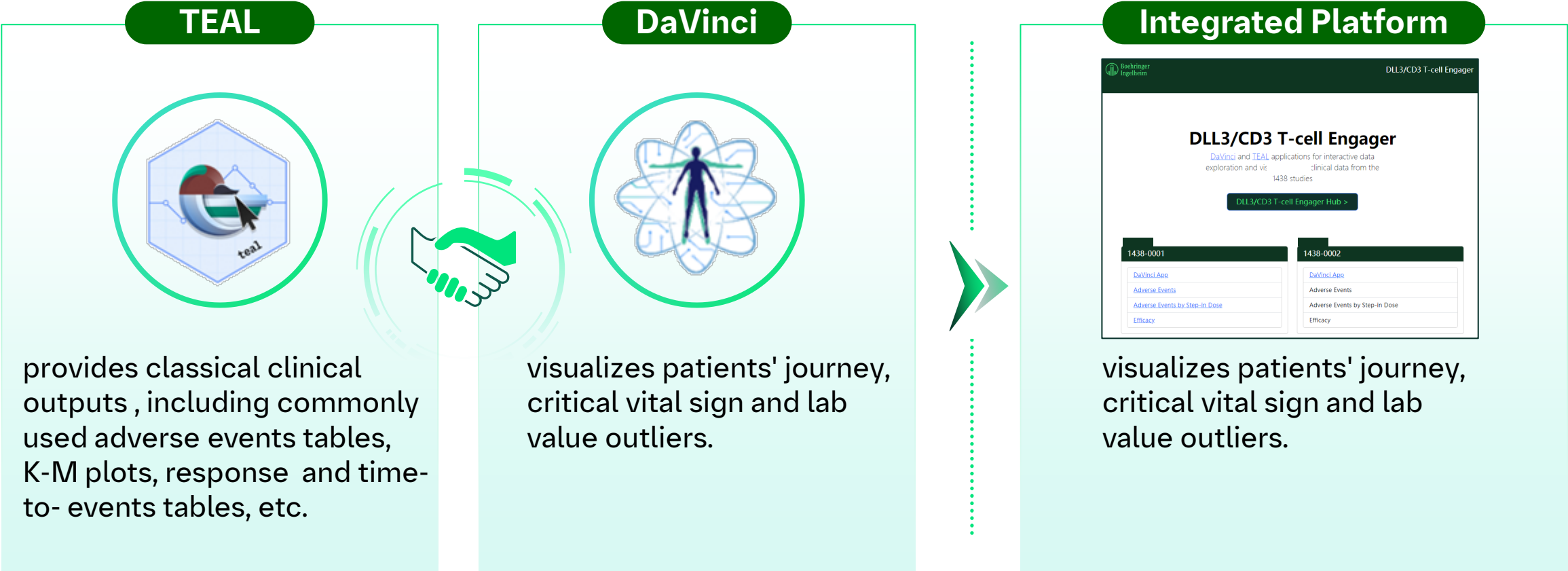
Vivid outlier display

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DaVinci can be integrated with TEAL through HTML



Both TEAL and DaVinci share Module mindset, maybe we can....

DaVinci can be integrated with TEAL through R

Data Exploration

App Info Demographic Adverse Events Laboratory Efficacy **Patient Profile** Variable Browser Report previewer

BI Patient profile

Select Patient ID: 001

Patient Information

Study Site Identifier : FRA1 Age : 20 Sex : M
RACE : missing Ethnicity : ARM : Dummy_BI
End of Study Status : TRT01A : Dummy BI

Data Table

Select Domain: **Adverse Events** Concomitant Medication

Select Extra Columns: USUBJID, AETERM, AEDECOD, AESOC

Reset Columns Order

Unique Subject Identifier	Reported Term for the Adverse Event	Dictionary-Derived Term	Primary System Organ Class	Action Taken with Study Treatment	Trea
1	001 RHINITIS	Rhinitis	Infections and infestations	DOSE NOT CHANGED	
2	001 RHINOPHARYNGITIS	Nasopharyngitis	Infections and infestations	DOSE NOT CHANGED	
3	001 RHINITIS	Rhinitis	Infections and infestations	DOSE NOT CHANGED	
4	001 STUFFY NOSE	Nasal congestion	Respiratory, thoracic and mediastinal disorders	DOSE NOT CHANGED	

