

**REVIEW**

Use of the Naphthoquinone YM155 (Sepantronium Bromide) in the Treatment of Cancer: A Systematic Review and Meta-Synthesis

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ABSTRACT

Most cancer cells overexpress the anti-apoptotic protein survivin and display redox dysregulation originating from genotypic and phenotypic alterations. These disturbances contribute to the uncontrolled proliferation, invasion, and chemoresistance of cancer cells, yet they also represent a specific vulnerability that could be exploited therapeutically in selected tumors. YM155 (sepantronium bromide) is a naphthoquinone-containing imidazole-based compound that selectively inhibits survivin expression at the transcriptional and post-transcriptional levels. Here, we performed a systematic review and meta-analysis of clinical studies in which YM155 was administered as monotherapy or combination therapy for patients with cancer. We assessed fully or partially reported clinical outcomes and pharmacological parameters, and further performed subgroup analysis based on tumor type and treatment regimen. Our comprehensive analysis, which included patients of many ethnicities, demonstrated that YM155 was effective as a monotherapy or combination therapy. Clinical benefits, including regression and/or stabilization of tumor progression and prolonged survival, were observed within a reasonable time after treatment initiation, and YM155 displayed good synergistic effects with combination drugs. YM155 appears to be effective against a wide range of tumor types and has an acceptable safety profile, with the main toxicities being decreased blood cell counts; fatigue/weakness; renal, hepatic, and/or cardiac issues; and electrolyte disturbance.

KEYWORDS

YM155 (sepantronium bromide); systematic review; safety; anticancer effect; meta-synthesis; Naphthoquinone



Nomenclature

AE	Adverse events
AUC	Area under the curve
BIRC5	Baculoviral inhibitor of apoptosis repeat-containing 5
CBR	Clinical benefit rate
CCNS	Cell cycle nonspecific
CCS	Cell cycle specific
Cl	Clearance
Cmax	Maximum plasma concentration
Css	Steady-state plasma concentration
DLT	Dose-limiting toxicity
DOR	Duration of response
Exc	Renal excretion
HAE	Hematological adverse effect
HM	Hematological malignancy
IAP	Inhibitor of apoptosis
MTD	Maximum tolerated dose
NHAE	Non-Hematological adverse effect
NHL	Non-Hodgkin lymphoma
NQ	Naphthoquinone
OR	Overall response
OS	Overall survival
PFS	Progression-free survival
PICOSO	Participants, interventions, outcomes, comparisons, study, other
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
QNRT	Quantitative non-randomized study
QRCT	Quantitative randomized controlled trial
ST	Solid tumor
T1/2	Half-life
TTR	Time to response
Vd	Volume of distribution
YM155	Sepantronium bromide

1 Introduction

Survivin (also known as BIRC5), a member of the inhibitor of apoptosis (IAP) family, is essential for cell division and is highly expressed during embryonic development [1,2]. Although it is rarely expressed in adult tissues, survivin is also upregulated in nearly all human tumors [3,4], where it is associated with a more aggressive phenotype, shorter survival times, and a decreased response to chemotherapy [5–7]. Due to its key role in apoptosis, proliferation, and angiogenesis, survivin has received increasing attention as a potential oncotherapeutic target [8,9]. However, survivin is an intracellular protein, does not have intrinsic enzymatic activity, and has few potential druggable sites, making it a relatively complex and difficult therapeutic target [10].

Despite these problems, various strategies have been employed to develop drugs that interfere with survivin expression at the transcriptional and post-translational levels or impair its function [11–14]. Among the candidate drugs, YM155 (sepantronium bromide) is a selective inhibitor of survivin gene expression that has been comprehensively evaluated in both preclinical and clinical studies with promising results [3].

YM155 is a low molecular weight, Naphthoquinone (NQ)-containing imidazole-based compound that was first described in 2007. YM155 suppresses survivin gene transcription by binding specifically to an SP1-rich region in the survivin core promoter, and its inhibition of cell proliferation is thought to be cell cycle-independent [15,16].

The main goal of cancer chemotherapy is to selectively destroy cancer cells while minimizing toxicity to normal cells [17]. In this regard, YM155 holds promise as a chemotherapeutic agent for several reasons. First, as noted above, survivin is overexpressed in almost all malignancies but is virtually undetectable in most normal adult tissues [18]. Second, YM155-mediated repression of survivin transcription is highly selective, and no activity against other IAP family proteins has been reported to date [15,19]. Third, redox dysregulation originating from metabolic alterations contributes to the control of cancer cell proliferation, survival, invasion, and metastasis, suggesting that these features could provide a specific vulnerability of malignant cells that can be selectively targeted by redox chemotherapeutic agents [20,21]. YM155 has been shown to generate reactive oxygen species in the mitochondria. Its NQ pharmacophore undergoes two-electron reduction within the cell, causing profound depletion of reducing elements and disturbing redox homeostasis in cancer cells [22–26].

Vitamin K was first shown to be an NQ-containing antineoplastic agent in 1967 [27], and was tested in clinical research for the first time in 1987 [28]. Since then, an increasing number of preclinical and clinical studies have explored the therapeutic potential of natural and synthetic NQ compounds. The members of NQs' large family, all contain a common “quinone” ring, which binds and alters macromolecules through arylation reaction, and the electron-donating group, such as—methoxy (-OCH₃) and -methyl (-CH₃), which can promote the anti-proliferation effect [29–32]. The common NQs molecular structures are depicted in Fig. 1.

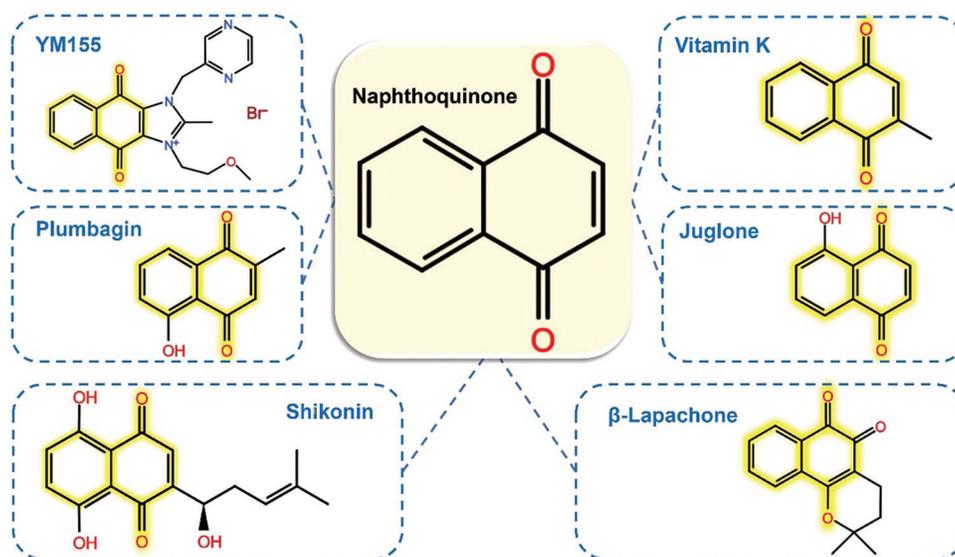


Figure 1: Structural comparison of the most common Naphthoquinone derivatives for anticancer activity

To date, several observational clinical studies have been performed with YM155; however, inconsistent results have been reported with regard to its efficacy in inhibiting cancer progression.

Systematic reviews are the gold standard method of synthesizing and summarizing all relevant primary publications in an unbiased manner, and with high evidence; facilitating decision-making and developing guidelines for patient care [33,34]. Recent advances in systematic review methods have made it possible

to combine quantitative and qualitative methods, approaches, and concepts [35–40]. Through this powerful study design, we aimed here to clarify the anticancer effects of YM155 in clinical trials and thereby facilitate clinical decision-making for the treatment of cancer patients.

2 Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [41] and followed an established protocol that has been registered at PROSPERO (record #CRD42019135273, protocol #135273).

2.1 Strategy for Literature Search

To search relevant articles, a concept map was created via MeSH terms and controlled vocabularies based on PICOSO design (Participants, Interventions, Outcomes, Comparisons, Study, Other), then integrated with electronic databases through an advanced filter and update system. The sources were MEDLINE, Cochrane Library, ClinicalTrials.gov, Japan Medical Abstract Society, J-Stage, and Web of Science. Additional manual searches were performed for references from these systematically gathered articles. No restrictions were applied to identify eligible studies, except only articles published in English and Japanese were included. Ethics Committee approval for this study was waived because no human participants or animals were involved.

