LYNPARZA® (olaparib) in prostate cancer:

Managing adverse events

This document has been developed as a Healthcare Professional Aid. For use by UK healthcare professionals only.

Lynparza olaparib

LYNPARZA (olaparib) is indicated:

- In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated[1]
- As monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA1/2 mutations (germline and/or somatic) who have progressed after prior therapy that included a new hormonal agent (NHA)[2]

NICE recommended/SMC accepted

- LYNPARZA in combination with abiraterone and prednisone or prednisolone is NICE recommended/SMC accepted for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated[1,3]
- LYNPARZA monotherapy is recommended by NICE and accepted by SMC for treating hormone-relapsed prostate cancer (HRPC) in adult men that has progressed after first-line hormonal therapy or enzalutamide or abiraterone[4,5]

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk. Adverse events should also be reported to AstraZeneca UK Ltd on 0800 ... or medicalinformationuk@astrazeneca.com

For a full list of adverse events (AEs), please refer to the Great Britain SmPC and Northern Ireland SmPC here.

Click on the Medicines Q&A tab to view the Prescribing Information (SB) or Prescribing Information (NI) for LYNPARZA® (olaparib) Great Britain/Northern Ireland.

LYNPARZA is a PARP inhibitor:

- Developed to specifically **target DNA repair pathways**[6]
- Preferentially **kills cancer cells with defective DNA repair** compared for a range of indications, including those with wild-type BRCA1/2 genes, compared with those with functional DNA repair[7-12]
- Indicated as monotherapy for the treatment of patients with **metastatic castration-resistant prostate cancer (mCRPC) and BRCA1/2 mutations** (germline and/or somatic) who have progressed after prior therapy that included a NHA[2]
- Indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated[1]

LYNPARZA clinical trials

PROlonged was a Phase III, randomised, open-label, multicentre study that evaluated the efficacy and safety of LYNPARZA monotherapy versus physician's choice of NHA in patients with mCRPC.[13,14]

PROlonged study design[13,14]

PROlong was a Phase III, randomised, double-blind, placebo-controlled, multicentre study evaluating the efficacy and safety of LYNPARZA in combination with abiraterone and prednisone or prednisolone versus placebo in combination with abiraterone and prednisone or prednisolone in patients with mCRPC in the first-line setting.[15]

PROlong study design[15]

AEs are mostly mild or moderate in patients treated with LYNPARZA[1]

The most frequently (very common (≥10%)) observed all-grade AEs in clinical trials investigating LYNPARZA monotherapy were:

- Anaemia
- Nausea
- Vomiting
- Diarrhoea
- Dyspepsia
- Arasenia
- Leukopenia
- Fatigue (including asthenia)
- Decreased appetite
- Headache
- Dizziness
- Dysgeusia
- Cough

AEs associated with LYNPARZA are generally of **mild or moderate severity (CTCAE grade 1 or 2)**

When LYNPARZA is used in combination with abiraterone and prednisone or prednisolone for mCRPC, the safety profile is generally consistent with that of the individual therapies.

Anaemia, fatigue and nausea are commonly reported AEs with PARPi[16]

- Very common (≥10%) all-grade AEs reported with abiraterone and LYNPARZA in the Phase III PROlong study were anaemia (20.8%), nausea (19.6%), fatigue (including asthenia) (17.8%), vomiting (11.2%), diarrhoea (10.8%), constipation (10.8%), decreased appetite (10.8%), dyspepsia (10.8%), hypertension (15.3%), arthralgia (14.6%), COVID-19 (12.8%), peripheral oedema (12.3%), dizziness (12.3%), cough (11.8%) and urinary tract infection (11.8%)[17]

Haematological toxicity and pneumonitis are included as special warnings on the LYNPARZA SmPC and should be monitored for in patients taking LYNPARZA monotherapy. Hypertension is included as a special warning on the LYNPARZA SmPC when used in combination with abiraterone and prednisone or prednisolone.

AEs associated with LYNPARZA monotherapy in PROlonged[1]

AEs associated with LYNPARZA plus abiraterone and prednisone or prednisolone in PROlong[1]

Very common (≥10% people) Common (≥1/100 to <1/10 people)

AEs with special warnings and precautions associated with LYNPARZA can be found below in the assessment, it's a full list of AEs, please see the SmPC.

Blood, GI, general disorders and respiratory disorders are the most frequently reported AEs after treatment with LYNPARZA[1]

Frequency of selected blood, GI, general and vascular grade ≥3 AEs[1]

Blood disorders	GI disorders	General disorders	Vascular disorders
Anaemia	Nausea	Fatigue (including asthenia)	VTE
Neutropenia	Vomiting		
Thrombocytopenia	Diarrhoea		
Leukopenia			
Lymphopenia			

AEs observed with LYNPARZA monotherapy in PROlonged

AEs observed with LYNPARZA plus abiraterone and prednisone or prednisolone in PROlong

Very common (≥10 people) Common (≥1/100 to <1/10 people)

AEs with special warnings and precautions associated with LYNPARZA can be found below in the assessment, it's a full list of AEs, please see the SmPC.

In LYNPARZA monotherapy, common AEs typically occur early in the treatment of mCRPC and are expected to resolve within 6 months of treatment initiation[18]

AEs associated with LYNPARZA[18]

Figure adapted from Fizazi et al. Ann Oncol 2017;28:465-472.

