Current challenges in the management of follicular lymphoma

Maryam Sarraf Yazdy¹ & Chaitra Ujjani^{*,1}

Practice points

Prognostic models

- The M7 Follicular Lymphoma International Prognostic Index is a newer risk stratification model which incorporates both genetic and clinical data to determine prognosis in patients with follicular lymphoma.

Front-line regimens

- Bendamustine plus rituximab and rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone are accepted front-line regimens for symptomatic advanced stage follicular lymphoma. The latter has become increasingly popular based on tolerability.

Postinduction prognostic features

- Postinduction features including achievement of a PET-negative complete remission and maintenance of a complete remission at 30 months have prognostic implications.
- Progression of disease within 2 years of front-line immunotherapy is associated with an inferior overall survival.

Improving treatment regimens

- The combination of lenalidomide and rituximab has produced ORRs >90% and CR >70% in previously untreated disease, prompting the Phase III RELEVANCE trial of chemoimmunotherapy versus lenalidomide + rituximab.
- Although improved in relapsed follicular lymphoma after two lines of therapy, idelalisib has produced serious infectious adverse events.
- Obinutuzumab is currently approved for rituximab-refractory follicular lymphoma and has demonstrated an improvement in progression-free survival when combined with chemotherapy in the front-line setting compared with rituximab-based chemoimmunotherapy.

Conclusion

- Newer antibody-based therapies, small molecule inhibitors and immune-directed agents carry the promise of effective treatment with less toxicity.
- Considerable effort must be placed on incorporating these avenues into treatment algorithms in order to improve long-term outcomes in follicular lymphoma.

Although typically indolent in nature, follicular lymphoma remains an ongoing challenge for practicing oncologists. While response rates >90% can be achieved with rituximab-based chemoimmunotherapy in advanced stage patients, the complete remission rates are substantially lower and patients inevitably relapse. The inability to achieve a complete remission and an early progression of disease have recently been determined to be indicative of poorer long-term outcomes. A greater understanding of the pathogenesis of follicular lymphoma has enabled the development of targeted therapies, which may improve standard treatment approaches. Examples include lenalidomide and obinutuzumab, which are currently in front-line Phase III investigation. Other therapies

¹Lombardi Comprehensive Cancer Center, Medstar Georgetown University Hospital, Washington, DC 20007, USA

*Author for correspondence: Tel.: +1 202 444 0596; Fax: +1 202 444 9429; csu@georgetown.edu

of interest include small molecule inhibitors, immune checkpoint inhibitors and chimeric antigen receptor T cells.

First draft submitted: 14 February 2017; Accepted for publication: 24 March 2017; Published online: TBC

KEYWORDS

- antibody–drug conjugate
- CAR T cell • follicular lymphoma • ibrutinib
- idelalisib • immune checkpoint inhibitor
- lenalidomide • minimal residual disease
- obinutuzumab • PET-CT

Although typically indolent in nature, follicular lymphoma remains an incurable disease and an ongoing challenge for practicing oncologists. As the second most common type of non-Hodgkin lymphoma (NHL), it has an estimated incidence of 3.18 cases per 100,000 people in the USA annually [1]. The incidence varies with age, sex and ethnicity; the median age of diagnosis is 60 years and there is a higher incidence among whites than blacks [2]. The presence of an affected family member increases the risk of developing follicular lymphoma up to fourfold based on a retrospective analysis of 2668 patients [3].

The pathogenesis of the disease is a complex, multistep process which begins with the translocation (14; 18), resulting in overexpression of the anti-apoptotic BCL2 protein. The occurrence of t(14, 18) in 50–70% of healthy individuals implies that the translocation alone is not sufficient for the tumorigenesis and other genetic abnormalities and tumor microenvironment factors facilitate the process [4,5]. Tonic signaling through the B-cell receptor (BCR) and its downstream pathways, such as phosphatidylinositol 3-kinase (PI3K) and Bruton's tyrosine kinase, is theorized to be an additional critical element in supporting cell proliferation and survival [6]. Furthermore, the short survival of follicular lymphoma cell lines *in vitro* highlights the need for stimulation from nonmalignant immune-related cells such as T cells and macrophages in the tumor microenvironment [7]. Tumor cells are known to secrete IL-12 in order to escape immunosurveillance and induce T-cell exhaustion [8].

