Abstract:

Background: The prognostic value of the systemic inflammatory response in cancer has been well established in observational studies. This review aims to examine and rationalise the evidence for the role of systemic inflammation based prognostic scores in randomised clinical trials.

Method: An extensive literature review using targeted medical subject headings was carried out in the MEDLINE, EMBASE, and CDSR databases until January 2018. Titles were examined for relevance and after exclusions bibliographies were hand searched to identify additional trials.

Results: There were 29 trials containing data on 37,020 patients presented in full paper form and 8 trials containing data on 3,805 patients presented in abstract form. Most trials were published within the last three years. Seven trials containing data on 6,044 patients were published in 2015. Eight trials containing data on 4,384 patients were published in 2016. Twelve trials containing data on 27,228 patients were published in 2017. The majority of trials were in advanced inoperable cancer and colorectal cancer was the most common cancer type with 11 articles containing data on 27,909 patients. The GPS/mGPS was shown to have prognostic value in randomised clinical trials in NSCLC, oesophageal cancer, pancreatic cancer, prostate cancer and breast cancer. The NLR/dNLR was shown to have prognostic value in randomised clinical trials in nasopharyngeal cancer, oesophageal cancer, pancreatic cancer, biliary cancer, prostate cancer and multiple cancer types.

Conclusion: The prognostic value of systemic inflammation based prognostic scores has been confirmed in multiple trials and should be incorporated into future prospective randomised clinical trials.

Introduction:

Cancer remains one of the leading causes of mortality worldwide and is responsible for 8.8 million deaths each year. In the westernised countries, it has been estimated that one in three people will develop cancer in their lifetime, and one in four will die from it. Such a large burden of disease accounts for a significant proportion of the healthcare budgets in the UK, US and worldwide (Bosanquet and Sikora, 2004; Organization, 2017).

The prognostic value of the systemic inflammatory response in cancer has been well established in observational studies. Over the course of the last 30 years multiple markers of the systemic inflammatory response such as C-reactive protein, albumin, neutrophil count, lymphocyte count and that of other white cells have been reported to have prognostic value in patients with cancer, at all stages of disease (Guthrie et al., 2013; McMillan, 2013). In the last 15 years there has been a movement towards the use of combined prognostic scores such as the GPS/mGPS (C-reactive protein and albumin) and ratios such as the NLR (neutrophils and lymphocytes) to standardise and maximise prognostic value (Dolan et al., 2017a; Dolan et al., 2017b).

Despite the proven utility of these prognostic tools there has been an ongoing reluctance by the oncology community to incorporate these into routine clinical trial design. In 2012, MacDonald commented "The seminal observation by McMillan and colleagues that the presence of a dysregulated state as evidenced by a high CRP connotes a dire prognosis has been generally ignored to date and not used to stratify patients in oncology clinical trials. Particularly in the more aggressive tumour types (e.g. pancreas and lung), the future of patients with elevated mGPS scores is so grim that they should be given precachexia status and offered multimodal therapy which may delay the onset of cachexia and/or death

(MacDonald, 2012)." More recently, Laird and co-workers in large prospective cohorts of patients with advanced cancer have added weight to this assertion (Laird et al., 2016; Laird et al., 2013).

Based on work to date and the sound rationale for the use of prognostic tools in oncology trials, the aim of this systematic review was to examine and rationalise the evidence for the role of systemic inflammation based prognostic scores in the setting of randomised control trials.

Methods:

This systematic review of published literature was undertaken according to a pre-defined protocol described in the PRISMA-P statement and in a similar fashion to that recently reported with both advanced inoperable and operable cancer (Dolan et al., 2017a; Dolan et al., 2017b). Inclusion criteria consisted of randomised controlled clinical trials carried out in adult patients (aged 18-99) with curable and incurable cancer treated with any systemic anti-cancer therapy using validated combined scores of the systemic inflammatory response in both prospective and retrospective analysis with a primary outcome measure of survival. The primary aim was to assess the prognostic value of the validated combined scores of the systemic inflammatory response (NLR, PLR, LMR, GPS and mGPS) in the setting of randomised controlled clinical trials.