In LYNPARZA plus abiraterone combination treatment of mCRPC, common AEs typically occur early and are expected to resolve within 9 months of treatment initiation[17]

AEs associated with LYNPARZA[17]

AEs associated with abiraterone[19]

Adverse events in both treatment arms, regardless of treatment relationship, occurring in ≥5% of patients receiving LYNPARZA plus abiraterone combination versus those receiving placebo plus abiraterone. Hypertension, hypokalaemia, muscle weakness and myopathies/myositis, hypertension/hypertensive disorders and flush/sweat, decreased appetite, nausea, fatigue, vomiting, anaemia, cardiac failure, and cardiac disorders were considered treatment-emergent adverse events of special interest.

Consistent with observations in other PARP inhibitor studies in mCRPC, VTEs were observed at a higher proportion of patients receiving LYNPARZA plus abiraterone combination versus those receiving placebo plus abiraterone[20]

Proportion of patients with VTE events (SMQ across treatment arms[20]

PEs have been observed in PARP inhibitor studies in mCRPC based on PROlong[20]

Cancer and cancer treatments are risk factors for PE[21]

- In PROlong, 4.3% of patients treated with LYNPARZA combination and 0.8% of patients in the control arm treated with abiraterone or enzalutamide developed PE[20]
- In OLAPARIS, 5.8% of patients treated with olaparib monotherapy experienced PE[22]

Currently, the mechanism of this effect is unknown.

Most PEs were asymptomatic and incidental on imaging,[20] being slight for VTEs in the assessment of patients with advanced prostate cancer is important.

Please refer to the section on AEs with special warnings and precautions for LYNPARZA in this document and the LYNPARZA SmPC for further information on patient monitoring.

Data in grouped adverse events (AEs) based on standardised MedDRA queries (SMQs) and preferred terms (PTs). Pulmonary embolism (PE) was reported in cases quoted by SMQ name and thromboembolic (TE) which can include venous and arterial events and haemorrhagic TE (HMTE) in a subjectively defined manner. Patients in each group were followed for a median of 12 months (range: 0.1-24.6+ months) for LYNPARZA plus abiraterone and 11.1 months (range: 0.1-24.6+ months) for placebo plus abiraterone.

The rate of CV and AEHF events is similar between the LYNPARZA plus abiraterone combination arm and the placebo plus abiraterone arm[20]

Proportion of patients with AEHF events (SMQ across treatment arms[20]

Proportion of patients with cardiac failure (SMQ across treatment arms[20]

Results from the third data cut-off: 13 October 2021.

Cardiac failure was reported in patients with cardiomyopathy/myocarditis/ischaemia/infarction/arrhythmia/conduction disorder/valvular disorder/congenital/pericardial and pulmonary disorders, respectively. Cardiac failure included acute pulmonary oedema, cardiac failure, acute cardiac failure, chronic congestive heart failure, congestive cardiomyopathy, congestive hepatopathy, and congestive hepatitis.

Rates of PE AEs and evaluation across treatment arms in the PROlong study[20]

	LYNPARZA + abiraterone (n=797)	Placebo + abiraterone (n=795)
Any PE AE (n,%)	34 (4.3)	6 (0.8)
Grade ≥3 AEs (n,%)	17 (2.1)	2 (0.3)
PE events (n,%)	37 (4.6)	7 (0.9)
LYNPARZA or placebo dose interruption (n,%)	12 (32.4)	2 (28.6)
Evaluation of PE events (n,%)		
Medical follow-up visit	10 (27.0)	2 (28.6)
Hospitalisation/prolonged hospitalisation	9 (24.3)	1 (14.3)
Administration of DTC prior to PE, n (%)	1 (2.7)	0 (0.0)
Administration of DTC post PE, n (%)	1 (2.7)	0 (0.0)

- In the LYNPARZA plus abiraterone arm, PE led to LYNPARZA and abiraterone dose interruption in 32.4% and 8.1.5% patients, respectively
- In the placebo arm, PE led to LYNPARZA and abiraterone dose interruption in 28.6% and 0.1.5% patients, respectively

Results from the third data cut-off: 13 October 2021.

Patients in both treatment arms are included (patients randomised to 1 mg BID, patients who received prednisone/prednisolone 5 mg BID, patients who received unknown dose of prednisone/prednisolone).

Most patients recovered from the event and were able to continue LYNPARZA with the introduction of anticoagulant treatment based on standard medical practice.[1]

Patients in both treatment arms are included (patients randomised to 1 mg BID, patients who received prednisone/prednisolone 5 mg BID, patients who received unknown dose of prednisone/prednisolone).

