Michael Onyeka / Bio.Med.Pharm.Rev. 1(1) (2025) 36-43
https://doi.org/10.62587/BMPR.1.1.2025.36-43 ISSN: 3136-5248

Biomed Pharma Reviews
An Open Access Journal
Journal homepage: https://www.biomedpharmareviews.com

Review Article **Open Access**

A Predicted Dichotomy and a Mismatched Endpoint: Epigenetic Therapeutics in Haematological against Solid Malignancy

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Article Info

Volume 1, Issue 1, January 2025
Received : 09 August 2024
Accepted : 13 December 2024
Published : 25 January 2025
doi: 10.62587/BMPR.1.1.2025.36-43

Abstract

Background: Hypomethylating agents and histone deacetylase inhibitors are licensed for myelodysplastic syndrome and cutaneous T-cell lymphoma and remain absent from standard treatment of solid tumours despite two decades of trials. The disparity is usually described as a translational failure awaiting a solution. **Methods:** Reviews and clinical trials of DNA methyltransferase or histone deacetylase inhibitors in malignancy reporting a response outcome were eligible. Reported response rates were compared across compartments, and the relationship between mechanism and proliferative fraction was set out. Trial-level endpoints were compared within a single solid tumour study reporting response, disease control and duration. No pooling was performed. Analyses were performed in Python 3. **Results:** In haematological malignancy, vorinostat produced partial responses in approximately 30% of patients with advanced cutaneous T-cell lymphoma, and a class I selective inhibitor produced tumour reduction in 63% of patients with T-cell, follicular and Hodgkin lymphoma including after allogeneic transplantation. In solid tumours, azacitidine with entinostat produced objective responses in 4% of 45 heavily pretreated patients with non-small cell lung cancer, and histone deacetylase inhibitors showed negligible activity in colorectal cancer as monotherapy or in combination. The gap spans 7.5- to 15.8-fold on these figures. Hypomethylating agents are nucleoside analogues incorporated during DNA synthesis and therefore act only on cells traversing S phase, so the fraction of a tumour the mechanism can reach is bounded by its growth fraction—which differs between compartments by roughly the same order as the response gap. In the same lung cancer trial, disease control at 12 weeks reached at least 27% against an objective response rate of 4%, one complete response lasted 14 months and one partial response 8 months, responses continued after the epigenetic agents were discontinued, and five patients subsequently received checkpoint blockade. **Conclusions:** The haematological-solid dichotomy is a prediction of the mechanism rather than an unexplained translational failure: an agent requiring DNA replication cannot reach the non-cycling majority of a solid tumour. The pattern in the lung cancer trial—low response, substantially higher disease control, durability outlasting exposure and subsequent checkpoint sequencing—is more consistent with a priming effect than with cytotoxicity. If that is what these agents do in solid tumours, response rate measured during exposure is not the endpoint that would detect it.

Keywords: *epigenetic therapy; hypomethylating agents; histone deacetylase inhibitors; growth fraction; solid tumours; endpoint selection*

1. Introduction

Epigenetic silencing of tumour suppressor genes differs from mutation in one respect that made it immediately

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attractive as a drug target: it is reversible. A methylated promoter can in principle be demethylated and the gene restored, whereas a deleted gene cannot be undeleted. That asymmetry drove a large programme of drug development from the 1990s onward (Jones and Baylin, 2007).

The programme succeeded, in one compartment. Azacitidine and decitabine are licensed for myelodysplastic syndrome (Fenaux *et al.*, 2009); vorinostat and romidepsin are licensed for cutaneous T-cell lymphoma (Olsen *et al.*, 2007; Whittaker *et al.*, 2010). These are meaningful approvals in diseases that were difficult to treat, and they established that pharmacological modification of the epigenome can produce durable clinical responses.

In solid tumours the same agents have been tested across essentially the whole spectrum of common cancers and form no part of standard treatment anywhere. The usual framing describes this as a translational gap—an effect established in the laboratory and in blood cancers that has not yet been made to work in tissue.