This was carried out by a wide-ranging literature search to identify trials carried out from January 1947 to 31st January 2018. Medical subject heading (MeSH) terms (Cancer, Randomised Control Trial, GPS, Glasgow Prognostic Score, mGPS, modified Glasgow Prognostic Score, NLR, Neutrophil Lymphocyte Ratio, LMR, Leucocyte Monocyte Ratio, PLR, Platelet Lymphocyte Ratio), were used in the US National Library of Medicine (MEDLINE), the Excerpta Medica database (EMBASE) and the Cochrane Database of Systematic Reviews (CDSR) to identify published papers and abstracts.

On completion of the online search, the title and abstract of each identified study was examined for relevance. Animal studies, those not in cancer patients, and trials not available in English were excluded. Where there were multiple publications from the same cohort the most recent paper was included. Once further exclusions outlined below were carried out, the

bibliographies of all included articles were subsequently hand searched to identify any additional trials. All potentially eligible papers were reviewed in full by two authors independently and graded according to GRADE recommendations.

Only articles that reported survival were included. Results were reported in terms of (1) cancer type and (2) combined markers of the systemic inflammatory response used.

Figure 1: PRISMA flowchart demonstrating study selection

Results:

The study selection process is summarised in Figure 1. Initial search strategy identified 382 papers and abstracts whose titles and abstracts were reviewed. Trials were excluded as they were not clinical trials (n=173) and as survival was not their primary measure (n=72). This led to a review of the full text of 137 articles. A further 106 articles were excluded as they were not in English (n=51), were animal studies (n=32), were not carried out in patients with cancer (n=20) and were carried out in duplicate datasets (n=3). The remaining 31 articles, had their bibliographies reviewed in a systematic manner and this identified a further 5 articles to be included in the final analysis leading to final figure of 36 reports containing data on 40,354 patients considered in the present systematic review (Tables 1 and 2).

There were 28 trials containing data on 36,549 patients presented in full paper form and 8 trials containing data on 3,805 patients presented in abstract form. Most trials were published within the last three years. Seven trials containing data on 6,044 patients were published in 2015. Seven trials containing data on 3,913 patients were published in 2016. Twelve trials containing data on 27,228 patients were published in 2017. In all 36 trials the predominant treatments being investigated was chemotherapy and radiotherapy. The majority of trials were in advanced inoperable cancer and colorectal cancer was most common cancer type with 10 articles containing data on 27,438 patients.

The prognostic utility of the GPS/mGPS was assessed in 7 trials with data on 1,284 patients and NLR/dNLR was assessed in 33 trials with data on 39,313 patients. All 36 trials were analysed in a post hoc manner. The thresholds used for GPS/mGPS were the same in all trials. The GPS/mGPS was shown to have prognostic value in randomised clinical trials in

NSCLC (Rinehart et al., 2013), oesophageal cancer (Okuno et al., 2017), pancreatic cancer (Hurwitz et al., 2015), prostate cancer (Linton et al., 2013) and breast cancer (Honecker et al., 2017). The thresholds for NLR varied between 3 to 6 and for dNLR between 2 to 5. The most common threshold for NLR was ≥3 and was used in 9 trials containing data on 4,042 patients. The most common threshold for dNLR was 2 and was used in 3 trials containing data on 3,810 patients. The NLR/dNLR was shown to have prognostic value in randomised clinical trials in nasopharyngeal cancer (Chua et al., 2016), oesophageal cancer (Cox et al., 2017), pancreatic cancer (Vivaldi et al., 2016), biliary cancer (Grenader et al., 2015), prostate cancer (van Soest et al., 2015) and multiple cancer types (Kumar et al., 2015). A combination of both GPS/mGPS and NLR/dNLR were measured in 2 trials containing data on 461 patients (Chua et al., 2012; Thomsen et al., 2016). Thomsen and colleagues showed that both mGPS (HR: 2.16, 95%CI 1.52-3.06, p<0.001) and dNLR (HR: 1.68, 95%CI 1.35-2.08, p<0.001) were prognostic in 68 patients with multiple cancer types (Thomsen et al., 2016). Chua and colleagues showed that both GPS (HR: 4.1, 95%CI 2.2-7.7, p<0.0001) and NLR (HR: 2.0, 95%CI 1.2-3.3, p=0.010) were prognostic in 393 patients with colorectal cancer (Chua et al., 2012).