Overview of the LYNPARZA AE management process[23,24,25]

Supportive therapy
Dose interruption
Dose reduction
Discontinuation
Assess for underlying causes
Consider other causes
Consider other causes
Consider other

PROfound study design[1,9,11]

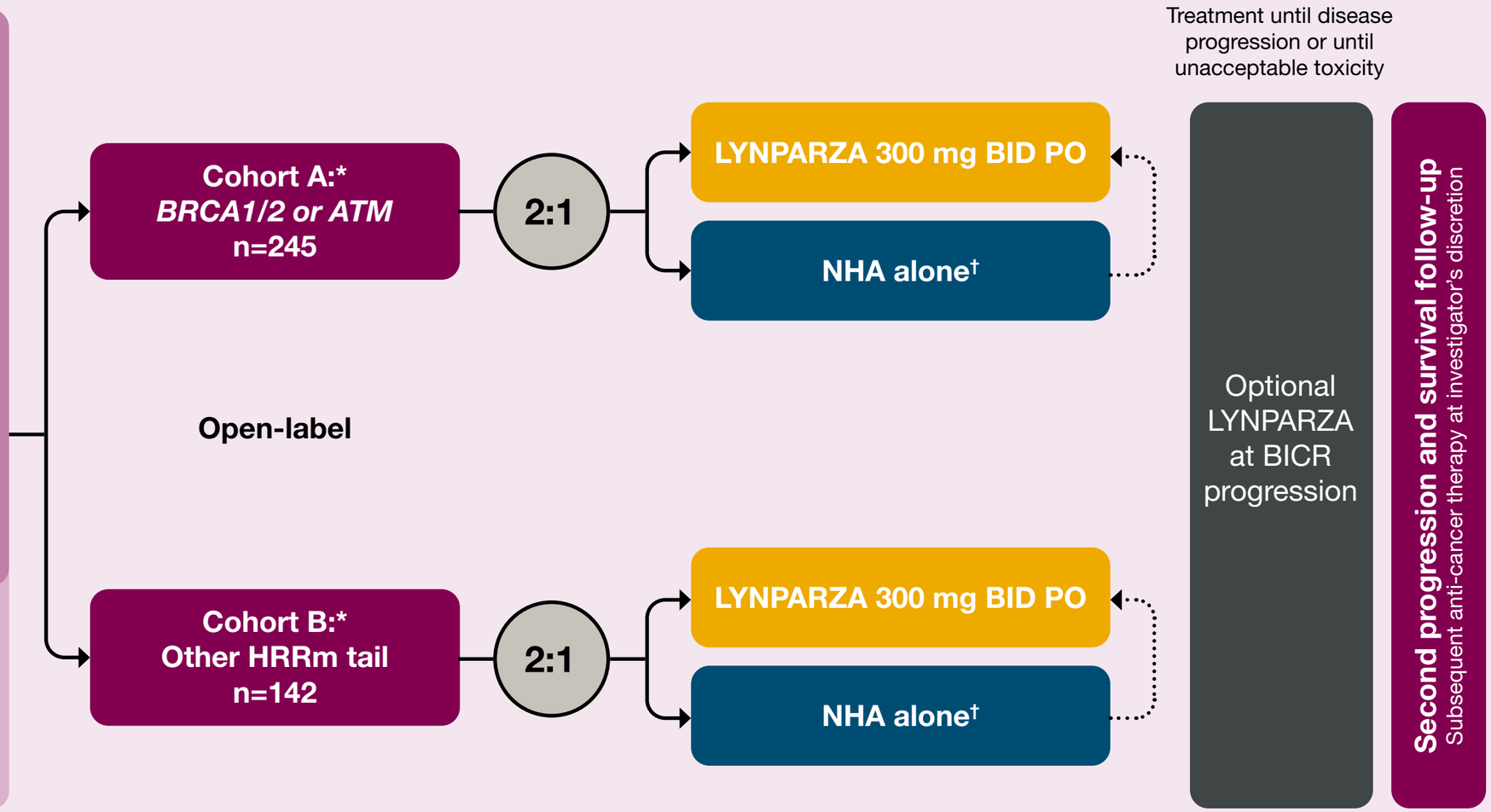
N=387

Patient population

- Documented mCRPC
- Qualifying HRR mutation
- Investigator-assessed progression on NHA for metastatic prostate cancer and/or CRPC
- Radiographic progression at study entry while on ADT (or after bilateral orchiectomy)
- ECOG PS 0–2
- No prior treatment with a PARPi/any DNA-damaging cytotoxic chemotherapy for prostate cancer

Stratification factors

- Previous taxane therapy (yes or no)
- Measurable disease at baseline v1.1 (yes or no)



Primary endpoint

- rPFS by BICR in Cohort A, using RECIST v1.1 (soft tissue) and PCWG3 (bone) criteria

Key secondary endpoint

- BICR-confirmed ORR (Cohort A)
- rPFS by BICR (Cohorts A + B)
- TTPP (Cohort A)
- OS (Cohort A)
- Safety and tolerability

*Cohort A included patients with *BRCA1, BRCA2 or ATM mutations, Cohort B* included patients with *BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D or RAD54L* mutations.[9]

†Physician's choice of enzalutamide (160 mg QD) or abiraterone (1000 mg QD plus prednisone at 5 mg BID).[9]

BICR, blinded independent central review; BID, twice daily; CRPC, castration-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; ORR, objective response rate; OS, overall survival; PCWG3, Prostate Cancer Clinical Trials Working Group 3; RECIST, Response Evaluation Criteria in Solid Tumours; rPFS, radiographic progression-free survival; TTPP, time to pain progression.

