Responder Screen

vemurafenib

Predicted response across all 17 modelled cancer indications · basis: DepMap measured · confidence Elevated

01 What this report is, and is not

Status

Hypothesis-generating, not a validated prediction

Screen: vemurafenib has 1 true responder indication(s) of 17 — strongest skin at +41.7% predicted viability change (2.6x the noise floor, clear). 5 further indication(s) are relatively better but below threshold. Of 8 responder zone(s) covering 56 cell lines, 8 are true responders and 0 are below threshold.

1 of 17 indications are true responders (better than this compound's own average and clearing the noise floor); 5 more are relatively better but below threshold. Strongest true responder: skin at +41.7% (2.6x the noise floor, clear) — the magnitude above the floor is the promise signal; clearing it means real, not large.

Disclaimer — verbatim

Hypothesis-grade triage, not a validated prediction. Imputed from chemical structure on cell-line (DepMap/PRISM) data; committed scaffold-LDO accuracy is per-indication r ~0.39. Read the two metrics together: the absolute predicted viability change says whether this compound does anything at all to a tissue, and the relative effect says only how a tissue compares with this compound's own average -- a high relative effect on a compound with no absolute activity is that compound's least-inactive tissue, not a lead. Responder zones are mixed-tissue cell-line subgroups meeting both committed criteria -- clearing the absolute noise floor and responding better than this compound's own average -- so an inactive compound returns none, and a zone must always be read next to the absolute metric. Not a clinical or efficacy prediction.

How to read the table

Read the two metrics together — the pair is the triage. The absolute metric says whether the compound does anything to a tissue; the relative metric only ranks tissues against this compound's own average. A high relative effect on a compound with no absolute activity is that compound's least-inactive tissue, not a lead.

Absolute. Predicted viability change at the assayed dose, signed: positive means viability reduction (cell killing), negative means viability increase (proliferation). An indication counts as absolutely active when its predicted response reaches -0.30 log2 or beyond — the committed 0.30 log2 response floor, the single cut used throughout this analysis.

Relative. This indication versus the compound's own mean across the 17 indications. The sign is meaningful and the value is unclamped; it sits near zero everywhere for a flat or pan-cytotoxic profile. A within-compound contrast only: it cannot establish activity.

Responder zones. Responder zones are cell-line subgroups meeting both committed criteria: they respond better than this compound's own average, and their response clears the committed 0.30 log2 noise floor. An inactive compound returns no zones (nothing clears the floor), and a uniformly cytotoxic one returns only the subgroups that stand out against its own baseline — not every subgroup it kills. The report also states how many subgroups cleared the floor without standing out, so nothing is hidden. Each zone carries its magnitude tier (modest but real / clear / strong, in multiples of the floor) — clearing the

floor means the response is real, not that it is large. A zone can reveal a responsive subgroup inside an indication whose average is unpromising, which is why zones are reported, but zone scores are node-means over mixed-tissue cells: a zone is never by itself evidence of activity in any one tissue, and a strongly-responding tissue can still be diluted below the floor by its node-mates. Read the zone tier and the indication metric together.

What counts as a responder

> **Definition — verbatim**
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> A true responder is a unit that (relative) responds better than this drug's own average, and (absolute) clears the committed 0.30 log2 noise floor. The floor is a noise gate ('distinguishable from no effect'), not an efficacy bar. Units that meet the relative criterion but fail the floor are reported in full and labelled 'does not clear the response threshold — not a true responder'.

What the threshold is. The response threshold is a noise floor at 0.30 log2 — the point at which a predicted response becomes distinguishable from no effect at all. It is not an efficacy bar and not a claim about clinical usefulness.

Clearing it. Clearing the floor means the predicted response is real rather than noise. It does not mean the response is large, and it does not mean the compound will work.

Reading the magnitude. The absolute magnitude above the floor is the promise signal — that is the number to judge. A potent compound clears the floor easily and with high magnitude. A weak-but-real compound (a typical OTC drug or dietary supplement) may sit just above the floor: real, potentially useful, and entirely your judgment to act on. Both are reported the same way, with the magnitude shown, so you can tell them apart.

Failing it. Failing the floor means the apparent response is within noise — not a true responder — even when it is relatively better than the drug's own average. A weak drug still has a 'best' subgroup; that is arithmetic, not activity. These are labelled 'does not clear the response threshold' and their full analysis is still reported, so you can see exactly what was and was not found.