Discussion:

The results of the present systematic review are consistent with previous observational studies and confirm the clinical utility and prognostic value of systemic inflammation based prognostic tools in the randomised control trial setting. Therefore, we propose that the time has now come for the universal incorporation of measures of the systemic inflammatory response into the design of randomised clinical trials in patients with cancer. Monitoring of both tumour and host responses will enable a more reliable estimate of benefit from oncological treatment. This will in turn highlight opportunities not only to target the tumour but also host systemic inflammatory responses.

Despite supportive meta-analysis of hundreds of reports of the prognostic value of markers of the SIR(Dolan et al., 2017a; Dolan et al., 2017b) , one of the main reasons for the lack of incorporation on monitoring of the systemic inflammatory response into standard randomised control trial protocols has been the apparent lack of prospective data and also the lack of a clear biological rationale behind their clinical utility. Therefore, the present review has only included prospective randomised trials and these confirm the prognostic value of the SIR. Moreover, with the explosion of interest in immunological treatments in patients with cancer, including several dedicated journals, the biological rationale for such systemic inflammation based prognostic scores has now become clear(Rosales, 2018; Roxburgh and McMillan, 2015). It remains to be established which of the markers of the SIR will be used in the RCT setting. However, compared with a ratio such as the NLR with its variable and poorly defined cut-off, a score such as the GPS with its well defined cut-off has a clear advantage(Dolan et al., 2018).

In the present systematic review only two small RCTs reported two measures of the Systemic Inflammatory Response (SIR) and in both trials the GPS/mGPS and the NLR/dNLR were shown to have independent prognostic value (Chua et al., 2012; Thomsen et al., 2016).

Therefore, in the context of the large preponderance of RCTs using NLR/dNLR it would suggest that NLR/dNLR should become the tool of choice for the measurement of the SIR in randomised trials. However, recently the NLR/ dNLR ratio approach to combining markers of the SIR as a prognostic tool has been questioned (Dolan et al., 2018; Dupre and Malik, 2018).

In particular it is not clear from a ratio what component is abnormal, what component is the prognostic value derived from and therefore the optimal threshold for prognostic value. This is confirmed in the variety of thresholds that have been reported for NLR/dNLR both in observational studies and the RCT setting. In contrast, the cumulative score approach such as the GPS/mGPS uses consistent thresholds and have been successfully applied to the RCT setting. Although, in many centres in the USA CRP has not been routinely measured either in clinical oncology practice or in the randomised control trial setting, recently CRP, albumin, and NLR have been listed as mandatory measurements in the first international consensus on mandatory baseline and prognostic characteristics in future trials for the treatment of unresectable pancreatic cancer (Ter Veer et al., 2018).

The advantage of a differential white cell count on which to base a prognostic score is that currently it is universally examined in clinical practice in patients with cancer. We have recently proposed that a number of scores based on the differential white cell count could be used to replace the ratios currently used (Dolan et al., 2018). For example, the neutrophil lymphocyte score (NLS) could replace the NLR, the platelet lymphocyte score (PLS) could replace the PLR and the lymphocyte monocyte score (LMS) could replace the LMR (Dolan et

al., 2018). Indeed, recent analysis of the ARCAD database of >22,000 patients with advanced colorectal cancer confirms the value of the cumulative score approach compared with the ratio approach (Sjoquist et al., 2017).

In summary, the prognostic value of systemic inflammation-based prognostic scores established extensively in observational studies over the past two decades has now been confirmed in the randomised controlled setting. The time has now come for prospective incorporation of such scores into randomised controlled trials in patients with cancer.