2.2 Study Selection and Inclusion Criteria

The studies that met the following inclusion criteria were accepted for the qualitative and quantitative analyses: (1) Participants: any patients with cancer, including solid and hematologic malignancies, with no gender, age, or ethnicity restrictions; (2) Intervention: YM155; (3) Controls: quantitative studies included a “non-exposed control group” or “standard of care” as comparators, whereas qualitative studies included “not applicable” as a control; (4) Outcome: studies that assessed the outcomes of clinical and pharmacological parameters; (5) Study design: prospective or retrospective clinical studies focused on the treatment of cancer patients with YM155. Exclusion criteria: (1) Non-cancerous patient, (2) Therapeutic agents other than YM155, (3) Pre-clinical studies or review articles.

2.3 Data Extraction and Management

Data from full texts of potentially eligible studies were extracted independently by two authors as follows. (1) Major characteristics, including the first author, country, year and type of publication, study design and time, comparator, sample size, information about patients, therapeutic strategy, follow-up time with measuring interval, and achievement of the individual study; (2) clinical outcomes, comprising overall response (OR), clinical benefit rate (CBR), overall survival (OS), progression-free survival (PFS), duration of response (DOR), time to response (TTR), and adverse events (AEs); (3) pharmacological parameters, including toxicity (dose-limiting toxicity [DLT] and maximum tolerated dose [MTD]), absorption (maximum plasma concentration [C_{max}] and steady-state plasma concentration [C_{ss}]), volume of distribution (V_d), elimination (clearance [Cl], renal excretion [Exc], and half-life [T_{1/2}]), and area under the curve (AUC). Microsoft Access was used to collect all information at this stage to improve efficiency and minimize mistakes.

2.4 Quality Assessment and Grading of Evidence

The methodological quality of the included studies was assessed via the Mixed Methods Appraisal Tool (MMAT, version 2018) [42], which permits the appraisal of five categories of studies with a selection algorithm. Each item was classified as “yes”, “no”, or “can’t tell”, which determined the general quality when taken together. Two investigators independently evaluated the data and disagreements were resolved by discussion with a third investigator. Ultimately, a total of 14 studies was included in the

analysis (Appendixes A and B) [43–56]. GRADEpro from “Cochrane Consumers and Communication” was employed for assessing the quality of evidence [53].

3 Results

3.1 Study Selection

Using a cutoff date of July 1st, 2020, a total of 83 publications were identified, from which 17 duplicates and 7 considered irrelevant were excluded (Fig. 2). The remaining 59 articles originated from 14 countries and were written in English or Japanese. Detailed information on the included clinical studies is provided in Appendix C. Through the initial screening of titles and abstracts, 15 clinical studies and 44 non-clinical studies were identified, and the non-clinical studies were reserved for a future preclinical systematic analysis.

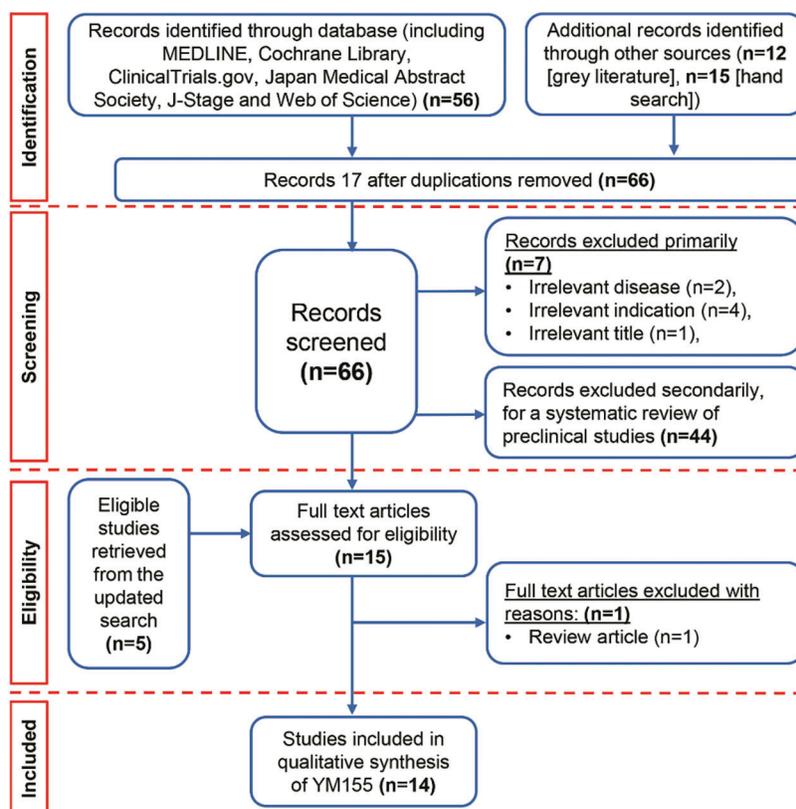


Figure 2: PRISMA chart for YM155

Finally, a total of 14 studies of acceptable quality were included for systematic review, of which 1 was a quantitative randomized controlled trial (QRCT) [47], and 13 were quantitative non-randomized studies (QNRSS) [43–46,48–56]. The quality assessment of all included studies is provided in Appendix D. For the QNRSSs, the most common bias was related to completeness of outcomes, with estimations of six (42.8%) high risk and two (14.3%) unclear. This bias may be related to the inclusion of patients with advanced cancer in those studies.

3.2 Study Characteristics

The study characteristics are shown in Table 1. The outcomes were influenced by the trial phase and fell into two main categories: clinical efficacy and pharmacological outcomes. Regarding the clinical outcomes,

13 phase I or II studies included data on AEs (n = 13) [43,44,46–56], OR (n = 11) [46–56], CBR (n = 10) [46–56], OS (n = 8) [46–48,50–53,56], PFS (n = 8) [46–48,50–53,56], TTR (n = 2) [48,53], DOR (n = 8) [47,48,52–56], and synergism (n = 4) [47,50,51,53]. Eleven of the phases I and II studies included pharmacological outcome data on absorption (Cmax [n = 1] [55] and C_{ss} [n = 11] [43–46,48,50,51,53–56], V_d (n = 4) [43,44,50,55], Cl (n = 8) [43–46,50,54–56], Exc (n = 2) [43,55], T_{1/2} (n = 6) [43,45,48,50,54,55], AUC (n = 4) [43,45,50,55], and toxicity (DLT [n = 5] [43,50,54–56], and MTD [n = 3] [50,54,55]).

Table 1: Characteristic table of included studies

General information		Patients		Intervention	
First author (country)	Publication type (year)	Sample size	Cancer type	Route: LD regimen (d/w) × cycle	Combo? (dose)
Aoyama et al. (Japan) [43]	JA (2012)	33	ST (mixed)	CIVI: 1.8–10.6 mg/m ² (d1-7/3w)	no
Aoyama et al. (Japan) [44]	JA (2013)	96	ST (mixed)	CIVI: 4.8 mg/m ² (d1-7/3w)	no
Aoyama et al. (Japan) [45]	JA (2013a)	74 (FAS), 67 (PPS)	Mixed (ST+HM)	CIVI: 1.8–10.6 mg/m ² (d1-7/3w)	no
Cheson et al. (USA) [46]	JA (2012)	41 (FAS), 39 (PPS)	HM (DLBCL)	CIVI: 5 mg/m ² (d1-7/3w) × 15	no
Clemens et al. (Germany) [47]	JA (2015)	50	ST (breast cancer)	CIVI: 5 mg/m ² (d1-7/3w)	Docetaxel (75 mg/m ²)
Giaccone et al. (Holland) [48]	JA (2009)	37	ST (lung cancer)	CIVI: 4.8 mg/m ² (d1-7/3w) × 6c	no
Karavasilis et al. (UK) [49]	Poster (2016)	32	ST (prostate)	CIVI: 4.8 mg/m ² (d1-7/3w)	no
Kelly et al. (USA) [50]	JA (2013)	41 [p1 = 22, p2 = 19]	ST (lung cancer)	p1: CIVI: 3.6–12 mg/m ² (d1-3/3w) × 6; p2: 10 mg/m ² × 6	Carboplatin (St/D), Paclitaxel (200 mg/m ²)
Kudchadkar et al. (Georgia) [51]	JA (2015)	64	ST (melanoma)	CIVI: 5 mg/m ² (d1-7/3w)	Docetaxel (75–100 mg/m ²)
Lewis et al. (USA) [52]	JA (2011)	34	ST (melanoma)	CIVI: 4.8 mg/m ² (d1-7/3w) × 6	no
Papadopoulos et al. (USA) [53]	JA (2016)	41 (FAS), 34 (PPS)	HM (NH lymphoma)	CIVI: 5 mg/m ² (d1-7/2w) × 10	Rituximab (375 mg/m ²) (d1&8/c1-4) × 4
Satoh et al. (Japan) [54]	JA (2009)	33	ST (mixed)	CIVI: 1.8–10.6 mg/m ² (d1-7/3w) × 6	no
Tolcher et al. (USA) [55]	JA (2008)	41	Mixed (ST+HM)	CIVI: 1.8–6.0 mg/m ² (d1-7/3w)	no

(Continued)