Why "its own average". The relative criterion compares each unit against this drug's own average, not against other drugs. That is deliberately toxicity-adaptive: a mild supplement and a potent chemotherapeutic are each judged against their own baseline, so a modest compound is not dismissed for being modest and a broadly cytotoxic one earns no credit for killing everything uniformly.

1	5	1	-0.0600	17/17
True-responder indications	Below threshold	Absolutely active	Compound's own average (log_2)	Indications measured

02 Predicted response, by indication

All 17 modelled indications, ranked by absolute predicted response. The **absolute** column says whether the compound does anything to the tissue; the **relative** column ranks tissues against this compound's own average only. Read them together.

#	Indication	Absolute viability change	Relative effect	log_2	× floor	Tier	Responder state	Cells in responder zones	Zones	Basis
1	**Skin**	**+41.7%**	**+64.6%**	**-0.7792**	**2.60×**	**Clear**	**True responder**	**24/38**	**8/8**	**Measured**
2	Kidney	**+18.0%**	+17.0%	-0.2869	0.96×	Below floor	Below threshold	4/18	3/3	Measured
3	Ovary	**+13.4%**	+10.8%	-0.2078	0.69×	Below floor	Below threshold	6/30	5/5	Measured
4	Uterus	**+10.0%**	+6.6%	-0.1520	0.51×	Below floor	Below threshold	1/21	1/1	Measured
5	Thyroid	**+5.7%**	+1.7%	-0.0848	0.28×	Below floor	Below threshold	2/10	2/2	Measured

#	Indication	Absolute viability change	Relative effect	log_2	× floor	Tier	Responder state	Cells in responder zones	Zones	Basis
6	Liver	**+4.3%**	+0.2%	-0.0634	0.21×	Below floor	Below threshold	1/18	1/1	Measured
7	Lung	**+2.0%**	-2.1%	-0.0291	0.10×	Below floor	No differential response	2/82	2/2	Measured
8	Central Nervous System	**+0.2%**	-3.8%	-0.0035	0.01×	Below floor	No differential response	0/34	0/0	Measured
9	Rhabdoid	-0.3%	-4.3%	0.0038	-0.01×	Below floor	No differential response	1/10	1/1	Measured
10	Bone	-0.5%	-4.6%	0.0079	-0.03×	Below floor	No differential response	0/16	0/0	Measured
11	Pancreas	-1.1%	-5.1%	0.0157	-0.05×	Below floor	No differential response	0/30	0/0	Measured
12	Esophagus	-1.2%	-5.2%	0.0178	-0.06×	Below floor	No differential response	4/19	2/2	Measured
13	Urinary Tract	-4.8%	-8.4%	0.0671	-0.22×	Below floor	No differential response	2/22	2/2	Measured
14	Upper Aerodigestive	-6.5%	-9.9%	0.0906	-0.30×	Below floor	No differential response	3/26	2/2	Measured
15	Breast	-7.0%	-10.4%	0.0980	-0.33×	Below floor	No differential response	0/24	0/0	Measured
16	Gastric	-10.0%	-12.8%	0.1374	-0.46×	Below floor	No differential response	2/15	2/2	Measured
17	Colorectal	-10.8%	-13.4%	0.1483	-0.49×	Below floor	No differential response	3/29	3/3	Measured

† Value imputed from chemical structure rather than measured in DepMap/PRISM. Imputed values are compressed toward the training mean and are **not** on the same scale as measured ones — see the Basis column for the per-row source and reason. · Basis reasons, abbreviated: not in DepMap = no measured data for this compound; too few lines = too few measured cell lines in this tissue; structure unmatched = structure could not be matched to DepMap. · **Zones** = true-responder / all zones touching that tissue. · **Cells in responder zones** = this tissue's cell lines that fall inside one of this compound's true-responder zones, out of all its cell lines. It is **not** a count of individually responding cell lines: response is modelled at indication resolution, so every cell line of a tissue carries that indication's predicted value. What distinguishes these cells is zone membership, not a separate per-cell test. · **× floor** = multiples of the -0.30 log_2 noise floor. · Tier column, abbreviated: **Modest** = modest but real (1–2× the floor), **Clear** = clear (2–3×), **Strong** = strong (3× or more). · **vs own avg** = how far the zone sits below this compound's own average, in log_2. · In the zone table, **Effect** is the predicted log_2 response and **vs own avg** is the margin over this compound's own average, both in log_2.