PROpel study design[12,13]

N=796

Patient population

- First-line mCRPC
- Docetaxel during neoadjuvant/adjuvant treatment for localised prostate cancer and mHSPC was permitted
- Other NHAs permitted if treatment was stopped >12 months prior to randomisation*
- ECOG PS 0–1

Stratification factors

- Metastases: bone only vs visceral vs other
- Docetaxel treatment at mHSPC stage: yes or no

1:1

Double-blind

LYNPARZA 300 mg BID†
+
Abiraterone 1000 mg QD†
+
prednisone/prednisolone 5 mg BID
n=399

Placebo
+
Abiraterone 1000 mg QD†
+
prednisone/prednisolone 5 mg BID
n=397

Treatment was initiated with full doses of LYNPARZA and abiraterone, maximising the effectiveness of the combination

Primary endpoint

- rPFS by investigator assessment§
- Pre-specified sensitivity analysis of rPFS by BICR

Key secondary endpoint

- OS

Additional endpoints:

- TFST
- PFS2
- HRQoL (FACT-P)
- ORR
- Time to an SSRE
- CTC conversion
- Time to opiate use
- HRRm prevalence (pre-defined, post-randomisation testing)
- Safety and tolerability

*Except abiraterone; †Both therapies were used at full dose, equivalent to monotherapy regimens;[12] ‡Following objective disease progression, further treatment was at investigator discretion; §rPFS assessed by investigator per RECIST 1.1 (soft tissue) and PCWG-3 (bone) criteria; ¶AEs and serious AEs as defined by CTCAE version 4.03.[12]
BICR, blinded independent central review; BID, twice daily; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PFS2, time to second progression or death; rPFS, radiographic progression-free survival; TFST, time to first subsequent therapy or death.

CTCAE[14]

- A descriptive terminology used for AE reporting
- A grading (severity) scale is provided for each AE term

Mild
- Asymptomatic or mild symptoms
- Clinical or diagnostic observations only
- Intervention not indicated

Severe or medically significant, but not immediately life-threatening
- Hospitalisation or prolongation of hospitalisation indicated
- Disabling and limiting self-care ADL*

Grade 1 — Grade 2 — Grade 3 — Grade 4 — Grade 5

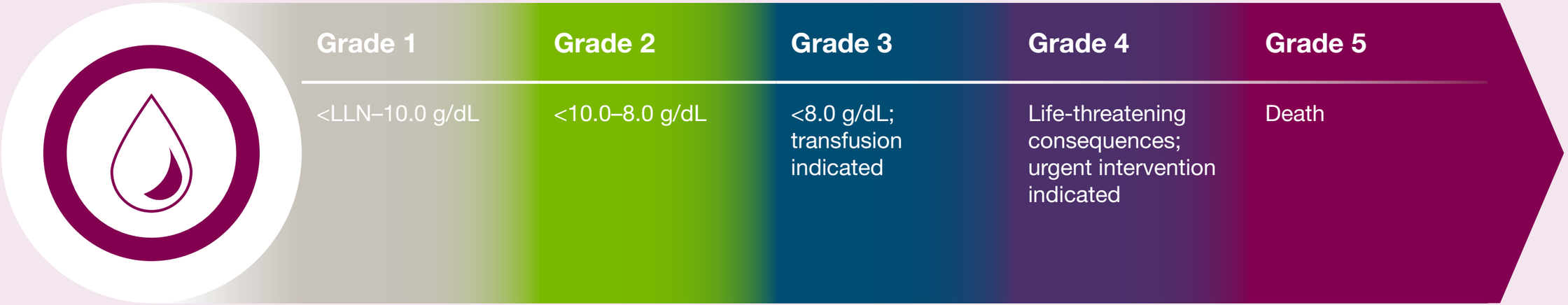
Moderate
- Minimal, local or non-invasive intervention indicated
- Limiting age-appropriate instrumental ADL†

Life-threatening consequences
- Urgent intervention indicated

Death
- Related to AE

*Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden; †Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
ADL, activities of daily living; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

Anaemia: A reduction in the amount of haemoglobin in the blood[14]



Signs and symptoms: Pallor of skin and mucous membranes, shortness of breath, heart palpitations, soft systolic murmurs, lethargy and fatigability[14]

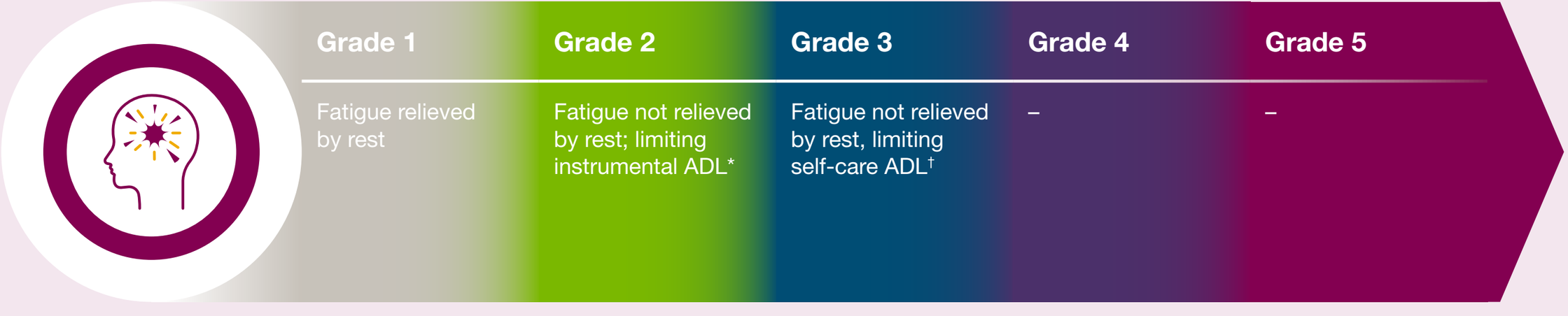
LLN, lower limit of normal.