The heterogeneity in follicular lymphoma, including the pathologic distinctions and the lack of uniformity in clinical course, may be attributed to variations in the above mentioned components of pathogenesis and other contributing factors. Understanding how some of these features contribute to poorer outcomes for patients is an important part of combating this disease. Current challenges in the management of follicular lymphoma entail identification of better prognostic models and predictive markers, incorporation of targeted therapies to devise superior front-line regimens and improving outcomes for relapsed and refractory patients.

Prognostic models

Aside from histologic grade, the Follicular Lymphoma International Prognostic Index (FLIPI) has been the traditional method for evaluation of prognosis. The FLIPI, devised based on a retrospective analysis of 4167 patients, includes five parameters: age >60 years, stage III or IV, hemoglobin level <12.0 g/dl, number of involved nodal areas >4 and serum lactate dehydrogenase level greater than the upper limit of normal. The 10-year overall survival (OS) rates for the low, intermediate and high risk groups were 71, 51 and 36%, respectively [9]. As FLIPI was based on data prior to rituximab, the FLIPI-2 was designed to evaluate long-term outcomes in the era of anti-CD20 directed therapy. It was developed based on a prospective analysis performed on 942 patients receiving their first line of treatment, 559 of whom received rituximab. Five parameters, with some overlapping features of the original FLIPI, were identified: age >60 years, bone marrow involvement, hemoglobin level <12.0 g/dl, greatest diameter of the largest involved node >6 cm and an elevated serum β -2 microglobulin level [10]. The 5-year progression-free survival (PFS) rates for low, intermediate and high risk groups were 80, 51 and 19%. An external validation was performed on a sample of 231 cases, which showed the 5-year OS to be 96, 80 and 59%.

The M7-FLIPI is a newer risk stratification model which has incorporated both genetic and clinical data obtained retrospectively from symptomatic, advanced stage patients receiving front-line chemoimmunotherapy [11]. DNA deep sequencing was used to analyze 74 genes from 151 biopsy samples collected within 1 year of starting treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) in the Phase III GLSG2000 trial. The model incorporated the mutational status of seven genes (*EZH2*, *ARID1A*, *MEF2B*, *EP300*, *FOXO1*, *CREBBP* and *CARD11*), performance status and FLIPI. The failure-free survival at 5 years was 77% in the low-risk group compared with 38% in the high-risk group. The M7-FLIPI was validated in an independent cohort of 107 patients receiving R-CVP (rituximab,

Table 1. Front-line Phase III randomized clinical trials in follicular lymphoma.

Study	Regimen	n	ORR (CR)	PFS	OS	Ref.
FOLL05	R-CHOP	178	93% (73%)	3-year PFS (p = 0.11)	3-year OS: 95% for all arms	[19]
	R-CVP	178	88% (67%)	68%		
	R-FM	178	91% (72%)	52% 63%		
StiL NHL-1	R-CHOP	140	*91% (30%)	Median PFS:	Estimated 10-year OS:	[20,21]
	BR	139	93% (40%) p = 0.02	41 months Not reached p = 0.0072	62% 72% p = 0.08	
BRIGHT	R-CHOP/ R-CVP	149	94% (25%)	N/A		[22]
	BR	148	>99% (30%) p = 0.0569			
PRIMA	R-CHOP/CVP/FCM followed by:	505	CR/CRu 71.5%	6-year PFS:	6-year OS:	[23,24]
	R maintenance	513	CR/CRu 52%	59%	87%	
	Observation		p = 0.0001	43% p < 0.0001	89%	
GALLIUM	R-(CHOP, CVP, B) and R	601	87% (24%)	3-year PFS	3-year OS:	[52]
	maintenance	601	89% (20%)	73%	92%	
	O-(CHOP, CVP, B) and O			80% p = 0.001	94% p = 0.210	

B: Bendamustine; BR: Bendamustine plus rituximab; CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone; CR: Complete response; CVP: Cyclophosphamide, vincristine, prednisone; FCM: Fludarabine, cyclophosphamide, mitoxantrone; FM: Fludarabine, mitoxantrone; O: Obinutuzumab; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; R: Rituximab.