Section confidence — elevated (chemistry similarity); committed per-indication r ~0.39. Both metrics are indication-level derivations of the same underlying prediction and share that reliability.

03 Responder zones

1/17	8/482	8	0	56
Indications clearing floor	Subgroups clearing floor	Zones selected	Clear floor, not selected	Cell lines in zones

How this compound's zones were selected — verbatim

1 of 17 indications clear the -0.30 log2 noise floor, and 8 of 482 cell-line subgroups do. The 8 zone(s) reported are those that also respond better than this compound's own average (-0.0600 log2); the remaining 0 floor-clearing subgroup(s) are real but do not stand out against it, and are counted here rather than listed. Clearing the floor means a response is real, not that it is large — read each zone's tier. Hypothesis-grade, cell-line data.

A true responder is a unit that (relative) responds better than this drug's own average, and (absolute) clears the committed 0.30 log2 noise floor. The floor is a noise gate ('distinguishable from no effect'), not an efficacy bar. Units that meet the relative criterion but fail the floor are reported in full and labelled 'does not clear the response threshold — not a true responder'.

All 8 zone(s)

Geometry	Node	Dominant tissue	Effect	× floor	vs own avg	Cells	Tier	Basis	Composition
1-0	8	Skin	-0.516	1.72×	0.456	8	Modest	Mixed	Skin 5; Fibroblast 1; Rhabdoid 1; Lung 1
10-0	8	Skin	-0.479	1.60×	0.419	6	Modest	Measured	Skin 4; Colorectal 1; Ovary 1
8-1	77	Skin	-0.425	1.42×	0.365	6	Modest	Measured	Kidney 1; Thyroid 1; Skin 3; Liver 1
6-1	142	Skin	-0.416	1.39×	0.356	6	Modest	Measured	Colorectal 1; Skin 3; Kidney 2
12-0	2	Skin	-0.379	1.26×	0.319	14	Modest	Measured	Skin 8; Gastric 1; Upper Aerodigestive 2; Uterus 1; Colorectal 1; Ovary 1
11-1	5	Skin	-0.366	1.22×	0.306	6	Modest	Measured	Ovary 1; Skin 3; Thyroid 1; Gastric 1
1-1	3	Skin	-0.353	1.18×	0.293	10	Modest	Measured	Skin 5; Urinary Tract 1; Esophagus 2; Lung 1; Ovary 1
3-1	1	Skin	-0.316	1.05×	0.256	14	Modest	Measured	Kidney 1; Ovary 2; Skin 6; Esophagus 2; Upper Aerodigestive 2; Urinary Tract 1

A zone is a mixed-tissue cell-line subgroup, so the Composition column matters: the dominant tissue is not the only tissue, and a zone is never by itself evidence of activity in any one tissue. Read each zone next to that indication's absolute metric in the table above.

Section confidence — elevated (chemistry similarity); committed proxy node-rank rho ~0.40, elevated-tier ~0.62. Zones require both committed criteria -- clearing the absolute noise floor and responding better than this compound's own average -- so an inactive compound returns none.

04 Method and limitations

Basis

- Cell-line data (DepMap / PRISM single-dose viability), resolved measured-first: 17 of 17 indications are measured (vemurafenib), 0 imputed from chemical structure.
- Model `measured`, schema `screen-1.3`. Compound confidence **Elevated** — chemistry-similarity tier (max ECFP4 Tanimoto to v0.3 training set): elevated >=0.5 (committed node-rank rho ~0.62, 62.5% reach rho>0.5); moderate 0.4-0.5

(rho ~0.50, 50%); exploratory <0.4 (rho ~0.30, ~18%). Estimated, not guaranteed (committed outlier: doxorubicin tanimoto 1.0 yet rho 0.46).

- Zone selection: two-criterion responder definition; noise floor -0.30 $\log_2$ (the committed 0.30 log2 response floor, the single cut used throughout this analysis).

Limitations

- **Relative effect.** This indication versus the compound's own mean across the 17 indications. The sign is meaningful and the value is unclamped; it sits near zero everywhere for a flat or pan-cytotoxic profile. A within-compound contrast only: it cannot establish activity.
- Zone scores are means over mixed-tissue cell-line subgroups, so a responding tissue's signal is diluted by its non-responding subgroup-mates.
- Single-dose viability conflates cytotoxic and cytostatic effects; "predicted viability change" is not a claim about mechanism, potency or clinical benefit.
- Measured and imputed values are not on one scale. Any ordering spanning both mixes two scales.

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