Nausea: A queasy sensation, with or without the urge to vomit[14]

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition or hospitalisation indicated	–	–

A dash (–) indicates a grade is not available. Not all grades are appropriate for all AEs.
AE, adverse event.

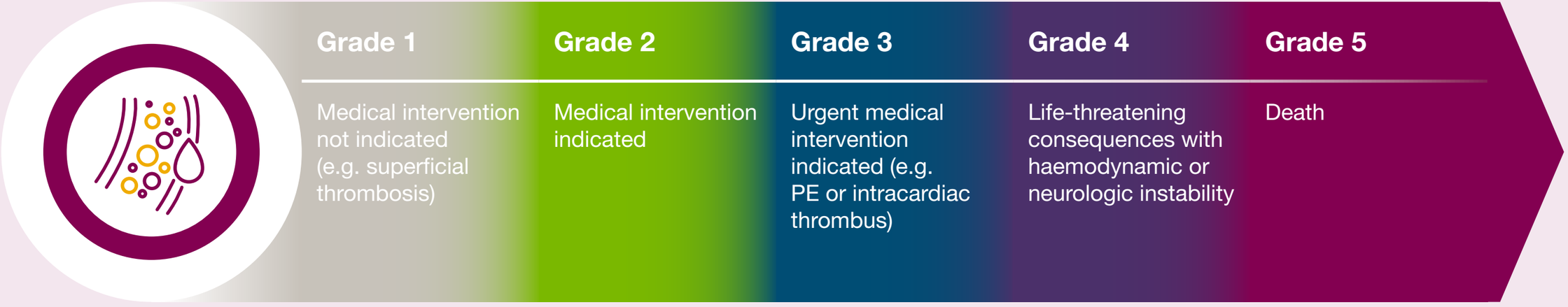
Fatigue: A state of generalised weakness with a pronounced inability to summon sufficient energy to accomplish daily activities[14]



Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL*	Fatigue not relieved by rest, limiting self-care ADL†	–	–

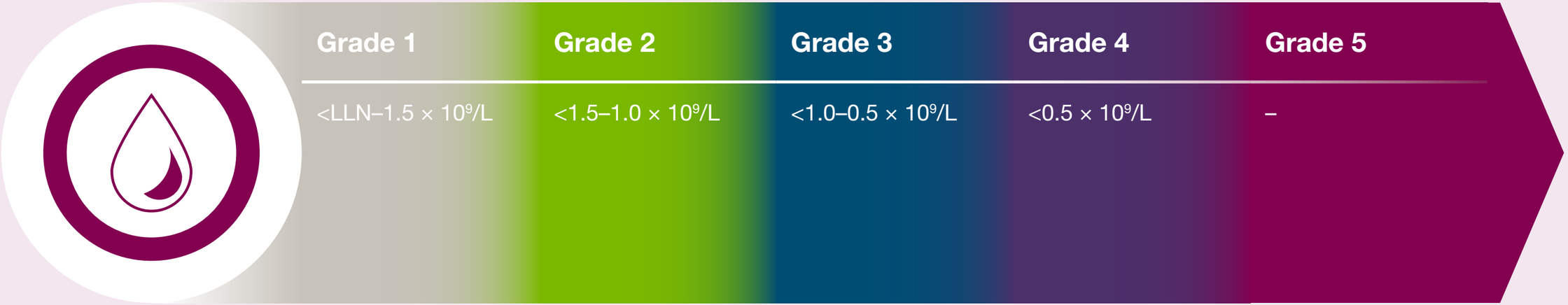
*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc; †Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.
A dash (–) indicates a grade is not available. Not all grades are appropriate for all AEs.
ADL, activities of daily living; AE, adverse event.

VTE: An occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream[14]



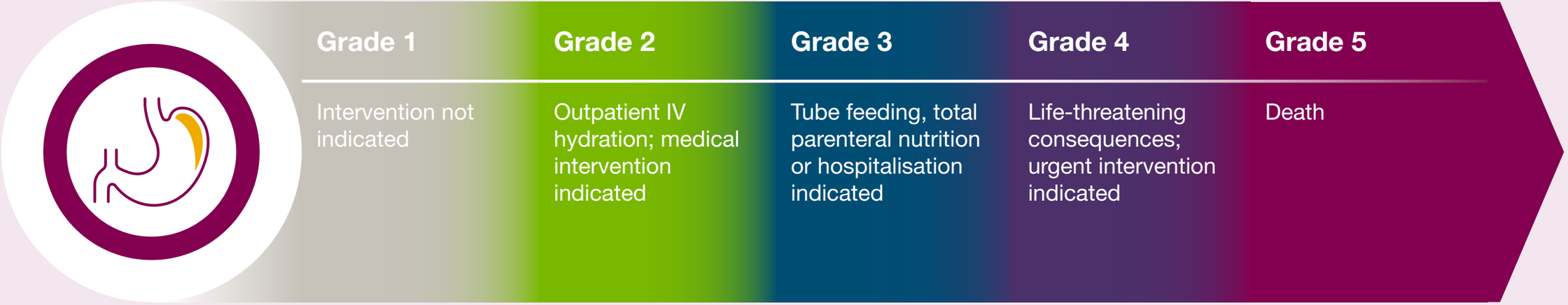
PE, pulmonary embolism; VTE, venous thromboembolism.