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Figure Legend:

- Figure 1: PRISMA flowchart demonstrating study selection

Table 1: The relationship between the systemic inflammatory response and survival in randomised clinical trials in patients with cancer (published papers)

Table 2: The relationship between the systemic inflammatory response and survival in randomised clinical trials in patients with cancer (published abstracts)

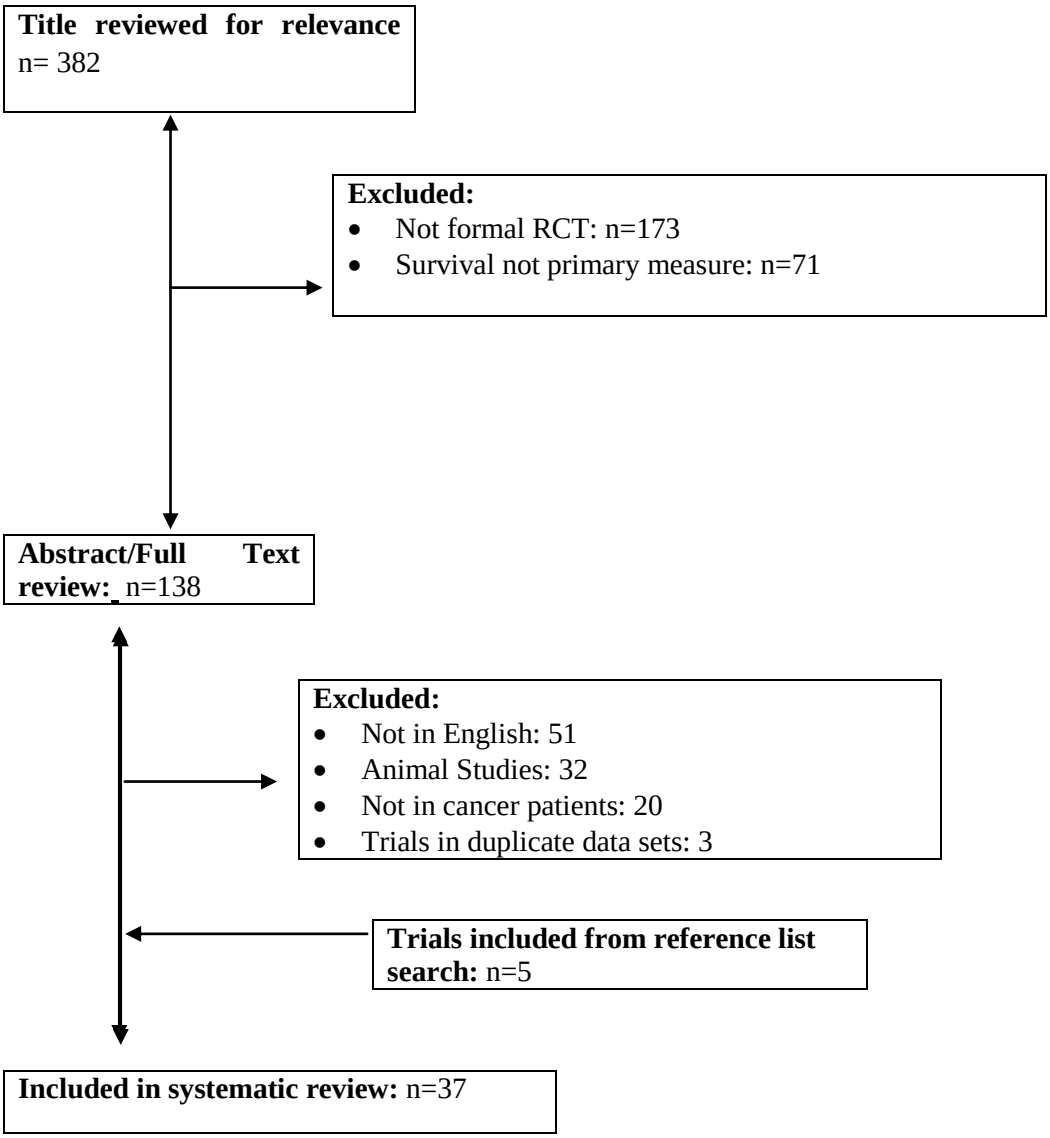

Figure 1: PRISMA flowchart demonstrating study selection

Table 1: The relationship between the systemic inflammatory response and survival in randomised clinical trials in patients with cancer (published papers)