Showing 1 to 4 of 4 entries

Graphical Display

Please Select Parameter for Lab plot : Nothing selected

Please Select Parameter for Vital Sign Plot : Nothing selected

Please Select Parameter for IASI plot : Nothing selected

Please Select Parameter for NASA plot : Nothing selected

Please Select Parameter for NS Itch plot : Nothing selected

Please Select Parameter for Severity of NS Pain plot : Nothing selected

Please Select Parameter for IGA plot : Nothing selected

Please Select Parameter for ISS plot : Nothing selected

One-stop data analysis platform

Use Case #1: avoid overwhelming lab listings



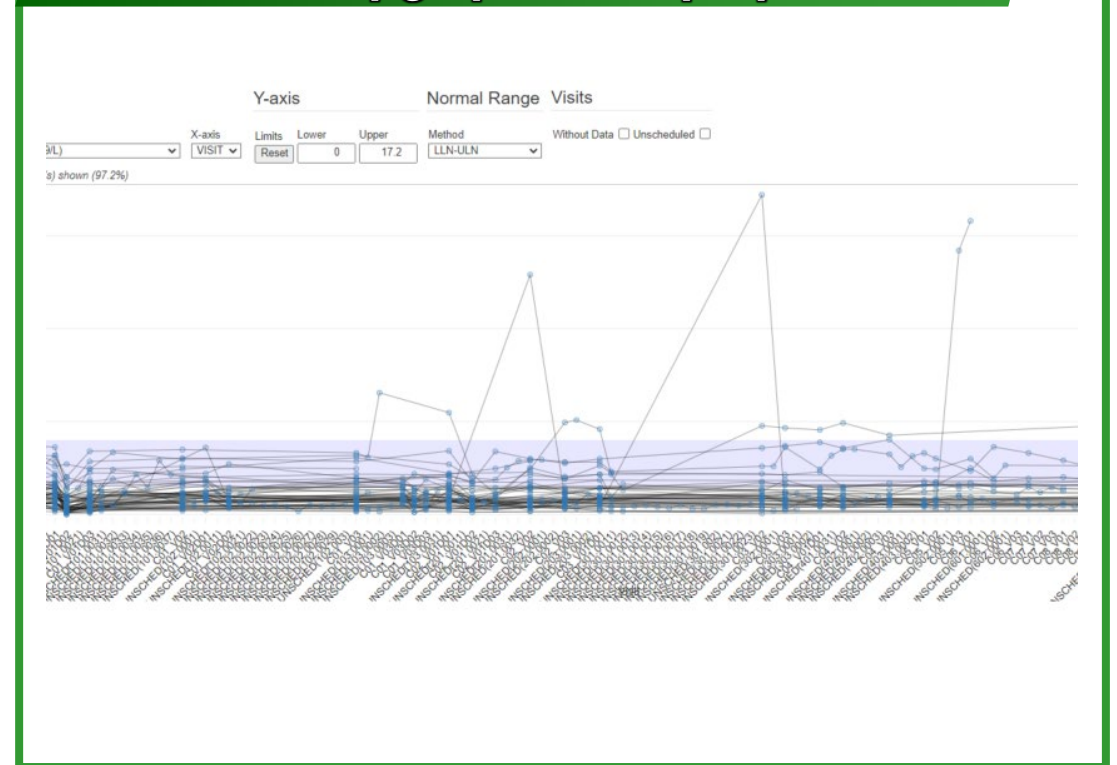
“Remove all lab listings and only display abnormal lab values. DaVinci would help.”

Before: lengthy lab listings

Patient number	Lab test	Visit	Specimen collection date	Specimen collection time		
1003	Prothrombin Intl. Normalized Ratio	C01_V01D01	07OCT2020	8:30		
		C01_V01D02	08OCT2020	5:00		
		C01_V01D03	09OCT2020	6:00		
		C01_V02	14OCT2020	9:34		
		C01_V03	21OCT2020	10:00		
		C02_V01D01	28OCT2020	9:15		
		C02_V01D02	29OCT2020	5:30		
		C02_V02	04NOV2020	10:15		