Neutropenia: A decrease in the number of neutrophils in the blood[14]



A dash (–) indicates a grade is not available. Not all grades are appropriate for all AEs.
AE, adverse event; LLN, lower limit of normal.

Vomiting: The reflexive act of ejecting the contents of the stomach through the mouth[14]



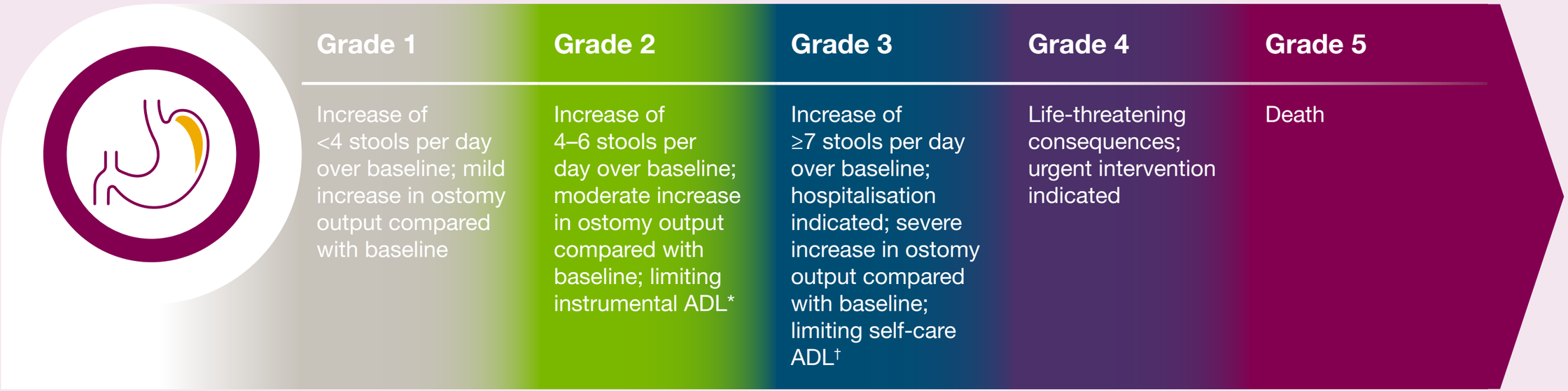
IV, intravenous.

Thrombocytopenia: A decrease in the number of platelets in the blood[14]

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
<LLN–75.0 × 10^9/L	<75.0–50.0 × 10^9/L	<50.0–25.0 × 10^9/L	<25.0 × 10^9/L	–

A dash (–) indicates a grade is not available. Not all grades are appropriate for all AEs.
AE, adverse event; LLN, lower limit of normal.

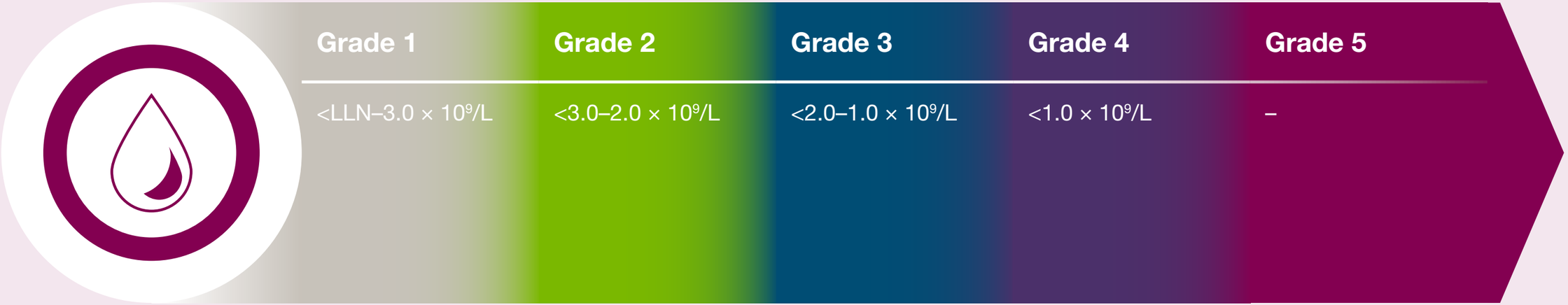
Diarrhoea: An increase in the frequency of or loose or watery bowel movements[14]



Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared with baseline; limiting instrumental ADL*	Increase of ≥7 stools per day over baseline; hospitalisation indicated; severe increase in ostomy output compared with baseline; limiting self-care ADL†	Life-threatening consequences; urgent intervention indicated	Death

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc; †Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.
ADL, activities of daily living.