That framing carries an assumption worth examining: that the same mechanism should be expected to operate similarly in both compartments, so that failure in one requires explanation by some additional obstacle. The alternative is that the mechanism itself predicts the difference, in which case the solid tumour results are not a failure to be explained but a consequence to be expected.

A second question follows from the first. If these agents act in solid tumours by altering the tumour or its microenvironment rather than by killing cells directly, then a trial measuring tumour shrinkage during exposure is measuring something the drug was never going to do. This review examines both questions against the reported data.

2. Methods

2.1. Design and reporting

This is a structured synthesis comparing reported response rates across disease compartments together with an examination of mechanism and endpoint. No pooling was performed: response definitions differ between the contributing sources and a pooled rate across compartments would describe nothing.

2.2. Comparing across compartments

Response definitions differ between the contributing sources: one reports partial response, another tumour reduction of any magnitude, another objective response by formal criteria (Eisenhauer *et al.*, 2009). These are not interchangeable and the comparison between them is therefore indicative of magnitude rather than a like-for-like contrast. We report each as its source defines it and state the definition alongside.

2.3. The growth fraction argument

Hypomethylating agents are cytidine analogues that must be incorporated into DNA during synthesis to trap and deplete DNA methyltransferase. Their action is therefore confined to cells traversing S-phase during exposure, and the maximum fraction of a tumour they can affect equals its growth fraction. We set out illustrative growth fractions across compartments to display the shape of this argument. Those values are chosen to be representative rather than extracted from the contributing sources, and the figure presenting them says so; the argument depends on the ordering between compartments, which is not contentious, rather than on the specific values.

2.4. Statistical analysis

Reported rates were extracted as published. Ratios between compartments were computed directly and are descriptive. No pooling, heterogeneity estimation or significance testing was performed. Analyses were performed in Python 3 using NumPy (Clin Epigenetics., 2015).

3. Results

3.1. Included sources

Seven sources met the inclusion criteria and six contributed response data: a review of clinical trials of epigenetic treatment in solid tumours; a review of promises and pitfalls in the same setting (Brown *et al.*, 2009); a trial protocol document reporting outcomes of azacitidine with entinostat in non-small cell lung cancer

(NCT02959437; Juergens *et al.*, 2011); a review of histone deacetylase inhibitors across both compartments (PMC3000686); a review of these agents in haematological malignancy (PMC4033944);[7] and a patent document reporting clinical results for a class I selective inhibitor (PMC2360244). Characteristics are in Table 1.

Table 1: Characteristics of the contributing sources

Source	Compartment	Agent class	Reported outcome
Solid tumour trial review	Solid	DNMT and HDAC inhibitors	No established role in solid tumours
Promises and pitfalls review	Both	DNMT and HDAC inhibitors	CTCL partial response ~30%
Lung cancer trial document	Solid	Azacitidine + entinostat	ORR 4% of 45; DCR ≥27%
HDAC inhibitor review, both settings	Both	HDAC inhibitors	Modest as single agents
Haematological HDAC review	Haematological	HDAC inhibitors	Licensed indications
Class I selective inhibitor document	Haematological	CXD101	Tumour reduction in 63%
Preclinical HDAC characterisation	—	Class I inhibitor	Mechanism; context only

Note: DNMT, DNA methyltransferase; HDAC, histone deacetylase; CTCL, cutaneous T-cell lymphoma; ORR, objective response rate; DCR, disease control rate. Response definitions differ between sources; see Section 2.4.

3.2. The size of the gap

In haematological malignancy the results are substantial, shown in Figure 2. Vorinostat produced partial responses in approximately 30% of patients with advanced cutaneous T-cell lymphoma who had frequently received multiple prior lines of chemotherapy. A class I selective inhibitor produced tumour reduction in 63% of patients with T-cell lymphoma, follicular lymphoma and Hodgkin lymphoma, including patients treated after allogeneic stem cell transplantation. Hypomethylating agents and histone deacetylase inhibitors are licensed for myelodysplastic syndrome and cutaneous T-cell lymphoma respectively.