Table 1 (continued)					
General information		Patients		Intervention	
First author (country)	Publication type (year)	Sample size	Cancer type	Route: LD regimen (d/w) × cycle	Combo? (dose)
Tolcher et al. (USA) [56]	JA (2011)	35	ST (prostate)	CIVI: 4.8 mg/m ² (d1-7/3w) × 6	no
Abbreviation: JA = Journal article, SD = Study design, St/D = Standard dose, QNRS = Quantitative non randomized study, QRCT = Quantitative randomized controlled Trials, SC = Standard care, BA = Before-after, p = phase, ST = Solid tumour, HM = Haematological malignancy, NHL = Non-Hodgkin lymphoma, N/A = Not available, y = year, m = month, w = week, d = day, c = cycle, PPS = Per protocol set, FAS = Full analysis set, CBR = Clinical benefit rate, CIVI = Continuous intravenous infusion, AUC = Area under curve, C _{ss} = Plasma steady-state concentration, C _{max} = Plasma maximum concentration, Cl = Clearance, V _d = Volume distribution, T _{1/2} = Half-life, MTD = Maximum-tolerated dose, DLT = Dose limiting toxicity, AE = Adverse effect, Exc = Renal excretion, OR = Overall response, OS = Overall survival, DOR = Duration of response, PFS = Progression free survival, TTR = Time to response.					
Comparison	Outcome/study aim		Other		
Study arm	PD	PK	Study design		Achievement of endpoint
BA, 1-arm	AE	C _{ss} , T _{1/2} , Cl, AUC, V _d , DLT, Exc	QNRS, phase I (open-label, single centre)		success
BA, 1-arm	AE	C _{ss} , Cl, V _d	QNRS, phase II (open-label, multi-centre)		success
BA, 1-arm	N/A	C _{ss} , Cl, AUC, T _{1/2} , MTD, DLT,	QNRS, phase I (open-label, multi centre)		success
BA, 1-arm	OR, AE, OS, PFS, CBR	C _{ss} , Cl	QNRS, phase II (open-label, multi-centre)		failure
SC, 2-arm	OR, DOR, OS, PFS, AE, CBR	N/A	QRCT, phase II (open-label, multicentre)		failure
BA, 1-arm	OR, AE, OS, PFS, TTR, DOR, CBR	C _{ss} , T _{1/2}	QNRS, phase II (open-label, multicentre)		success
BA, 1-arm	OR, AE, CBR	N/A	QNRS, phase II		success
BA, 1-arm	OR, AE, OS, PFS, CBR	MTD, DLT, T _{1/2} , Cl, C _{ss} , V _d , AUC	QNRS, phase I/II		failure
BA, 1-arm	OR, DOR, AE, OS, PFS, CBR	C _{ss}	QNRS, phase II (open-label, multi-centre)		failure
BA, 1-arm	OR, AE, OS, PFS, DOR, CBR	N/A	QNRS, phase II (open-label, multi-centre)		failure
BA, 1-arm	OR, TTR, AE, OS, PFS, DOR, CBR	C _{ss}	QNRS, phase II (multi-centre, open-label)		success
BA, 1-arm	OR, AE, DOR, CBR	DLT, MTD, C _{ss} , Cl, T _{1/2}	QNRS, phase I (open-label, single-centre)		success
BA, 1-arm	OR, AE, DOR, CBR	DLT, MTD, C _{ss} , Cl, T _{1/2} , AUC, V _d , C _{max} , Exc	QNRS, phase I		success
BA, 1-arm	OR, AE, PFS, OS, CBR, DOR	Cl, C _{ss} , DLT	QNRS, phase II		success

3.2.1 Participants

The number of participants in each study ranged from 32 to 96, and the mean and median age both ranged between 59 and 67 years of age. A total of 652 patients were included, of whom 391 (67.7%) were male and 187 (32.3%) were female, with the data being unclear for the remaining 74 patients. The tumor types were heterogeneous, therefore, we formed three subgroups of hematological malignancies (HM), which included 2 studies [46,53]; solid tumors (ST), which included 10 studies [43,44,47–52,54,56]; and mixed HM/ST, which included 2 studies [45,55].

Specifically, the HM group consisted of 87 patients with 4 cancers (79 with diffuse large B-cell lymphoma, 1 with peripheral T-cell non-Hodgkin lymphoma [NHL], 2 with follicular NHL, and 5 with unknown NHL). The ST group consisted of 129 patients with melanoma, 110 with prostate cancer, 52 with breast cancers (37 ductal, 4 lobular, 2 Paget's disease, 2 unknown breast, and 7 others), and 47 with other STs (9 colorectal, 6 esophageal, 3 thymic, 2 thyroid, 2 malignant fibrous histiocytoma, 2 mesothelioma, 4 sarcoma, 2 liver, 2 ovarian, 15 others), The ST/HM group consisted of 33 patients with unknown mixed STs and 74 with unknown mixed STs and HMs. Detailed information about the patients is given in [Table 2](#).

Table 2: Characteristics of patients

First author	Gender (M/F)	Mean or median age	Race or ethnicity	Cancer type [III–IV stage of people]
Aoyama et al. [43]	23/10	59 (26–81)*	All Japanese	ST (mixed) [All]
Aoyama et al. [44]	79/17	64 (29–90)	African American 4 (4.2%), Caucasian 44 (45.8%), Caucasian, Hispanic or Latino 8 (8.3%), Caucasian, Non-Hispanic or Latino 40 (41.7%)	ST (mixed) [All]
Aoyama et al. [45]	N/A	N/A	American 35 (52.2%), Japanese 32 (47.8%)	Mixed (ST+HM) [All]
Cheson et al. [46]	26/15	61 (23–85)	White 38 (92.7%), Black/African American 2 (4.9%), Asian 1 (2.4%)	HM (DLBCL) [30 (73.2%)]
Clemens et al. [47]	0/50	57.0 (34–79)*	White 47 (94%), Black/African American 1 (2%), Asian 1 (2%), Other 1 (2%)	ST (breast cancer) [15 (30%)]
Giaccone et al. [48]	28/9	61.5 (36–79)	All white	ST (NSCLC) [All]
Karavasilis et al. [49]	32/0	67 (53–81)*	N/A	ST (prostate) [All]
Kelly et al. [50]	21/20	62 (38–79)*	White 13 (59%), African American 1 (4%), Asian 5 (23%), Hispanic/Latino 3 (14%)	ST (lung cancer) [All]
Kudchadkar et al. [51]	44/20	59 (26–79)*	Not Hispanic/Latino 63 (98.4%), Hispanic or Latino 1 (1.6%)	ST (melanoma) [All]
Lewis et al. [52]	23/11	63 (29–90)*	N/A	ST (melanoma) [All]
Papadopoulos et al. [53]	26/15	64 (29–82)*	White 40 (97.6%), Black/African American 1 (2.4%)	HM (NHL) [All]
Satoh et al. [54]	23/10	59 (26–81)*	N/A	ST (mixed) [All]
Tolcher et al. [55]	31/10	61 (29–78)*	N/A	Mixed (ST+HM) [All]

(Continued)

Table 2 (continued)