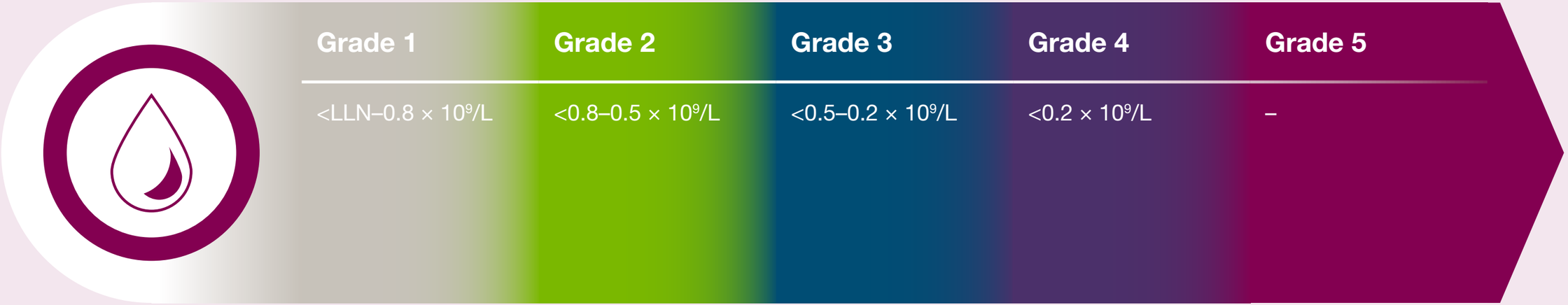
Leukopenia: A decrease in the number of white blood cells in the blood[14]



Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
<LLN–3.0 × 10^9/L	<3.0–2.0 × 10^9/L	<2.0–1.0 × 10^9/L	<1.0 × 10^9/L	–

A dash (–) indicates a grade is not available. Not all grades are appropriate for all AEs.
AE, adverse event; LLN, lower limit of normal.

Lymphopenia: A decrease in the number of lymphocytes in the blood[14]



Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
<LLN–0.8 × 10^9/L	<0.8–0.5 × 10^9/L	<0.5–0.2 × 10^9/L	<0.2 × 10^9/L	–

A dash (–) indicates a grade is not available. Not all grades are appropriate for all AEs.
AE, adverse event; LLN, lower limit of normal.

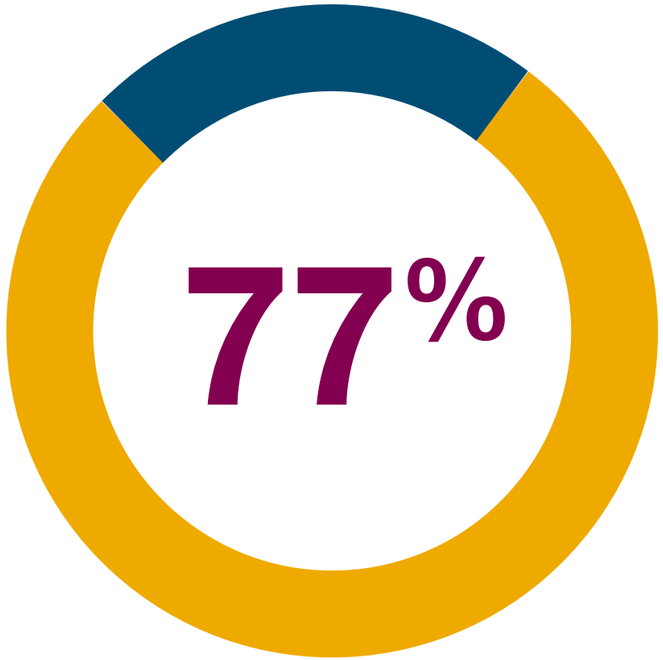
AEs observed in the LYNPARZA monotherapy arm of the PROfound study[22]

AE, n (%)	All grades	Grade ≥3
Anaemia	127 (50)	58 (23)
Nausea	110 (43)	4 (2)
Fatigue or asthenia	107 (42)	8 (3)
Decreased appetite	80 (31)	4 (2)
Diarrhoea	55 (21)	2 (<1)
Constipation	49 (19)	0
Back pain	34 (14)	2 (<1)
Peripheral oedema	34 (13)	0
Cough	29 (11)	0
Dyspnoea	27 (11)	6 (2)
Vomiting	51 (20)	6 (2)
Arthralgia	26 (10)	1 (<1)
Urinary tract infection	21 (8)	5 (2)

n=256.
AE, adverse event.

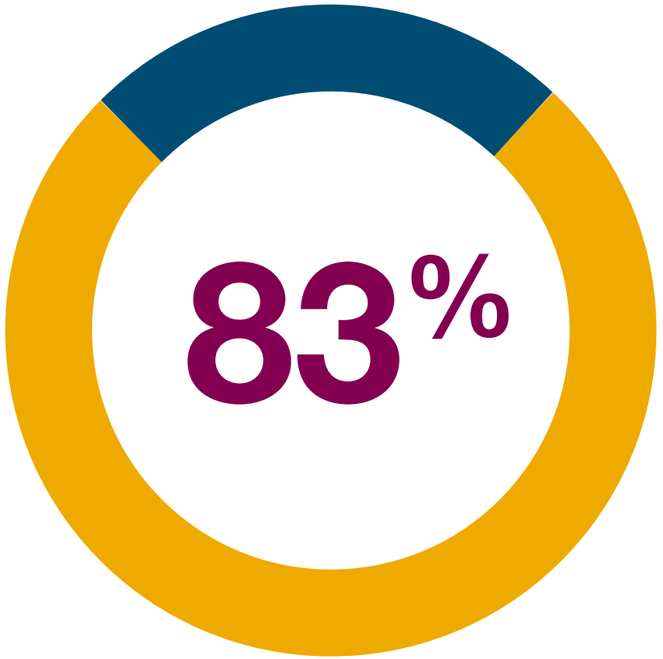
In the LYNPARZA plus abiraterone combination arm of the PROpel study, 8 out of 10 patients remained on LYNPARZA without discontinuation due to AEs[23]