*Indicates activity for entire cohort of patients, including all histologies.

cyclophosphamide, vincristine and prednisone) and found similar results. This study revealed that risk stratification by M7-FLIPI was superior to FLIPI alone, FLIPI and ECOG performance status, and genetic analysis alone. Using a variety of techniques, including whole genome sequencing, targeted deep sequencing and digital droplet PCR, Kridel *et al.* have also identified a number of genes frequently mutated in patients with early progression (*TP53*, *BTG1*, *KMT2C*, *MKI67*, *XBPI*, *SOCs1*, *IKZF3*, *B2M*, *FAS* and *MYD88*) and high-grade transformation (*TP53*, *B2M*, *EZH2*, *MYC*, *CCND3*, *EBF1*, *PIM1*, *GNA13*, *ITPKB*, *CHD*, *SIPR2* and *P2RY8*) [12]. These data were concluded from the analyses of 94 genes in samples from 277 patients. The feasibility and practical role for these types of prognostication model, however, remain a point of discussion.

Front-line regimens

While prognostic models are useful in determining long-term outcomes for patients, thus far, they do not impact the timing or choice of front-line therapy. The Groupe d'Etude des Lymphomes Folliculaires criteria are generally accepted guidelines providing indications for treatment: cytopenias, splenomegaly, effusion, threat of end organ damage, three nodal sites >3 cm or a single lesion >7 cm [13]. For

approximately 15–25% of patients who present with limited stage disease, a variety of treatment modalities have been successfully implemented as evident by the National Lymphocare Study. In this prospective observational study, 471 patients with Stage I disease received chemoimmunotherapy (28%), radiation (27%), combined modality (13%) or single-agent rituximab (12%) [14]. Interestingly, the OS did not differ significantly among these approaches. Furthermore, 17% of patients included in the analysis underwent observation instead and also had a similar OS. However, after adjustment for histology, LDH and the presence of B symptoms, patients who received either chemoimmunotherapy or combined modality had a significantly improved PFS compared with those who received radiation alone (HR: 0.36 [95% CI: 0.16–0.82], 0.11 [95% CI: 0.01–0.83]). In general, treatment strategies should be individualized, accounting for age, performance status, comorbidities, symptoms and tumor burden.

Rituximab-based chemoimmunotherapy has been the standard of care for patients with high tumor burden as defined by a clinical indication for treatment (Table 1) [15–18]. The Phase III FOLLO5 trial aimed to identify the best chemotherapy arm for combination with rituximab: CVP, CHOP or FM (fludarabine and

mitoxantrone) [19]. The 3-year PFS was found to be higher in R-CHOP and R-FM compared with R-CVP (68, 63 and 52%, respectively), but R-CHOP had a better risk-benefit ratio compared with R-FM as it resulted in lower adverse events and secondary malignancies. In the German Study Group for Indolent Lymphomas (StiL) NHL-1 noninferiority trial, R-CHOP was compared with bendamustine plus rituximab (BR) as a first-line regimen for patients with indolent B-cell or mantle cell lymphoma [20]. Although the overall response rates (ORR) and OS were similar between the arms, BR produced a higher complete response (CR) rate: 40% versus 30%, $p = 0.021$. The median PFS in the follicular lymphoma cohort in the BR group was not reached versus PFS of 40.9 months in the R-CHOP group. Furthermore, achievement of a CR was associated with significantly prolonged OS compared with a partial response; the estimated 10-year OS rate was 72.6 versus 63.6% ($p = 0.006$) [21]. The front-line BRIGHt study was a similar noninferiority Phase III trial of BR versus R-CHOP/R-CVP in indolent and mantle cell lymphoma [22]. Of the 314 patients with follicular lymphoma, the CR rates were similar at 30 and 25%, respectively. Hypersensitivity reactions and emesis occurred more frequently with BR whereas peripheral neuropathy and alopecia were significantly higher in the other group. This study as well as the StiL NHL-1 study supports BR as an effective front-line regimen with better tolerability for patients with follicular lymphoma.

The additional benefit of rituximab maintenance therapy was explored prospectively in the PRIMA study [23]. In this randomized, open-label study in previously untreated advanced stage follicular lymphoma, 1217 participants received either R-CHOP, R-CVP or R-FCM. Those with a CR or partial response were randomly assigned to receive 2 years of maintenance rituximab therapy versus observation. At a median follow-up of 73 months, there was a significantly higher 6-year PFS of 59% with maintenance compared with 43% [24]. There was no difference in OS, however, attesting to the fact that maintenance therapy does not improve long-term outcomes in this disease and alternative interventions must be explored, particularly for those who do not achieve a CR.