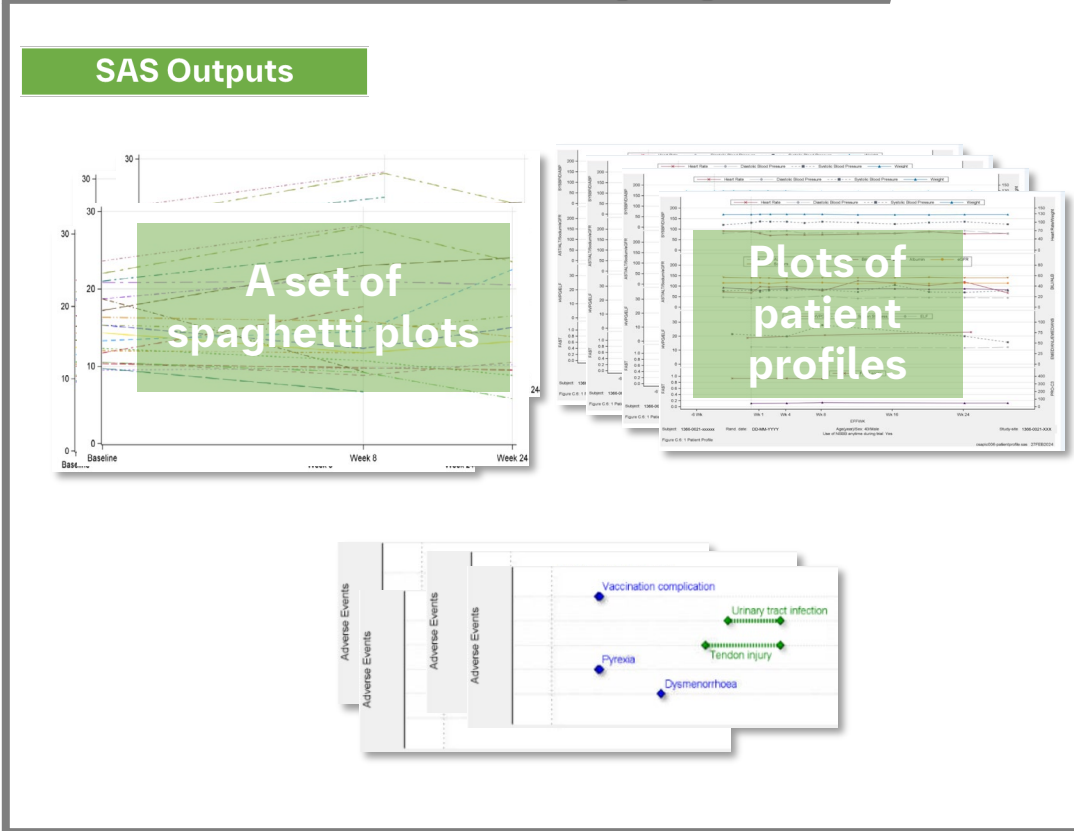
Value	Range flag	Unit	Lower limit	Upper limit
0.99	NORMAL	RATIO	0.90	1.20
1.06	NORMAL	RATIO	0.90	1.20
1.04	NORMAL	RATIO	0.90	1.20
0.98	NORMAL	RATIO	0.90	1.20
0.99	NORMAL	RATIO	0.90	1.20
1.01	NORMAL	RATIO	0.90	1.20
1.02	NORMAL	RATIO	0.90	1.20
1.01	NORMAL	RATIO	0.90	1.20