No dose reduction



of patients **remained on the full dose of LYNPARZA** without needing a dose reduction due to AEs

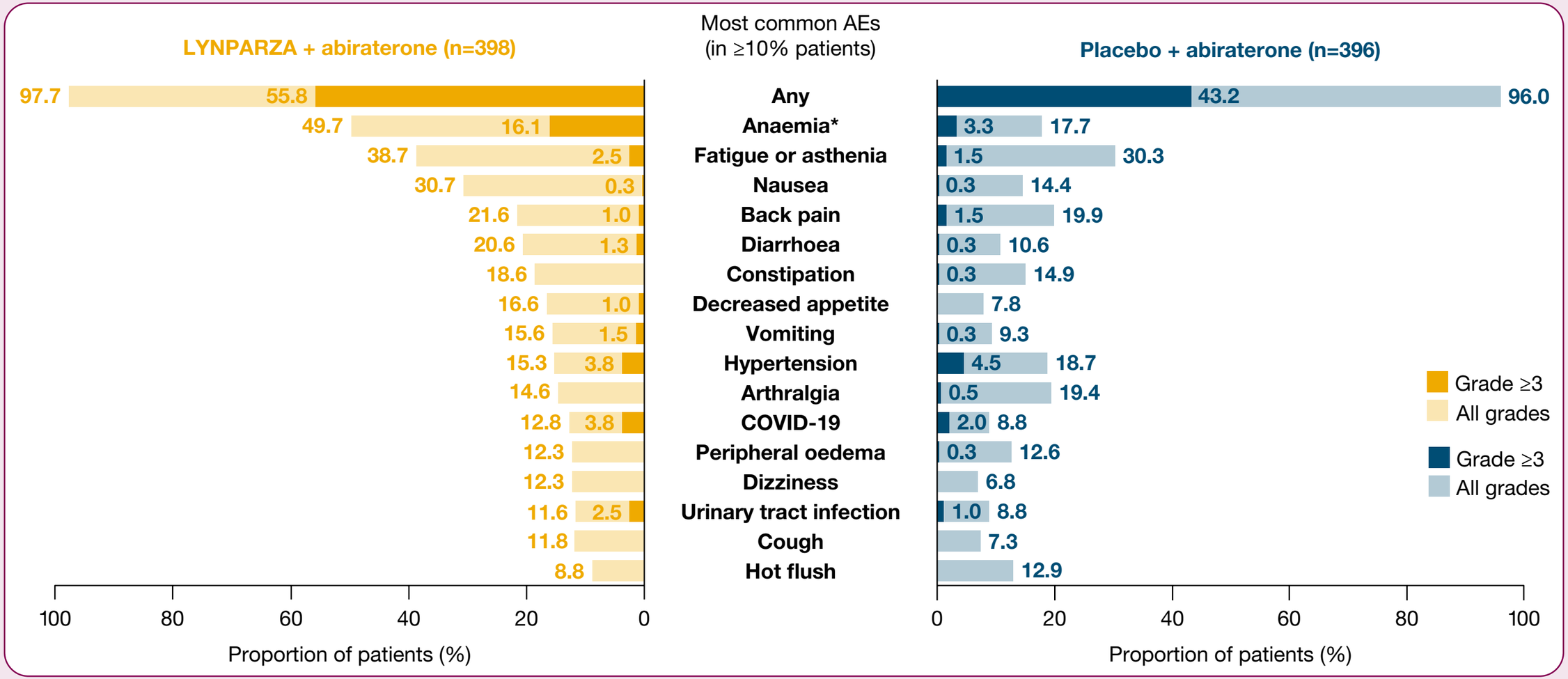
No discontinuation



of patients **remained on LYNPARZA** without discontinuation due to AEs

Patients in both treatment arms also received prednisone/prednisolone 5 mg BID.
Results from the data cut-off at final pre-specified analysis: 12 October 2022.
AE, adverse event.

AEs observed in the LYNPARZA plus abiraterone combination arm of the PROpel study[15]



Results from the third data cut-off at primary analysis: 12 October 2022.
Safety was assessed through the reporting of AEs according to the NCI CTCAE v4.03 and laboratory assessments.
Patients in both treatment arms also received prednisone/prednisolone 5 mg BID.
*Anaemia category includes anaemia, decreased haemoglobin level, decreased red blood cell count, decreased haematocrit level, erythropenia, macrocytic anaemia, normochromic anaemia, normochromic normocytic anaemia and normocytic anaemia.
AE, adverse event.

Posology[1,13]

Recommended dose[1] →

Two 150 mg tablets → **300 mg twice daily**

If dose reduction is required to manage AEs

Dose reduction[1] →

One 150 mg tablet and one 100 mg tablet → **250 mg twice daily**

Following dose reduction, the patient cannot recommence the starting dose at any point[13]

Further dose reduction[1] →

Two 100 mg tablets → **200 mg twice daily**

There are only two dose reductions indicated for LYNPARZA

Tablets not to scale.
For concomitant administration with CYP3A inhibitors, or for patients with hepatic or renal impairment, please consult the LYNPARZA 100 mg and 150 mg tablet SmPC for specific dose reductions.
AE, adverse event; CYP3A, cytochrome P450, family 3, subfamily A; SmPC, Summary of Product Characteristics.