First author	Gender (M/F)	Mean or median age	Race or ethnicity	Cancer type [III–IV stage of people]
Tolcher et al. [56]	35/0	67 (53–81)*	Caucasian 32 (91.4%), Black 3 (8.6%),	ST (prostate) [All]
Note: * = median; Abbreviation: p = phase, ST = Solid tumour, HM = Haematological malignancy, NHL = Non-Hodgkin lymphoma, N/A = Not available, c = cycle, CTX = Chemotherapy, DLBCL = Diffuse large B-cell lymphoma, NSCLC = Non-small-cell lung carcinoma, HRPC = Hormone refractory prostate cancer, ASCT = Autologous stem cell transplant, FL = Follicular lymphoma, N = Number.				
Detailed information about cancer			Median cycle/time	ECOG performance status
N/A (refractory advanced)			1 cycle = 31; 2 cycles = 15	All <3
NSLC = 33 (34.4%), HRPC = 34 (35.4%), Melanoma = 29 (30.2%)			1–6 cycles	Grade 0 = 38 (39.6%), Grade 1 = 53 (55.2%), Grade 2 = 5 (5.2%)
N/A (refractory advanced)			All 2 cycles	N/A
Confirmed histology 34 (82.9%), Samples were not available 5 (12.2%), Transformation 2 (4.9%) [1- peripheral T-cell NHL, 1-follicular NHL]			3 (1–12) cycles*	All ≤2
Ductal 37 (74%), Lobular 4 (8%), Paget's disease 2 (4%), Other 7 (14%)			6 cycles*	All ≤1
Adenocarcinoma 17 (45.9%), SCC 15 (40.5%), Large cell carcinoma 5 (13.5%)			2 (1–10) cycles	Grade 0 = 5 (13.5%), Grade 1 = 29 (78.4%), Grade 2 = 3 (8.1%)
HRPC			3 (1–10) cycles	All ≤2
Adenocarcinoma 25 (60.9%), Bronchioalveolar 4 (9.8%), Squamous cell carcinoma 5 (12.2%), Large cell 3 (7.3%), Small cell 1, Adenoid cystic 1 (2.4%), Angiosarcoma 1 (2.4%), Unknown origin 1 (2.4%)			p1 = at least 1 cycle, p2 = at least 2 cycles	N/A
Metastatic (M) classification: M1a and M1b 17 (26.6%), M1c 47 (73.4%)			70.5 days*	Grade 0 = 41 (64.1%), Grade 1 = 23 (35.9%),
Stage: IIIc 4 (11.8%), IV 30 (88.2%), M1a 1 (3%), M1b 12 (40%), M1c 17 (57%)			32/34 (94.1%) received 2 or more; 9/34 (26.5%) received 6 or more	Grade 0 = 27 (79.4%), Grade 1 = 7 (20.6%)
DLBCL 40 (97.6%), Grade III FL 1 (2.4%)			8 (0–61)*	All ≤1
NSCLC 7 (21.2%), Oesophageal 6 (18.2%), Colorectal 4 (12.1%), Thymic 3 (9.1%), Thyroid 2 (6.1%), MFH 2 (6.1%), Mesothelioma 2 (6.1%), Others 7 (21.2%)			All at least 1 (1–19)	Grade 0 = 3 (9.1%), Grade 1 = 29 (87.9%), Grade 2 = 1 (3%)
Prostate 9 (21.9%), Colorectal 5 (12.2%), NHL 5 (12.2%), Sarcoma 4 (9.8%), Breast 2 (4.9%), Liver 2 (4.9%), NSCLC 2 (4.9%), Melanoma 2 (4.9%), Ovarian 2 (4.9%), others 8 (19.5%)			3 (1–16)	Grade 0 = 9 (22%), Grade 1 = 30 (73.2%), Grade 2 = 2 (4.8%)
Gleason score at diagnosis mean of 8 (5–9)			3 (1–16+)	Grade 0 = 10 (28.6%), Grade 1 = 22 (62.9%), Grade 2 = 3 (8.5%)

Note: * = median; Abbreviation: p = phase, ST = Solid tumour, HM = Haematological malignancy, NHL = Non-Hodgkin lymphoma, N/A = Not available, c = cycle, CTX = Chemotherapy, DLBCL = Diffuse large B-cell lymphoma, NSCLC = Non-small-cell lung carcinoma, HRPC = Hormone refractory prostate cancer, ASCT = Autologous stem cell transplant, FL = Follicular lymphoma, N = Number.

Among the 14 studies, 10 used YM155 as monotherapy [43–46,48,49,52,54–56], and 4 used YM155 in combination with other chemotherapeutic agents [47,50,51,53]. Therefore, we created subgroups based on the therapeutic strategy. In 12 studies, YM155 was administered by continuous intravenous infusion at doses ranging from 1.8 to 12 mg/m² for 168 h on a 21-day cycle.

3.2.2 Therapeutic Strategy

The remaining two studies used combined regimens [50,53]: one used an infusion time of 72 h, and the second performed the treatment on a 14-day cycle. The treatment plans are described in Table 1. Depending on the tumor types, the combination therapies consisted of YM155 and either cell cycle-specific and or cell cycle-non-specific agents. The cell cycle-specific/mitotic inhibitors (docetaxel, paclitaxel) were administered for melanoma and breast and lung cancers, whereas the cell cycle-non-specific agent was rituximab for patients with B-cell NHL and platinum-based therapy (carboplatin) for patients with lung cancers. Crosstalk between single and combination treatment of YM155 in different cancer types can be seen in Table 3.

Table 3: Single and combination treatment of YM155 in different cancer types

Treatment	Tumor type	Tumor types in detail	Sample size	
Single treatment	YM155	Solid tumor		
		Lung	Adenocarcinoma 17, SCC 15, Large cell carcinoma 5, NSCLC 42, Mesothelioma 2	81
		Melanoma	Stage: IIIc 4, IV 30, M1a 1, M1b 12, M1c 17, N/A stage: 31	95
		Prostate	HRPC 66, Gleason score at diagnosis mean of 8 (5–9) 44	110
		GI cancer	Colorectal 9, Esophageal 6, Liver 2	17
		Others	Sarcoma 4, Breast 2, Ovarian 2, Thymic 3, Thyroid 2, MFH 2, Others 15, N/A (refractory advanced) 33	63
	Hematological malignancies	Confirmed histology 34, Samples were not available 5, Transformation 2 [1- peripheral T-cell NHL, 1-follicular NHL], NHL 5	46	
	Mixed (ST+HM)	N/A (refractory advanced)	74 (FAS), 67 (PPS)	
Combined treatment	Carboplatin, Paclitaxel	Solid tumor		
		Lung cancer	Adenocarcinoma 25, Bronchioalveolar 4, Squamous cell carcinoma 5, Large cell 3, Small cell 1, Adenoid cystic 1, Angiosarcoma 1, Unknown origin 1	41 [p1 = 22, p2 = 19]
	Docetaxel	Melanoma	Metastatic (M) classification: M1a and M1b 17, M1c 47,	64
		Breast cancer	Ductal 37, Lobular 4, Paget's disease 2, Other 7	50
Rituximab	HM (NHL)	DLBCL 40, Grade III FL 1	41 (FAS), 34 (PPS)	

Abbreviation: p = phase, ST = Solid tumor, HM = Hematological malignancy, NHL = Non-Hodgkin lymphoma, N/A = Not available, DLBCL = Diffuse large B-cell lymphoma, NSCLC = Non-small-cell lung carcinoma, HRPC = Hormone refractory prostate cancer, FL = Follicular lymphoma.

3.3 Clinical Outcomes

3.3.1 Efficacy of YM155

All outcomes related to efficacy from the primary studies are listed in Tables 4 and 5. Data on OR were extracted from the QRCT study and 10 QNRS studies [46–56], which in total involved 449 cancer patients treated with YM155 monotherapy or combination therapy. Among the 11 studies, one [56] did not provide CBR outcomes, resulting in data for 408 patients from 10 studies for CBR. The average OR rate (ORR) was 14.04% (range 0%–43.9%, n = 11) and the average CBR was 49.4% (range 6.3%–89.5%, n = 10). For the HM and ST subgroups based on tumor types, the average ORR was 37.1% (7.3%–60.0%, n = 3) and

11.1% (0%–27.3%, n = 10), respectively; and the average CBR was 50.03% (34.2%–65.9%, n = 2) and 49.2% (6.3%–89.5%, n = 9), respectively. After subgrouping based on therapeutic strategy, the YM155 monotherapy and combination therapy subgroups had ORRs of 6.9% (0%–14.6%, n = 7) and 24.04% (10.55%–43.9%, n = 5), respectively, and CBRs of 28.1% (6.35%–43.2%, n = 7) and 74.8% (64.1%–89.5%, n = 5), respectively. The average median TTR was 1.78 months (n = 2, 78 patients), while the average median DOR was greater than 2 months (n = 8, 301 patients) although the precise DOR could not be determined because the original data were expressed in various forms (e.g., range, median). A total of 6 studies involving 261 patients provided data on OS [43,44,46–48,52], and 4 studies involving 176 patients also gave estimates of the 1-year OS rate [44,46–48].

Table 4: Clinical efficacy of YM155 treatment in advanced cancer patients

First author	OR	CBR	TTR	DOR
Cheson et al. [46]	3/41 (7.32%)	14/41 (34.15%)	N/A	N/A
Clemens et al. [47]	13/50 (26%)	41/50 (82%)	N/A	7.72 m (95% CI, 7.28–8.75 m)*
Giaccone et al. [48]	2/37 (5.4%)	16/37 (43.2%)	1.65 m (1.6–1.7)*	range 3.7 m (2.7–4.7 m) [for SD = 2.8 m]*
Karavasilis et al. [49]	2/32 (6.25%)	2/32 (6.25%)	N/A	N/A
Kelly et al. [50]	p1 = 6/22 (27.3%), p2 = 2/19 (10.5%)	p1 = 16/22 (72.7%), p2 = 17/19 (89.5%)	N/A	N/A
Kudchadkar et al. [51]	8/64 (12.5%)	41/64 (64.1%)	N/A	2.35 m* [for SD = 5.03 m]*
Lewis et al. [52]	4/34 (11.8%)	9/34 (26.5%)	N/A	N/A
Papadopoulos et al. [53]	18/41 (43.9%)	27/41 (65.9%)	1.9 m (95% CI: 1.7–1.9)*	not reached (95% CI, 5.9 -N/E)
Satoh et al. [54]	0	9/33 (27.3%)	N/A	2.7 m (1.4–14.6 m)*
Tolcher et al. [55]	6/41 (14.6%)	N/A	N/A	range 8–48 m
Tolcher et al. [56]	PSA = 4/35 (11.4%), RECIST = 1/35 (2.9%)	PSA = 4/35 (11.4%), RECIST = 11/35 (31.43%)	N/A	range 0.7–3.73 m

Note: * = median; Abbreviation: OR = Overall response, TTR = Time to response, DOR = Duration of response, OS = Overall survival, PFS = Progression free survival, m = month, N/A = Not available, CI = Confidence interval, DP = disease progression, N/E = Not estimable, AE = Adverse effect, Tx = Treatment, DLT = Dose limiting toxicity, Dur/S = During study, Dur/F = During follow-up, p = phase, RECIST = Response evaluation criteria in solid tumours, PSA = Prostate-specific antigen.