Postinduction prognostic features

Unfortunately, despite advances with rituximab-based chemoimmunotherapy in advanced

stage disease, the CR rates are considerably lower and patients inevitably relapse. The correlation between an improved OS and achievement of a CR with front-line therapy was first established in the prerituximab era based on analysis of 536 patients enrolled in the GELF86 trials ($p < 0.001$) [25]. This finding was confirmed subsequently in the StiL NHL-1 study of BR versus R-CHOP in previously untreated follicular lymphoma which noted that the lack of a CR was associated with an inferior OS [20]. This appears to remain true with the incorporation of ^{18}F -fluorodeoxyglucose PET/computed tomography (CT) as a response assessment tool based on a pooled analysis of three front-line multicenter follicular lymphoma chemoimmunotherapy trials, including the FOLL05 and the PRIMA [26]. The presence of residual hypermetabolic activity on postinduction PET-CT was associated with a significantly inferior 4-year PFS and OS compared with those who became PET negative ($p < 0.001$). An early relapse of disease has also recently been found to be an important predictor of a poorer outcome. In an analysis of 920 newly diagnosed patients, Maurer *et al.* concluded that early events after chemoimmunotherapy at 12 and 24 months were associated with inferior outcomes [27]. In an analysis of 588 stage II–IV follicular lymphoma patients who received front-line R-CHOP, the National LymphoCare study demonstrated an inferior 5-year OS of 50% for those who progressed within 2 years of diagnosis compared with 90% for those who did not [28]. The results remained unchanged with adjustment for FLIPI and were confirmed in a validation cohort. Similarly, a meta-analysis of 13 front-line trials, which included chemotherapy plus/minus rituximab, identified that the preservation of a CR at 30 months was associated with a significantly longer PFS than for those who experienced an earlier relapse [29].

The presence of minimal residual disease (MRD) is a newer method of disease evaluation that is being explored in follicular lymphoma, which may provide prognostic information as well. MRD has traditionally been assessed via real-time quantitative PCR for the BCL2/IGH gene rearrangement or the identification of $t(14;18)$ [30]. In the FOLL05 study, the achievement of MRD negativity on bone marrow aspirate samples at 12 and 24 months after induction correlated with a higher 3-year PFS: 66 versus 41% at 12 months ($p = 0.015$), 84

Table 2. Early phase trials of targeted therapies in follicular lymphoma.

Regimen	Phase	Disease setting	n	ORR(CR)	Survival	Ref.
Lenalidomide 20 mg D1–21/28 days Rituximab 375 mg/m ² weekly × 4 during C1, C4, 6, 8, 10 D1	II	F-L	65	93% (72%)	2-year PFS: 89%	[34]
Idelalisib 150 mg twice daily	II	R/R	72	54% (6%)	Not reported for the FL cohort	[36]
Ibrutinib 560 mg daily	II	R/R	40	30% (3%)	Median PFS: 9.9 months	[40]
Obinutuzumab C1 D 1,8 1600 mg C2–8 D1 800 mg Obinutuzumab C1 D1,8 400 mg C2–8 D1 400 mg	II	R/R	22 18	55% (9%) 17% (0)	Median PFS: 11.9 months Median PFS: 6 months	[49]
PoV (2.4 mg/kg) R 375 mg/m ² every 21 days PiV (1.4 mg/kg) Rituximab 375 mg/m ² every 21 days PoV (1.8 mg/kg) R 375 mg/m ² every 21 days	II	R/R	20 21 20	70% (40%) 62% (10%) 44% (0)	Not reported Not reported Not reported	[55]
CD19 CAR T-cell therapy: Median CTL019 cell dose/kg is 6.08E + 0.6	II	R/R	14	79%(64% at 6 months)	11.4-month PFS: 77%	]
Venetoclax: Target doses from 200 to 1200 mg in dose-escalation and safety expansion cohorts	I	R/R	29	38% (14%)	Estimated median PFS: 11 months Estimated 12 months OS: 100%	[43]