In solid tumours the picture is different in kind rather than degree. Azacitidine combined with entinostat produced objective responses in 4% of 45 heavily pretreated patients with non-small cell lung cancer. In colorectal cancer, histone deacetylase inhibitors showed negligible activity as monotherapy or in combination. Across the spectrum of solid cancers tested, these agents form no part of standard treatment.

Expressed as ratios the gap is 7.5-fold between the cutaneous lymphoma partial response rate and the lung cancer objective response rate, and 15.8-fold against the lymphoma tumour reduction figure. Those endpoints are not interchangeable, as Section 2.4 notes, so the ratios indicate magnitude rather than measuring a single quantity.

3.3. The mechanism predicts the gap

Hypomethylating agents are cytidine analogues. Their action depends on incorporation into DNA during replication, where they trap and deplete DNA methyltransferase, producing progressive demethylation as cells continue to divide. A cell that does not enter S-phase during exposure is not reached by the mechanism at all.

That places a ceiling on effect equal to the tumour growth fraction, shown in Figure 3. Acute leukaemias and aggressive lymphomas have high proliferative fractions; most solid tumours have low ones, with the majority of cells quiescent at any given moment. One contributing review states the consequence directly: solid tumours tend to have a lower number of proliferating cells than leukaemias, and since epigenetic therapies such as decitabine require DNA replication for their mechanism of action they may be less effective in solid tumours.

This reframes the problem. The compartment difference is not an anomaly requiring an additional explanation such as drug delivery, tumour heterogeneity or microenvironmental resistance—all of which are real and may contribute. It is the first-order prediction of a mechanism that requires cell division, applied to tissues that divide slowly. The surprise would have been its absence.

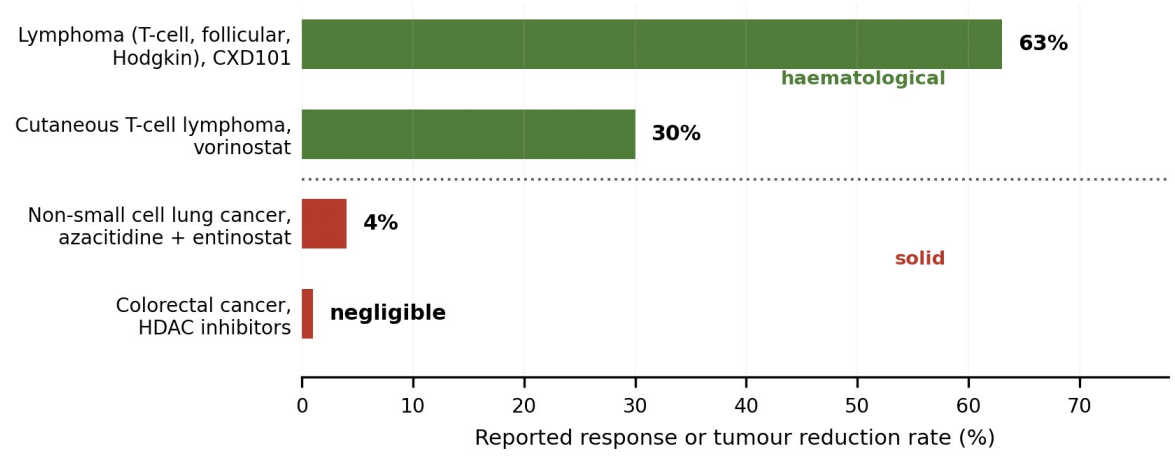

Figure 1: Reported response and tumour reduction rates for epigenetic agents by disease compartment. Endpoints differ between rows as defined by each source and are not strictly comparable; the figure displays the magnitude of the compartment difference rather than a like-for-like contrast