Authors	**Randomised Clinical Trial**	**Tumour Type**	**Country**	**Patients (n)**	**Randomised Clinical Trial**	**Systemic Inflammation**	**Outcome**	**Comment**
Rinehart et al. (2013)	DEX	NSCLC	United States	124	Standard chemotherapy vs. Standard chemotherapy and Dexamethasone	GPS	OS	Univariate analysis: GPS: p< 0.05
Lee et al. (2012)	First-SIGNAL NCT00455936	Lung	Korea	199	Gefitinib plus gemcitabine plus cisplatin vs gefitinib monotherapy	NLR	OS	Multivariate Post treatment NLR>2.52 HR 1.13, 95%CI 1.06-1.21, p<0.001
Chua et al. (2016)	SQNP01 NCC0901	Naso-pharyngeal	Singapore	221 172	Two-dimensional radiotherapy vs. Two-dimensional radiotherapy and chemotherapy Intensity modulated radiotherapy or concurrent chemotherapy vs. Intensity modulated radiotherapy and chemotherapy	NLR	OS	Multivariate: NLR≥3: HR 1.06, 95%CI 0.76-1.49, p>0.05
Cox et al. (2017)	SCOPE1: NCT00509561	Oesophageal	United Kingdom	258	Chemoradiotherapy vs Chemoradiotherapy and cetuximab	dNLR	OS	Multivariate dNLR≥2 HR 1.64 95%CI 1.17-2.29, p<0.01
Okuno et al. (2017)	JCOG0303: UMIN000000861	Oesophageal	Japan	142	Radiotherapy and standard cisplatin vs. Radiotherapy and low dose cisplatin	GPS	OS	Univariate GPS 2 vs GPS 0 HR 1.95 95%CI 1.19-3.18, p<0.01
Grenader et al. (2016)	REAL-2 ISRCTN51678883	Oesophago-gastric	United Kingdom	908	Epirubicin and cisplatin and either fluorouracil (ECF) or capecitabine (ECX) vs Epirubicin and oxaliplatin and either fluorouracil (EOF) or capecitabine (EOX)	NLR	OS	Multivariate NLR>3 HR 1.67 95% CI 1.45–1.93 p<0.001
Bruix et al. (2017)	Sharp NCT00105443 AP: NCT00492752	Hepatocellular	Multinational	827	Sorafenib vs. Placebo	NLR	OS	Multivariate NLR>3 (Sorafenib group) HR 2.356, p<0.0001 NLR>3.86 (Placebo group) HR 1.779, p<0.0001
Grenader et al. (2015)	ABC-02: NCT00262769 BT-22: UMIN 000001685	Biliary	United Kingdom Japan	462	Gemcitabine vs. Gemcitabine and cisplatin Gemcitabine vs. Gemcitabine and cisplatin	dNLR	OS	Multivariate dNLR≥3 HR 1.62, 95% CI 1.32–2.01, p<0.001
Vivaldi et al. (2016)	FLAP: NCT02351219	Pancreatic	Italy	137	Neoadjuvant FOLFOXIRI and Surgery vs Neoadjuvant FOLFOXIRI and radiotherapy	NLR	OS	Multivariate NLR ≥4