First author	Median OS, 1-year probability %	Median PFS, probability %
Cheson et al. [46]	not reached	1.93 m (95% CI, 1.43–2.13)
Clemens et al. [47]	20.03 m (95% CI, 19.1–22.9)	8.37 m (95% CI, 5.73–11.1)
Giaccone et al. [48]	6.6 m (95% CI, 4–12.2), 35.1% (95% CI, 20%–50%)	1.7 m (95% CI, 1.3–2.8)
Karavasilis et al. [49]	N/A	N/A
Kelly et al. [50]	16.1 m (95% CI, 14.4–17.8), 87% (95% CI, 62.1%–96.3%)	5.7 m (95% CI, 3.67–6.07) 3-month: 79%
Kudchadkar et al. [51]	14.9 m (95% CI, 8.8–24.3), 56.3% (95% CI, 52.1%–60.5%)	4.2 m (95% CI: 2.7–5.6), 6-month: 31.3%
Lewis et al. [52]	9.9 m (95% CI, 7.0–14.5), 41% (95% CI, 25%–57%)	1.3 m (95% CI; 1.3–2.7)
Papadopoulos et al. [53]	not reached (16.1-N/E)	8.5 m (95% CI, 4.4-N/E)
Satoh et al. [54]	N/A	N/A
Tolcher et al. [55]	N/A	N/A
Tolcher et al. [56]	11.2 m (95% CI, 7.57–24.5)	3.1 m (95% CI, 2.12–6.28)

Note: * = median; Abbreviation: OS = Overall survival, PFS = Progression free survival, m = month, N/A = not available, CI = Confidence interval, N/E = not estimable.

The average median OS was 13.12 months (range 6.6–20.03 months, $n = 6$) and the average estimated 1-year OS rate was 54.9% (35.1%–87.0%, $n = 4$). It is noteworthy that all of the studies reporting OS outcomes were of patients with solid tumors. Subgrouping based on the treatment regimens gave an average median OS of 9.23 months (6.6–11.2 months, $n = 3$) for YM155 monotherapy and 17.01 months (14.90–20.03 months, $n = 3$) for combination therapy, and the average estimated 1-year OS rates for YM155 monotherapy and combined therapy were 38.1% (35.1%–41.0%, $n = 2$) and 71.7% (56.3%–87.0%, $n = 2$), respectively. A total of 8 studies reported on PFS, with the average median PFS being 4.35 months (range 1.3–8.5 months, $n = 8$). Two studies estimated the 3- and 6-month PFS rates as 79% and 31.3%, respectively [46,47]. Subgrouping according to tumor types, the average median PFS in the HM and ST studies was 5.22 months (1.93–8.5 months, $n = 2$) and 4.06 months (1.3–8.4 months, $n = 6$), respectively. For the YM155 regimen subgroups, the average median PFS for YM155 monotherapy and combination therapy was 2.01 months (1.3–3.1 months, $n = 4$) and 6.69 months (4.2–8.5 months, $n = 4$), respectively.

3.3.2 Adverse Events Associated with YM155 Treatment

Data on grades III–IV AEs were extracted from 13 studies (12 QNRS and 1 QRCT) involving 578 patients who received YM155 as monotherapy or combination therapy (Tables 5 and 7). For the 13 studies combined, the mean percentage hematological AEs (HAEs) and non-hematological AEs (NHAEs) were 22.1% (range 0%–66.0%) and 20.5% (3.0%–41.5%), respectively. Subgrouping by tumor types, the average HAE and NHAe rates were 28.1% (17.1%–39.0%, $n = 2$) and 32.95% (24.40%–41.5%, $n = 2$), respectively, for 82 patients with lymphoma; and 22.6% (0%–66.0%, $n = 10$) and 19.1% (3%–39.6%, $n = 10$), respectively, for 455 patients with advanced solid tumors. One study reported the combined rate of AEs for 5 patients with lymphoma and 36 with solid tumors as 4.9% for HAEs and 9.8% for NHAEs. Subgrouping by therapeutic strategy, the average percentage HAEs and NHAEs was 7.6% (0%–24.2%, $n = 9$) and 15.2% (35%–30.0%, $n = 9$), respectively, for 382 patients who received YM155 monotherapy; and 54.8% (39%–66.0%, $n = 4$) and 32.4% (14.6%–41.5%, $n = 4$), respectively, for 196 patients who received YM155 as combination therapy. The most common types of AEs resulting from YM155 monotherapy were reported in various ways in the 14 individual studies.

Table 5: Overall YM155-treatment-related AE (grades III–IV)

The first author (year)	HAE	NHAE
Aoyama et al. (2012) [43]	0	6/33 (30%)
Aoyama et al. (2013) [44]	1/96 (1%)	10/96 (10.4%)
Cheson et al. (2012) [46]	7/41 (17.1%)	10/41 (24.4%)
Clemens et al. (2015)* [47]	29/48 (60.4%)	19/48 (39.6%)
Giaccone et al. (2009) [48]	0	10/37 (27%)
Karavasilis et al. (2016) [49]	3/32 (9.4%)	2/32 (6.3%)
Kelly et al. (2013)* [50]	22/41 (53.7%)	6/41 (14.6%)
Kudchadkar et al. (2015)* [51]	35/58 (66%)	18/58 (34%)
Lewis et al. (2011) [52]	0	4/34 (11.8%)
Papadopoulos et al. (2016)* [53]	16/41 (39.0%)	17/41 (41.5%)
Satoh et al. (2009) [54]	8/33 (24.2%)	1/33 (3.0%)
Tolcher et al. (2008) [55]	2/41 (4.9%)	4/41 (9.8%)
Tolcher et al. (2011) [56]	4/35 (11.4%)	5/35 (14.3%)

Note: * = Combined treatment, Abbreviation: AE = Adverse events, HAE = Haematological AE, NHAE = Non-haematological AE.

Therefore, we analyzed the AE data reported from 9 studies totaling 382 patients (Tables 6 and 7). A total of 33 types of grade III/IV AEs affecting 105 of the 382 patients (27.5%) were reported. Of the 105 patients, 33 (31.4%) reported HAEs of anemia/decreased hemoglobin (10/33, 30.3%), neutropenia (8/33, 24.2%), lymphocytopenia (7/33, 21.2%), thrombocytopenia (6/33, 18.2%), and coagulopathy (2/33, 6.1%). A total of 29 types of NHAEs were reported, of which the 5 most common (n = 48/72, 66.7%) were fatigue/weakness (19/72, 26.4%), renal and/or cardiac issue (15/72, 20.8%), abnormal liver function test (8/72, 11.1%), and electrolyte disturbance (6/72, 8.3%).

Table 6: Individual-based, treatment-related AE (\geq grade III) during single YM155

Criteria	Non-haematological					Haematological AE				
	III	IV	III/IV	V	Total	Criteria	III	IV	III/IV	Total
Fatigue	13	3	1		17	Anaemia/ \downarrow Hb	8	1	1	10
Abnormal liver function test*	7				7	Neutropenia	4	4		8
Nephrotoxicity	6				6	Lymphocytopenia	6	1		7
Unclear (cardiac & nephrotoxicity)	5				5	Thrombocytopenia	5		1	6
Vascular access complication	4				4	Coagulopathy	1		1	2
Stomatitis	3				3					
Haemorrhage, intracranial				2	2					
Upper respiratory tract infection	1		1		2					
Hypokalaemia	2				2					
Arrhythmia	2				2					
Muscular weakness	2				2					
MS and connective tissue disorders	2				2					
Deep vein thrombosis	2				2					
Hypophosphatemia	1				1					
Metabolism and nutrition disorders	1				1					
Cardiac disorders	1				1					
Myalgia	1				1					
Immune system disorders	1				1					
Hypersensitivity	1				1					
Cardiac failure congestive	1				1					
Staphylococcal bacteraemia	1				1					
Vena cava thrombosis	1				1					
Dyspnoea	1				1					
Pulmonary embolism	1				1					
Alkaline phosphatase increased	1				1					
Hyponatremia	1				1					
Hyperglycaemia	1				1					
Hypercalcemia	1				1					
Confusional state	1				1					
Total = 105/382 (27.5%)	65	3	2	2	72		24	6	3	33

Note: *Abnormal liver function test includes increased aspartate, increased alanine serum transaminase, and increased γ -glutamyl transpeptidase. MS = Musculoskeletal, Hb = Haemoglobin.