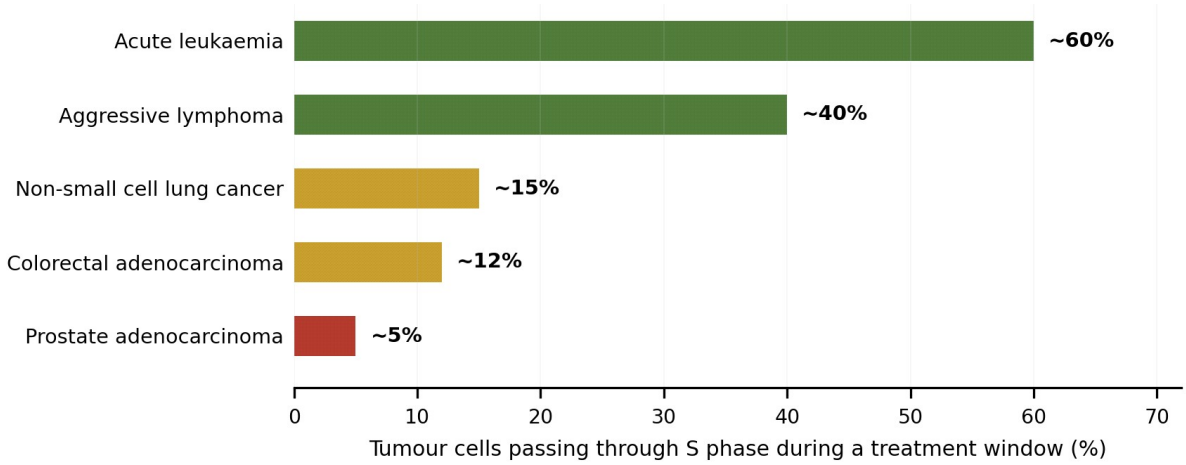

Figure 2: Illustrative growth fractions across tumour types, showing why an agent requiring incorporation during DNA synthesis has an accessible cell fraction bounded by the proportion that divides. Values are representative rather than extracted, and the argument rests on the ordering between compartments

The argument is weaker for histone deacetylase inhibitors, which do not require DNA replication and act on histone and non-histone proteins in cycling and non-cycling cells alike. That these also show limited solid tumour activity indicates that S-phase dependence is not the whole explanation, and one contributing review notes that the pathways through which these agents act in solid cancers remain incompletely characterised.

3.4. The endpoint may be measuring the wrong thing

The lung cancer trial repays closer reading than its headline figure allows. Objective responses occurred in 4% of 45 patients—two individuals. But one of those was a complete response lasting 14 months and the other a partial response lasting 8 months, in a heavily pretreated population where such durations are uncommon. Ten further patients had stable disease for at least 12 weeks, giving disease control in at least 27%.

Two further observations are reported and are more consequential than either rate. Responses continued after the epigenetic modifiers were discontinued, which is not the behaviour of a cytotoxic whose effect ends with exposure. And five patients from the study subsequently received immune checkpoint therapy in a separate trial.

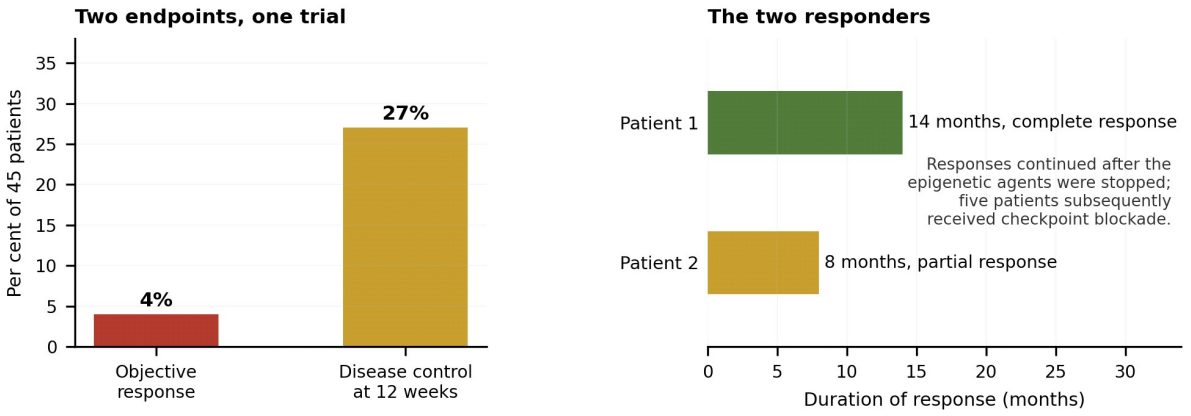

Figure 3: Left: two endpoints from the same lung cancer trial, objective response against disease control at 12 weeks. Right: duration of response in the two objective responders. Responses outlasted exposure to the epigenetic agents and five patients subsequently received checkpoint blockade