After: lively graphical display

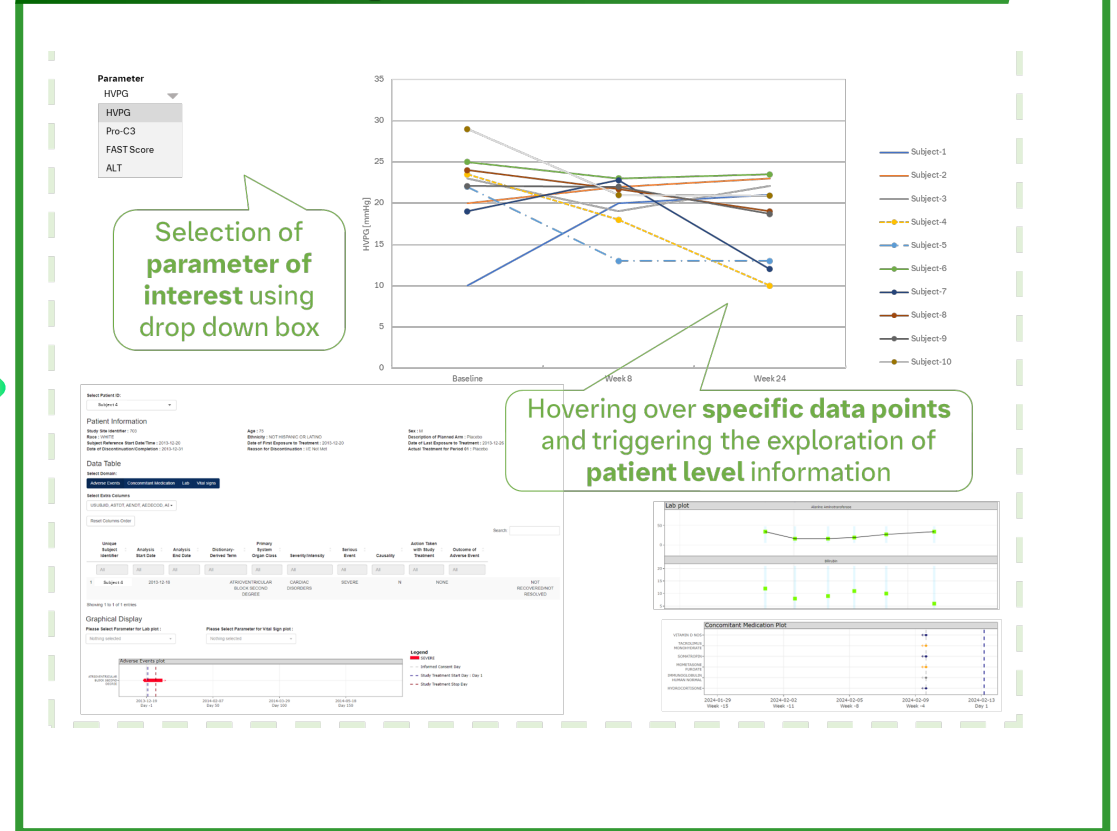


Use Case #2: turn tons of outputs to one lively dashboard

Before: hundreds of output plots



After: lively interactive dashboard



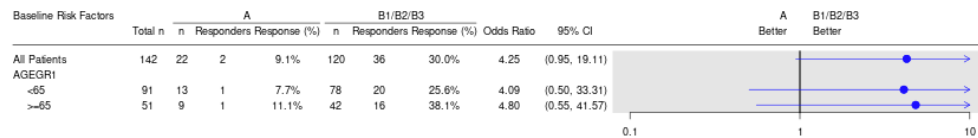
Use Case #3: automatically update data and app weekly

Workflow of data updates



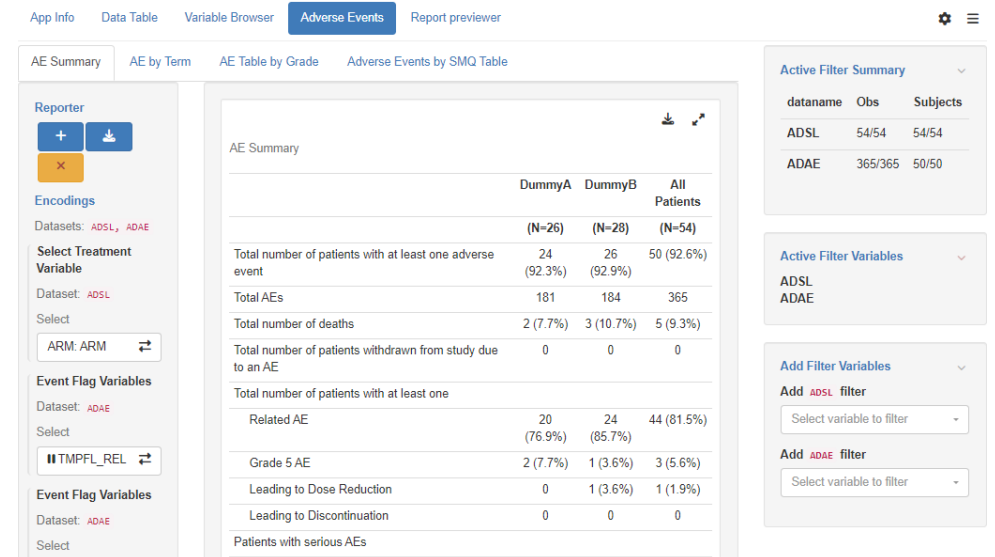
Example: forest plots

Programmers escape from repeated rerun work but **statisticians** are free to explore.



Example: default AE tables

Safety physicians is happy to build default AE table at their will.



Open Mic

Exploring more **R** chance in our daily scenario
i.e. R validation, R plotting, R Shiny, ..., etc.



Embrace OPEN-Source Era

We are actively contributing to several open-source initiatives to give back to the community:

- TEAL framework (Roche)
- FALCON initiative
- Pharmaverse
- Regulatory R Repo
- Riskmetrics WG



Thank you for listening!
Stay connected 😊