Table 7: Summary of clinical outcomes

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Impact
Overall response (OS), Assessed with: % of events	449 (1 QRCT, 10 QNRS)	⊕⊕○○ LOW ^a	Data on OR was assessed in cancer patients who received single or combined YM155 treatment. The average percentage of OR was 14.04%, ranging between 0%–43.9%.
Clinical benefit rates (CBR), Assessed with: % of events	408 (1 QRCT, 9 QNRS)	⊕⊕○○ LOW ^a	The average percentage of CBR was 49.4%, ranging between 6.3%–89.5%.
Time to response (TTR), Assessed with: Average of median month	78 (2 QNRS)	⊕○○○ VERY LOW ^{a, b}	The average median TTR related to YM155 therapy is 1.78 months with a range of 1.6–1.9 months.
Duration of response (DOR), Assessed with: Average of median month	301 (1 QRCT, 7 QNRS)	⊕○○○ VERY LOW ^{a, b}	The average median of the DOR was more than 2 months through 8 primary studies.
Overall survival (OS), Assessed with: Average of median month	261 (1 QRCT, 5 QNRS)	⊕○○○ VERY LOW ^{a, b}	Data on OS was obtained from 6 primary studies with a total of 261 cancer patients though, only 4 of the studies further estimated the probability of 1-year OS, including 176 cancer patients. The average median OS was 13.12 months with a range of 6.60–20.03 months, whereas the average estimated percentage for 1-year OS was 54.9% (35.1%–87.0%).
Progression-free survival (PFS), Assessed with: Average of median month	343 (1 QRCT, 7 QNRS)	⊕⊕○○ LOW ^a	The average median PFS was 4.35 months with a range of 1.3–8.5 months. Two studies estimated 3- and 6-months probability for PFS as 79% and 31.3%, respectively.
Adverse effect (AE), Assessed with: % of events (grades III–IV)	578 (1 QRCT, 12 QNRS)	⊕⊕○○ LOW ^a	Data on grades III–IV AEs obtained from cancer patients who received single YM155 or combined therapy. Mean percentages of haematological (HAE) and non-haematological adverse effects (NHAE) involving all individual studies, were 22.1 % (0%–66.0%) and 20.5% (3.0%–41.5%), respectively.

GRADE Working Group grades of evidence [57]:

- High certainty: We are very confident that the true effect lies close to that of the estimate of the effect;
- Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect;
- Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect;

Explanations:

a. Clinical heterogeneity is high due to cancer types and therapeutic regimens.

b. The sample size is relatively small (less than 300).

Abbreviation: QNRS = Quantitative nonrandomized study, QRCT = Quantitative randomized controlled Trials

3.4 Pharmacological Outcomes

Outcomes related to pharmacological parameters for the individual studies are shown in [Appendix E](#) and [Table 7](#). YM155 DLTs ranging from 4.8 to 12 mg/mg² were reported by 5 studies involving 183 patients [44,50,54–56], and MTDs ranging from 4.8 to 10 mg/mg² were reported by 4 studies of patients [45,50,54,55]. As a result of toxicity, an average of 6.74% (range 0%–11.8%) of 417 patients in 10 studies required dose reductions [46–48,50–56]. With respect to YM155 pharmacokinetic parameters, C_{ss} was shown to increase almost dose-proportionally based on 11 studies of 536 patients [43–46,48,50,51,53–56]. A similar dose-dependence for V_d was reported by 4 studies of 211 patients who received escalating YM155 doses of 1.8–12 mg/m² [43,44,50,55]. Cl was reported by 8 studies with 394 patients and ranged from 25 to 45 L/h depending on the dosage and infusion day [43–46,50,54–56]. Three phase I escalating dose studies involving 107 patients obtained renal Cl rates of about 20% to 50% [43,54,55]. YM155 T_{1/2} measurements were reported by 5 studies of 185 patients and the results varied [43,48,50,54,55], with some studies reporting constant T_{1/2} values across a range of doses and others reporting that T_{1/2} was dose dependent. AUC was reported to increase with escalating YM155 dose in four studies with a total of 189 patients [43,45,50,55].

4 Discussion

Despite rapid advances in the treatment of cancer, it remains a major cause of death and represents a serious public health problem worldwide [58,59]. Thus, there is an urgent need for novel therapeutic strategies based on an understanding of cancer biology. Among the characteristics of cancer cells, two are of particular interest: their universal overexpression of survivin and their poor antioxidant profile [60–63]. YM155, an inhibitor of survivin gene expression and inducer of redox dysregulation, has emerged as a promising chemotherapeutic agent [20,26,64–68].

Here, we performed a systematic literature review and meta-analysis with the goal of assessing pharmacological and clinical outcomes and the safety profile of YM155 as a monotherapy or combination therapy with other chemotherapeutic agents. Our analysis suggests that YM155 provides clinical benefits, such as regression and/or stabilization of tumor progression and prolonged survival, with an acceptable safety profile and good synergistic effects.

Due to the heterogeneity of tumor types and therapeutic regimens in the 14 studies analyzed, we performed subgroup analyses. The average ORR and CBR were higher for patients with HMs vs. STs, and for patients receiving YM155 as a combination therapy vs. monotherapy. Similarly, the median PFS and the estimated 1-year PFS rate were much longer and higher, respectively, in patients with HMs vs STs and in those receiving YM155 combination therapy vs. monotherapy. Although the OS and estimated 1-year OS rates were only assessed in patients with STs, subgroup analysis based on treatment strategy showed that the median OS and 1-year OS rate were almost two-fold longer and higher, respectively, in patients receiving YM155 combination therapy vs monotherapy. TTR and DOR were evaluated in relatively few studies, but it is worth mentioning that the overall median TTR was <2 months, and the DOR was >2 months.

In terms of AEs, both HAEs and NHAEs occurred at acceptable rates and affected an estimated 20% of YM155-treated patients. Subgroup analysis indicated that patients diagnosed with HMs or receiving YM155 combination therapy tended to experience more HAEs and NHAEs than patients with STs or receiving YM155 as a single therapy. To determine specific AEs caused by YM155, we aggregated all observed AEs from patients receiving only YM155. Of the 29 types of grades III–IV AEs reported, fatigue/weakness, renal and/or cardiac issues, abnormal liver function tests, and electrolyte disturbance were the five most common AEs.

The DLT and MTD for YM155 were both between 4.8 and 12 mg/mg², and related toxicities required dose reduction in 6.74% of the 417 patients in 10 studies analyzed. Other pharmacological parameters were generally affected in a dose-dependent manner. Pharmacological data obtained from a multicenter study concluded that there were no inter-ethnic differences in pharmacokinetics [45]. This is an important observation because ethnicity can potentially affect a drug's pharmacokinetics, pharmacodynamics, and safety profile, and is thus a key factor in drug development worldwide [69–72]. The patients involved in the studies assessed were from a wide range of races.

The finding YM155 had lower efficacy in patients with STs than HMs could be due to a limitation in the ability of YM155 to penetrate into solid tumors. Currently, the topic of drug delivery for solid tumors is an area of intense preclinical investigation, especially for drug-resistant cancer therapy [73,74]. Two groups have employed YM155-encapsulated liposomes as targeted nanocarriers for YM155 and examined efficacy in xenograft models of cancer. They concluded that nanocarriers extended the half-life of YM155, improved its accumulation in tumor tissues, and induced better antitumor efficacy than did free YM155 [75,76]. In another study, YM155-mediated genotoxicity was found to be dependent on the solute carrier protein SLC35F2 in both *in vitro* and *in vivo* experiments, suggesting a new route for targeting DNA damage by exploiting tumor and patient-specific import of YM155 [77].

While numerous therapeutic strategies are under investigation for cancer therapy, the safety and potential side effects of novel drugs are always of great concern. Most of the 14 studies included in the present meta-analysis reported that “YM155 treatment was well tolerated” [46–48,50–52,56]. Likewise, several studies of YM155 combination therapy found that the addition of YM155 allowed the dose of the partner drug to be reduced without sacrificing clinical benefits, and the number of AEs was actually reduced [47,50,51,53]. Our treatment-based subgroup analysis indicated that response rates (OR, CBR, TTR and DOR) and survival (median OS, median PFS and 1-year OS rate) were better in patients receiving combination treatment vs YM155 monotherapy. The next question for YM155 combination therapy is which drug partners would support optimal efficacy. To date, cell cycle-specific (e.g., mitotic inhibitors) and non-specific (rituximab, platinum) inhibitors have been successfully combined with YM155 at the clinical level [47,50,51,53]. We appreciated the idea of combining with mitotic inhibitors. Overexpression of survivin leads to the development of resistance toward different microtubule destabilizers [78,79] and the combination of a microtubule-destabilizing agent, BPROL075, with survivin siRNA can synergize to restore sensitivity to chemo-resistant cancer cells [80].