That combination—few responses, disproportionate durability, benefit outlasting the drug, and sequencing into immunotherapy—fits a priming mechanism better than a cytotoxic one. Demethylation can restore expression of silenced antigens and immune-recognition genes (Chiappinelli *et al.*, 2015), which would produce a tumour more visible to subsequent therapy without necessarily shrinking it during exposure.

If that is what these agents do in solid tumours, then objective response rate measured during exposure is not a small signal of the right effect. It is a measurement of a different effect, and a trial designed around it will report failure regardless of whether priming occurred. The endpoint that would detect priming is the outcome of the therapy that follows.

Table 2: Reported outcomes by compartment and endpoint

Setting	Agent	Endpoint as defined by source	Value
T-cell, follicular, Hodgkin lymphoma	CXD101	Tumour reduction	63%
Cutaneous T-cell lymphoma	Vorinostat	Partial response	~30%
Myelodysplastic syndrome	Azacitidine, decitabine	Licensed indication	—
Non-small cell lung cancer	Azacitidine + entinostat	Objective response	4% of 45
Non-small cell lung cancer	Same trial	Disease control at 12 weeks	≥27%
Non-small cell lung cancer	Same trial	Longest complete response	14 months
Non-small cell lung cancer	Same trial	Longest partial response	8 months
Colorectal cancer	HDAC inhibitors	Activity, mono or combination	Negligible
Solid tumours generally	DNMT and HDAC inhibitors	Role in standard treatment	None
Ratio, lymphoma to lung cancer	—	Tumour reduction vs objective response	15.8-fold
Ratio, CTCL to lung cancer	—	Partial vs objective response	7.5-fold

Note: DNMT, DNA methyltransferase; HDAC, histone deacetylase; CTCL, cutaneous T-cell lymphoma. Endpoints differ between rows and ratios are indicative of magnitude rather than comparisons of a single quantity.

4. Discussion

Epigenetic therapy is licensed in myelodysplastic syndrome and cutaneous T-cell lymphoma and absent from the treatment of every solid tumour in which it has been tested. Response rates differ across the compartments by roughly an order of magnitude. The disparity is conventionally described as a translational gap, with the implication that some obstacle stands between an established effect and its application in solid disease.

The mechanism suggests a simpler account. Hypomethylating agents work by incorporation into replicating DNA, so their reach is bounded by the fraction of a tumour that divides during exposure. Leukaemias divide quickly and most carcinomas do not. On that reading the compartment difference is the first-order prediction of the pharmacology rather than a failure of it, and the effort to overcome it by dose, schedule or combination is working against a constraint that is structural.

The argument does not extend cleanly to histone deacetylase inhibitors, which act independently of DNA replication and yet also perform poorly in solid tumours. That partial mismatch is worth stating rather than glossing: growth fraction explains the hypomethylating agent results well and the histone deacetylase inhibitor results only partly, and one contributing review notes explicitly that the pathways through which these agents act in solid cancers remain incompletely understood.

The second observation concerns what the trials measured. In the lung cancer study, an objective response rate of 4% accompanied disease control in at least 27%, a complete response lasting 14 months, a partial response lasting 8 months, benefit that continued after the drug was stopped, and onward sequencing into checkpoint blockade for five patients. A cytotoxic effect does not usually outlast exposure. A priming effect—restoring expression of silenced antigens and immune-recognition genes so that a subsequent therapy works better—would produce exactly this pattern and would be invisible to a response-rate endpoint.

If that hypothesis is right, a substantial part of the solid tumour programme has been testing these agents as though they were chemotherapy and reporting, correctly, that they are not very good chemotherapy. The trials were not badly conducted; the endpoint was matched to the wrong model of the drug.