								HR 2.42, 95%CI: 1.38-4.25, p<0.01
Hurwitz et al. (2015)	RECAP: NCT01423604	Pancreatic	United States	127	Capecitabine vs Capecitabine and ruxolitinib	mGPS	OS	Univariate mGPS 1/2 vs mGPS 0 HR 0.60, 95%CI 0.35-1.03, p<0.10
Goldstein et al. (2015)	MPACT: NCT00844649	Pancreatic	Multinational	861	Gemcitabine vs Gemcitabine and nab-paclitaxel	NLR	OS	Multivariate NLR≤5 HR 0.57, 95%CI 0.48-0.68, p<0.001
Renfro et al. (2017)	Multiple in ARCAD database	Colorectal	Multinational	22,654	Multiple chemotherapy trials	dNLR	30 day OS	Multivariate dNLR≥5 HR 1.74, 95%CI 1.25-2.41, p<0.01
Wood et al. (2017)	COIN: NCT00182715	Colorectal	United Kingdom and Ireland	1630	Oxaliplatin/fluoropyrimidine combination chemotherapy vs oxaliplatin/fluoropyrimidine combination chemotherapy and Cetuximab	dNLR	OS	Univariate dNLR≥2.2 HR 1.35, 95%CI 1.20-1.52, p<0.001
Thomsen et al. (2016)	NORDIC-VII: NCT00660582	Colorectal	Norway and Denmark	393	Cetuximab and FLOX vs. Cetuximab and intermittent FLOX	mGPS, dNLR	OS	Univariate mGPS1 vs 0 HR 1.60, 95%CI 1.27-2.01, p<0.001 mGPS 0 vs 2 HR : 2.16, 95%CI 1.52-3.06, p<0.001 dNLR>2.1 HR : 1.68, 95%CI 1.35-2.08, p<0.001
Passardi et al. (2016)	ITACa: NCT01878422	Colorectal	Italy	289	Standard chemotherapy vs. either FOLFIRI or FOLFOX4 and bevacizumab.	NLR	OS	Multivariate NLR ≥3 HR:1.78, 95%CI: 1.17-2.70, p<0.01
Correale et al. (2014)	GOLFIG-2 EUDRACT: 2005-003458-81	Colorectal	Italy	124	Gemcitabine, Oxaliplatin, Levofolinate, 5-Fluorouracil, Granulocyte-Macrophage Colony-Stimulating Factor, and Interleukin-2 (GOLFIG) Vs. FOLFOX Chemotherapy	NLR	OS	Univariate NLR< 3 HR 0.44, P< 0.001
Hazama et al. (2014)	Phase 1 HLA2402 matched	Colorectal	Japan	96	Comparison of five HLA-A*2402-restricted peptides, three derived from oncoantigens and two from vascular endothelial growth factor (VEGF)	NLR	OS	Univariate analysis: NLR≥3: p<0.05
Lorente et al. (2015)	Phase III TROPC trial	Prostate	United Kingdom	755	Cabazitaxel vs. mitoxantrone	NLR	OS	Multivariate NLR≥3 HR 1.55, 95% CI 1.3– 1.84, p<0.001
Van Soest et al. (2015)	VENICE: NCT00519285	Prostate	Multinational	1224 1006	Docetaxel/ prednisone and placebo vs Docetaxel/ prednisone and aflibercept	dNLR	OS	Multivariate dNLR ≥2.0 HR 1.29, 95% CI 1.11–1.50, p<0.001 dNLR ≥2.0

	TAX327: NCT01487902				Docetaxel/ prednisone and placebo vs Docetaxel/ prednisone and mitoxantrone			HR 1.43, 95% CI 1.20–1.70, p<0.001
Sonpavde et al. (2014)	SUN-1120: NCT00676650	Prostate	Multinational	848	Prednisone and sunitinib or placebo following docetaxel monotherpy	NLR	OS	Multivariate NLR Log-transformed HR 1.55, 95%CI 1.32-1.83, p<0.001
Linton et al. (2013)	AT-101-CS-205: NCT00571675	Prostate	United States and Russia	220	Docetaxel/prednisone vs Docetaxel/ pednisone and AT101	mGPS	OS	Multivariate mGPS HR 1.87, 95% CI 1.35-2.59, p<0.001 mGPS 2 vs 0 HR 3.44, 95%CI 1.75-6.76, p<0.001
Fox et al. (2013)	EGF20001	Renal	Multinational	362	Lapatinib versus hormone therapy	NLR PLR	OS	Multivariate: NLR>3 HR 1.42, 95%CI 1.10-1.84, p=0.008 Univariate: PLR>195 HR 1.88, 95%CI 1.48-2.37, p<0.0001
Ojerholm et al. (2017)	SWOG8710: NCT02756637	Bladder	United States	230	Cystectomy plus neoadjuvant chemotherapy vs. cystectomy alone	NLR	OS	Multivariate NLR (continuous) HR 1.04, 95%CI 0.98-1.11, p=0.24
Honecker et al. (2017)	PELICAN: NCT00266799	Breast	Germany	210	First-line pegylated liposomal doxorubicin (PLD) vs. capecitabine.	GPS	OS	Multivariate GPS: p<0.10
Romano et al. (2015)	Multiple: GIMEMA MMY-3006, GIMEMA MM03-05, RV-MM-PI209, J0231	Multiple Myeloma	Italy	309	Multiple trials on newly diagnosed multiple myeloma treated with novel therapies	NLR	OS	Univariate analysis: NLR≥2: p=0.0002
Bigot et al. (2017)	ICT –Phase 1 trial	Multiple	France	155	Standard treatment vs. Immune checkpoint treatment	NLR	OS	Multivariate NLR≥6 HR 1.75, 95%CI 1.04-2.94, p<0.05
Kumar et al. (2015)	Multiple Phase 1 (RMH)	Multiple	United Kingdom	1300	Dose and toxicity finding study for chemotherapy in multiple phase 1 chemotherapy trials	NLR	OS	Univariate Test Cohort, NLR>4.45 HR 1.78, 95%CI 1.41-2.87, p<.0001 Validation Cohort, NLR>4.45 HR 1.57, 95%CI 1.42-1.97, p<0.001
Chua et al. (2012)	Single Agent Phase 1	Multiple	Australia	68	Docetaxel monotherapy vs. standard treatment	GPS NLR	OS	Multivariate GPS HR 4.1, 95%CI 2.2-7.7, p<0.0001