Theoretically, the quinone ring of YM155 could synergize with antitumor antibiotics that generate free radicals by converting quinone to semi-quinone, and thus cause profound depletion of cellular reductants [81–86]. YM155 has been shown to cause DNA damage *in vitro* and *in vivo* through intercalation between base pairs in a manner contingent on SLC35F2 expression and drug-importing activity [77]. In these contexts, redox-directed cancer therapeutics may be good partners for YM155 combination therapy, since they specifically target redox susceptibilities, such as abnormal metabolism, downregulation of antioxidant enzymes, and impaired mitochondrial function [20,87–91].

It should also be mentioned that many preclinical studies have provided data on the synergism of YM155 with other treatment modalities, including radiotherapy [19,92], and other chemotherapeutic agents such as monoclonal antibodies [93,94], antimetabolites [95,96], DNA-targeted drugs [97,98], and signal transduction inhibitors [99–102]. Thus, the versatile synergistic effects of YM155 suggest that it could be combined with a wide range of agents to form an effective treatment strategy.

Accurate diagnosis and careful monitoring are crucial to the success of cancer management. The main goals of cancer biomarker research are rapid identification of tumor cells and prediction of treatment response, ultimately leading to a favorable therapeutic outcome [103–108]. A large body of evidence has indicated that one such marker can be survivin [109–114]. Indeed, much attention is currently paid to the

possibility of using this protein as a diagnostic marker of cancer or a prognostic factor. Therefore, YM155 and other survivin inhibitors are likely to be excellent selective anticancer therapies with their own monitoring biomarker. But it seems relatively different depending on tumor types because surviving's cancer roles slightly diverge through tissue types. For instance, pro-oncogenic effects in numerous tumors [115–117]; high expression correlates to lower survival in HCC, GIST [118,119], correlates to p53 mutations and metastases, cytoplasmic localization associated with aggressive disease in prostate cancer [120,121], anti-apoptotic function, low survival, chromosomal aberrations in brain tumors [122–126], and resistance to chemotherapy and radiotherapy-induced apoptosis in the lung [127]. In addition to survivin, as digging up monitoring YM155 intervention, observed YM155 therapy responses at pre-clinical levels are chemo and radiosensitization in colorectal cancer, ALL, melanoma, NSCLC, and glioblastoma [128–131]. In neuroblastoma cells, targeted survivin silencing by YM155 causes drug-induced heterogeneity and enables the identification of biomarker candidates for the acquired resistance settings, enhancing chemosensitization [132–135]. At the clinical level, Kelly et al. [50]. performed biomarker analysis in phase II patients, including M30 apoptosense, IL8, and VEGF. However, there was no association between any of these biomarkers, or the changes and response rate. Whereas, decreasing trends of cytokines IL-8, MIP-1b, and granulocyte colony-stimulating factor expression as a prognostic biomarker in non-small cell lung cancer correlated with improved progression-free survival in phase I study [136]. Another prompting result was obtained by Mitsuoka K et al. [137], who investigated ^{11}C -labeled YM155 and assessed tumor cell uptake through positron emission tomography (PET). The authors concluded that high uptake of ^{11}C YM155 by tumor tissue seems to be a positive predictive marker for a good response to the treatment, suggesting the potential utility of PET/CT imaging with ^{11}C YM155 for the treatment response [137].

This study has several limitations: First, only one QRCT study satisfied the criteria for meta-analysis. Second, the QNRS studies differed in the outcomes analyzed owing to the variation in trial phases, and they had high heterogeneity based on tumor types and treatment plans. Third, the most common bias was related to completeness of outcome, possibly because of the inclusion of patients with advanced cancer. Fourth, the number of studies associated with some of the subgroups was small, so the results for these analyses may be unreliable. Finally, data were extracted only from articles written in English or Japanese, which might lead to publication bias.

Future work should focus on the delivery of YM155 using nanocarriers, which could improve the efficacy by increasing tumor uptake, especially in solid tumors. Likewise, the application of nanoparticulate systems coupled with biocompatible therapeutics might overcome drug resistance cancer; and improved co-delivery tools with other chemotherapeutic agents can strengthen synergism [138–140]. The selectivity of YM155 may also promote its use in the early stages of cancer when it might have the best opportunity to provide clinical benefit. Additional randomized dual-armed clinical studies with patients at early disease stages might also increase the probability of approaching clinical endpoints, thereby increasing the effect size and accuracy of the results. Ample preclinical evidence suggests that YM155 can enhance sensitization of cancer cells to both radiotherapy and chemotherapy, and future studies should include exploration of optimal partner anticancer agents for combination therapy with YM155 based on tumor types. Moreover, YM155 molecular stabilization should be considered. Currently, it is still unclear whether the tumor growth would be inhibited continuously after stopping infusion [141,142]. YM155 downregulates survivin by blocking Sp1 and ILF3/p54nrb-mediated expression via removing these transcription factors from the nucleoplasm without degradation, raising a suspension that cancer cells might recover after the stopping YM155 intervention or excretion body [143,144].

As a prospective, survivin cancer therapeutics developing rapidly under five categories: 1) survivin-partner protein interaction inhibitors, 2) survivin homodimerization inhibitors, 3) survivin gene

transcription inhibitors, 4) survivin mRNA inhibitors, 5) survivin immunotherapy, due to many advantages as compared with other apoptosis-based anticancer agents, including compromises multiple signaling networks required for oncogenesis, a unique target for molecular antagonists, cancer vaccine and gene therapy, survivin antagonists may affect cancer stem cells, does not affect the normal cells or tissues suggesting a favorable toxicity profile [145–148]. Regarding inhibitors, such as Shepherdin and AICAR, which disrupt survivin interactions with its partner proteins, further studies need to clarify the effect of specificity on survivin. Whereas, survivin-directed immunotherapy and survivin-based vaccination have been showing promising efficacy, safety, and associated with antigen-specific immunologic responses, and advancing to several clinical trials.

5 Conclusion

Concern about inconclusive results from qualitative studies with YM155 prompted us to perform an integrated systematic analysis of relevant clinical trials with the goal of facilitating clinical decision-making in the use of YM155. Our results have several clinical implications. First, they showed significant beneficial clinical outcomes of YM155 treatment, including improved OR, CBR, OS, and PFS. Second, the results suggest that YM155 would be most effective when given in combination with another anticancer agent at an early stage of cancer. Third, the analysis showed that YM155 could be administered to cancer patients of any ethnicity with acceptable efficacy and safety profiles, with the exception of AEs of decreased blood cell counts; fatigue/weakness; renal, hepatic, and/or cardiac issues; and electrolyte disturbance. Finally, YM155 showed efficacy in both solid and hematological malignancies, confirming that the beneficial mechanism of action of YM155 is based on common genotypical and phenotypical features of cancer cells.

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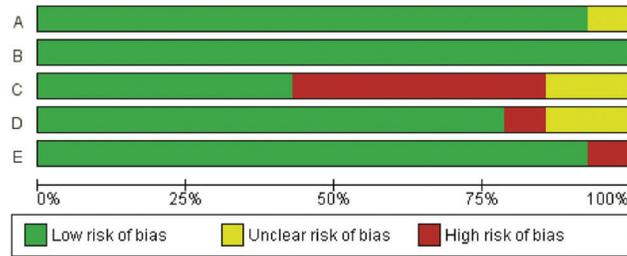
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Appendices



Appendix A: Risk of bias graph YM155

	A	B	C	D	W
Aoyama 2012	+	+	+	?	+
Aoyama 2012a	+	+	+	+	+
Aoyama 2013	+	+	+	+	+
Cheson 2012	+	+	-	+	+
Clemens 2015*	?	+	+	-	-
Giaccone 2009	+	+	-	+	+
Karavasillis 2016	+	+	-	?	+
Kelly 2013	+	+	?	+	+
Kudchadkar 2015	+	+	+	+	+
Lewis 2011	+	+	-	+	+
Papadopoulos 2016	+	+	-	+	+
Sato 2009	+	+	?	+	+
Tolcher 2008	+	+	+	+	+
Tolcher 2010	+	+	-	+	+

Appendix B: Risk of bias summary YM155

Appendix C: Detailed information of the articles (n = 14)