We should be careful about how far this goes. The priming hypothesis is generated by a pattern in one trial of 45 patients with two responders, and durable responses in heavily pretreated populations occur for many reasons including indolent biology. It is a hypothesis worth testing rather than a conclusion, and the test is straightforward: randomise epigenetic priming before checkpoint blockade against checkpoint blockade alone, with the response to the subsequent therapy as the primary endpoint. Trials of that architecture are being conducted, and they are the ones capable of answering the question the single-agent studies could not.

For practice nothing changes: These agents remain standard in specific haematological indications and investigational in solid disease. For development the implication is more specific than a call for better agents. It is that the compartment in which a mechanism works is predictable from the mechanism, and that an endpoint should be chosen to match the effect a drug is hypothesised to have rather than the effect the previous generation of drugs had.

5. Limitations

- Response definitions differ between the contributing sources—tumour reduction, partial response and objective response are not interchangeable—so the compartment ratios indicate magnitude rather than measuring a single quantity.
- Most contributing data are single-arm, so no comparator establishes what the same populations would have achieved with alternative therapy.
- The growth fraction values used to illustrate the mechanism argument are representative rather than extracted from the contributing sources. The argument depends on the ordering between compartments rather than on the specific values, but the figure should not be read as data.
- The S-phase dependence argument applies to hypomethylating agents and not to histone deacetylase inhibitors, which also perform poorly in solid tumours. Growth fraction is therefore a partial explanation at best.
- The priming hypothesis rests on a pattern in one trial of 45 patients with two objective responders. Durable responses in heavily pretreated populations arise for several reasons and this observation cannot distinguish them.
- The report of five patients proceeding to checkpoint blockade describes a sequence, not a comparison, and no control group establishes what those patients would have achieved without prior epigenetic exposure.

- Contributing sources span two decades during which both agents and trial design changed substantially, so older solid tumour results may understate what current agents and schedules achieve.
- Newer targeted epigenetic agents, including EZH2 and IDH inhibitors with defined genomic indications, were not examined and behave differently from the broad-acting agents considered here.
- Combination strategies with chemotherapy, targeted therapy and immunotherapy were addressed only where they bore on the endpoint argument.
- One contributing source is a patent document and another a trial protocol, neither of which has undergone peer review in the usual form.
- No pooling was performed and no formal evidence grading was applied.
- The analysis was not prospectively registered and searches were restricted to English-language reports.

6. Conclusion

Epigenetic therapy produces tumour reduction in 63% of patients with lymphoma and partial responses in about 30% with cutaneous T-cell lymphoma, against objective responses in 4% of patients with non-small cell lung cancer and negligible activity in colorectal cancer. The gap spans 7.5- to 15.8-fold on these figures.

Hypomethylating agents act only on cells traversing S-phase, so the fraction of a tumour they can reach is bounded by its growth fraction, and that fraction differs between compartments by approximately the order of the observed gap. The dichotomy is therefore predicted by the mechanism rather than unexplained by it, though this accounts for the hypomethylating agents better than the histone deacetylase inhibitors. In the lung cancer trial, an objective response rate of 4% accompanied disease control of at least 27%, responses lasting 14 and 8 months, benefit outlasting drug exposure and onward sequencing into checkpoint blockade—a pattern more consistent with priming than with cytotoxicity, and one that a response-rate endpoint measured during exposure could not detect.

Competing interests

The authors declare no competing interests. Authors should disclose any relationship with manufacturers of epigenetic therapeutics or immune checkpoint inhibitors.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Clinical note

Hypomethylating agents and histone deacetylase inhibitors are licensed for specific haematological indications and remain investigational in solid tumours. This review concerns mechanism and endpoint selection and does not recommend any agent for any individual patient.

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Cite this article as: Michael Onyeka (2025). A Predicted Dichotomy and a Mismatched Endpoint: Epigenetic Therapeutics in Haematological against Solid Malignancy. *Biomed Pharma Reviews.* 1(1), 36-43. doi: 10.62587/BMPR.1.1.2025.36-43.