								NLR>5 HR 2.0, 95%CI 1.2-3.3, p=0.010

Table 2: The relationship between the systemic inflammatory response and survival in randomised clinical trials in patients with cancer (published abstracts)

Authors	**Randomised Clinical Trial**	**Tumour Type**	**Country**	**Patients (n)**	**Randomised Clinical Trial**	**Systemic Inflammation**	**Outcome**	**Comment**
Diakos et al. (2016a)	CO.17 NCT00640471 CO.20 NCT00079066	Colorectal	Australia and Canada	572 750	CO.17: Cetuximab vs. best supportive care, CO.20: Brivanib (B) vs. placebo	dNLR	OS	Multivariate dNLR≥2 CO.17 HR 1.4, 95% CI 1.1-1.8, p <0.01 CO.20 HR 1.4, 95% CI 1.2-1.6, p<0.0001
Diakos et al. (2016b)	AGITG MAX	Colorectal	Australia	471	Capecitabine and bevacizumab vs. Capecitabine and bevacizumab and mitomycin C	NLR	OS	Multivariate NLR≥5 HR 1.8, 95%CI 1.3-2.3, p<.0001
De Maio et al. (2017)	ECRTC 62043/62072	Sarcoma	Belgium	333	Pazopanib vs placebo	NLR	OS	Univariate NLR>3 HR 1.86, 95%CI 1.43-2.41, p<0.001
Coleman et al. (2017)	Phase 1 Trial	Recurrent Primary Malignant Brain Tumour	United Kingdom	100	Primary corticosteroid vs. best supportive care	NLR	OS	Multivariate NLR≥4 HR 1.73, 95%CI 1.02-2.94, p=0.043
Wang-Gillam et al. (2017)	NAPOLI-1: NCT01494506	Pancreatic	Multinational	116	Iposomal irinotecan + 5-fluorouracil and leucovorin vs 5-fluorouracil and leucovorin alone	NLR PLR	OS	Univariate NLR≤5 HR 0.62, 95%CI 0.44-0.86, p=0.005 PLR≤150 HR 0.52, 95%CI 0.32-0.84, p=0.008
Smyth et al. (2017)	REAL 3: NCT00824785	Oesophagogastric	United Kingdom	553	Epirubicin, Oxaliplatin, Capecitabine (EOC) vs EOC plus panitumumab (EOC-P)	NLR	OS	Univariate NLR: Upper Tertile EOC cohort HR: 9.97, 95%CI 7.43-15.43, p<0.001 ECP-P cohort HR: 5.26, 95%CI 4.28-7.17, p<0.001
Clarke et al. (2018)	ASCENT: NCT01588990	Colorectal	Australia	128	First line BEV+XELOX or mFOLFOX6 in phase A (PhA) with planned continuation of BEV+FOLFIRI beyond 1st progression in phase B (PhB).	NLR	OS	Univariate: NLR>5 HR: 1.6, 95% CI 1.0-2.7, p = 0.052
Argiles et al. (2018)	RECOURSE: NCT01607957	Colorectal	Multinational	782	Trifluridine/tipiracil (TAS-102) vs placebo	NLR	OS	Multivariate: NLR≥3: p = 0.15