Characteristics	n	(%)
Country		
United States of America	6	42.9%
Japan	4	28.7%
United Kingdom	1	7.1%
Georgia	1	7.1%
Germany	1	7.1%
The Netherlands	1	7.1%
Chronological development		
2000–2009	3	21.4%
2010–2020	11	78.6%
Types of publication		
Journal article	12	85.8%
Conference abstract	1	7.1%
Short communication	1	7.1%
Research level		
QNRS, NRCT, phase II	9	64.3%
QNRS, NRCT, phase I	3	21.5%
QNRS, NRCT, phase I/II	1	7.1%
QRCT, phase II	1	7.1%
Tumor types		
Solid tumor	10	71.4%
Mixed	2	14.3%
Hematological malignancy	2	14.3%
Original organ of tumors		
Mixed solid	5	33.3%
Lymphoid neoplasm	3*	20.0%
Male reproductive system	2	13.3%
Respiratory system	2	13.3%
Skin	2	13.3%
Breast	1	6.7%
Combination		
Without combo	10	71.4%
With combo	4*	28.6%
CCS (docetaxel)		
CCNS (paclitaxel, carboplatin, rituximab)		

(Continued)

Appendix C (continued)		
Characteristics	n	(%)
Achievement of endpoint		
Success	10	71.4%
Failure	4	28.6%
*Study included more candidates		

Appendix D: Summary of methodological assessment

SD	Responses	A N/T	B N/T	C N/T	D N/T	E N/T
QNRS	Yes	13/14	14/14	6/14	11/14	13/14
	Can't tell	1/14	0	2/14	2/14	0
	No	0	0	6/14	1/14	1/14
QRCT	Yes	0	1	1	0	0
	Can't tell	1	0	0	0	0
	No	0	0	0	1	1

QNRS (Quantitative nonrandomized studies):

- A. Are the participants' representative of the target population?
- B. Are measurements appropriate regarding both the outcome and intervention?
- C. Are there complete outcome data?
- D. Are the confounders accounted for in the design and analysis?
- E. During the study period, is the intervention administered as intended?

QRCT (Quantitative randomized controlled trials):

- A. Is randomization appropriately performed?
- B. Are the groups comparable at baseline?
- C. Are there complete outcome data?
- D. Are outcome assessors blinded to the intervention provided?
- E. Did the participants adhere to the assigned intervention?

Abbreviation: SD = study design, N = number, T = total

Appendix E: Pharmacological outcomes of YM155 agent

First author (year)	Tolerance	Dose reduction	Toxicity	Absorption	
				Cmax	Css (ng/mL)
Aoyama et al. (2012) [43]	N/A	N/A	DLT = 10.6 mg/m ²	N/A	do1.8 = 3 ± 1, do3.6 = 7 ± 2, do4.8 = 10 ± 4, do6.0 = 14 ± 6, do8.0 = 13 ± 3, do10.6 = 19 ± 3,
Aoyama et al. (2013) [44]	N/A	N/A	N/A	N/A	6
Aoyama et al. (2013a) [45]	N/A	N/A	MTD = 8 mg/m ² (Japanese); MTD = 4.8 mg/m ² (USA);	N/A	1.141 (0.996–1.307)
Cheson et al. (2012) [46]	well	3 (7.3%) [AE]	N/A	N/A	*d1–8 = 10.4
Clemens et al. (2015) [47]	well	4 (8.3%), **8 (16.7%) for YM155, 9 (18.8 %) for docetaxel	N/A	N/A	N/A
Giaccone et al. (2009) [48]	well	0	N/A	N/A	11.2 ± 5.8; [9.71 (5–27)]*
Kelly et al. (2013) [50]	well	0	MTD = 10 mg/m ² , DLT = 12 mg/m ² ,	N/A	do3.6 = 4.23 (3.0–5.9), do5.0 = 7.95 (2.4–26.6), do6.0 = 7.99 (5.1–12.4), do8 = 7.96 (5.7–11.2), do10 = 10.27 (6.7–15.8), do12 = 9.94 (7.4–13.5),
Kudchadkar et al. (2015) [51]	well	7/64 (10.9%)	N/A	N/A	*d4 = 6.510 (c1), d4 = 6.070 (c2), d4 = 6.390 (c3); before d8 = 6.740–6.890, after d8 = 3.895–4.535
Lewis et al. (2011) [52]	well	4/34 (11.8%)	N/A	N/A	N/A
Papadopoulos et al. (2016) [53]	well	4/41 (9.8%); **24/41 (58.5%)	N/A	N/A	*d4 = 9.29 ng/ml, d8 = 7.15 ng/ml
Satoh et al. (2009) [54]	N/A	4/33 (9.1%)	MTD = 8 mg/m ² , DLT = 10.6 mg/m ²	N/A	Increased almost dose-proportionally
Tolcher et al. (2008) [55]	N/A	3/41 (7.3%)	DLT = 6 mg/m ² , MTD = 4.8 mg/m ² ,	*do1.8 = 5.5 ng/ml, do3.6 = 8.3 ng/ml, do4.8 = 9.4 ng/ml,	*do1.8 = 5.1ng/ml, do3.6 = 6.2 ng/ml, do4.8 = 7.8 ng/ml,
Tolcher et al. (2011) [56]	well	1/35 (2.9%)	DLT = 4.8 mg/m ²	N/A	*d4 = 9.63 ng/ml, d6 = 9.17 ng/ml, d8 = 9.50 ng/ml

Note: * = median,** = interruption; Abbreviation: N/A = not available, d = day, h = hour, do = dose, c = cycle.

First author (year)	Volume distribution (L)	Elimination			AUC (ng.hr/L)
		Clearance (L/h)	Renal excretion (%)	Half time (h)	
Aoyama et al. (2012) [43]	do1.8 = 436 ± 175, do3.6 = 1,197 ± 568, do4.8 = 759 ± 541, do6.0 = 795 ± 347, do8.0 = 1,169 ± 484, do10.6 = 1,544 ± 955,	do1.8 = 42 ± 7, do3.6 = 39 ± 13, do4.8 = 35 ± 11, do6.0 = 34 ± 11, do8.0 = 41 ± 14, do10.6 = 34 ± 7,	do1.8 = 31 ± 4%, do3.6 = 35 ± 8%, do4.8 = 35 ± 8%, do6.0 = 28 ± 6%, do8.0 = 29 ± 4%, do10.6 = 42 ± 8%,	do1.8 = 7 ± 3, do3.6 = 21 ± 9, do4.8 = 21 ± 9, do6.0 = 16 ± 6, do8.0 = 21 ± 9, do10.6 = 29 ± 14,	do1.8 = 538 ± 119, do3.6 = 1,186 ± 385, do4.8 = 1,738 ± 685, do6.0 = 2,239 ± 952, do8.0 = 2,233 ± 489, do10.6 = 3,235 ± 526,
Aoyama et al. (2013) [44]	319 L	42.1	N/A	N/A	N/A
Aoyama et al. (2013a) [45]	N/A	0.804 (0.700–0.924)	0.981 (0.855–1.125)	0.685 (0.559–0.839)	1.068 (0.932–1.224)
Cheson et al. (2012) [46]	N/A	d1–8 = 35.5	N/A	N/A	N/A

(Continued)

Appendix E (continued)					
First author (year)	Volume distribution (L)	Elimination			AUC (ng.hr/L)
		Clearance (L/h)	Renal excretion (%)	Half time (h)	
Clemens et al. (2015) [47]	N/A	N/A	N/A	N/A	N/A
Giaccone et al. (2009) [48]	N/A	N/A	N/A	14.57–27.43 h	N/A
Kelly et al. (2013) [50]	do3.6 = 290.21 (91.1–924.2), do5 = 256.52 (43.2–1523.9), do6 = 371.27 (132.2–1042.3), do8 = 446.39 (268.3–742.8), do10 = 670.47 (201.7–2228.8), do12 = 530.25 (319.0–881.3)	74L/h	N/A	~33 h	do3.6 = 304.4 (218.3–424.6), do5.0 = 572.57 (171.2–1914.7), do6.0 = 574.90 (369.2–895.2), do8 = 573.33 (408.3–805.1), do10 = 739.45 (481.1–1136.5), do12 = 715.85 (528.7–969.3)
Kudchadkar et al. (2015) [51]	N/A	N/A	N/A	N/A	N/A
Lewis et al. (2011) [52]	N/A	N/A	N/A	N/A	N/A
Papadopoulos et al. (2016) [53]	N/A	N/A	N/A	N/A	N/A
Satoh et al. (2009) [54]	N/A	Constant across the dose range	25%–42%	Constant across the dose range	N/A
Tolcher et al. (2008) [55]	*do1.8 = 691 L, do3.6 = 1406 L, do4.8 = 1591 L,	*do1.8 = 24.6 L/h, do3.6 = 42.9 L/h, do4.8 = 42.5 L/h,	do1.8 = 18.3%, do3.6 = 25.4%, do4.8 = 28.6%	do1.8 = 20.4 h, do3.6 = 19.8 h, do4.8 = 24.0 h,	*do1.8 = 843, do3.6 = 1106, do4.8 = 1408
Tolcher et al. (2011) [56]	N/A	CL = 44.01 L/h	N/A	N/A	N/A

Note: * = median,** = interruption; Abbreviation: N/A = not available, d = day, h = hour, do = dose, c = cycle.