C: Cycle; CAR: Chimeric antigen receptor; CR: Complete response rate; D: Day; F-L: Front-line; ORR: Overall response rate; PiV: Pinatuzumab vedotin; PoV: Polatuzumab Vedotin; R: Rituximab; R/R: Relapsed, Refractory.

versus 50% at 24 months ($p = 0.014$). A subset analysis was performed to evaluate the prognostic role of *BCL2/IGH* assessment with PET [31]. The results revealed that PET and MRD did not strongly correlate with each other; MRD analysis was sensitive in the bone marrow but PET was more accurate in nodal disease evaluation. The role of MRD assessment in clinical practice is unclear at this time, but remains a point of research interest in terms of response assessment and risk stratification.

Improving treatment regimens

Considerable effort has been placed on improving and expanding front-line treatment options. These endeavors have primarily been conducted with the incorporation of novel agents chosen, based on a greater understanding of the pathogenesis of follicular lymphoma. Newer therapies include but are not limited to immunomodulatory agents, small molecule kinase inhibitors and antibody-based therapies (Table 2). Learning how to safely and intelligently utilize these agents is the focus of current and upcoming studies.

• Lenalidomide

The immunomodulatory agent, lenalidomide, has demonstrated considerable activity in follicular lymphoma through its effects on the tumor cells and microenvironment. Its mechanisms of action include but are not limited to augmentation of antibody-dependent cellular cytotoxicity, modulation of B-cell signaling pathways and enhancement of T-cell function [32]. Furthermore, it is synergistic with rituximab in inducing apoptosis and cell-mediated cytotoxicity. Both the Alliance for Clinical Trials in Oncology (formerly CALGB) and the MD Anderson Cancer Center have demonstrated ORRs greater than 90% and impressive CR rates greater than 70% with the doublet in previously untreated disease [33,34]. A higher number of patients in both Phase II studies were felt to be in a complete remission by PET criteria but had not undergone confirmatory bone marrow biopsies to rule out residual lymphomatous involvement. The MD Anderson Cancer Center (MDACC) reported a 3-year PFS of 79% and the median PFS had not been reached at 40 months. In a similar Phase II study conducted by the Swiss Group for Clinical Cancer

Research and the Nordic Lymphoma group, the doublet produced a CR/unconfirmed CR rate of 61% by independent review of CT imaging [35]. The lower CR rate may have been attributed to the higher percentage of patients with poor-risk FLIPI scores; 47% compared with 28% in the MDACC study and two patients in the Alliance study. Based on these promising data, the Phase III RELEVANCE study of rituximab-lenalidomide versus chemoimmunotherapy was designed for previously untreated advanced stage follicular lymphoma (NCT01650701). This study has completed enrollment but the results are pending.

• Idelalisib

As in chronic lymphocytic leukemia (CLL), intracellular signaling pathways downstream of the BCR have been identified as potential therapeutic targets for the treatment in follicular lymphoma. Idelalisib, an inhibitor of the δ isoform of PI3K, is the only one thus far to be approved in follicular lymphoma. The approval was based on a Phase II, single-arm study of 125 patients with rituximab-refractory indolent NHL, 72 of whom had follicular lymphoma (54% high risk by FLIPI) [36]. Despite a median of four prior lines, idelalisib demonstrated an ORR of 56% (54% in follicular) and a median duration of response of 12.5 months.

Based on these encouraging data, it was combined with lenalidomide and rituximab by the Alliance in relapsed and refractory follicular and mantle cell lymphoma [37]. Of the first eight patients enrolled, four experienced severe dose limiting toxicities concerning for a cytokine release syndrome. The MDACC reported significant toxicity with the triplet as well, including severe hepatotoxicity, which was concerning for immune activation [38]. Unfortunately, idelalisib has been unable to move forward in combination with chemoimmunotherapy either. A Phase III trial of BR with or without idelalisib in relapsed and refractory indolent NHL was terminated due to greater than expected serious infectious adverse events found in a series of idelalisib studies (NCT01732926), as has a study of rituximab with or without idelalisib in previously untreated patients (NCT01732913). Duvelisib is a second-generation dual Δ/γ PI3K inhibitor that has a similar toxicity profile to idelalisib, but is no longer being explored in follicular lymphoma. TGR-1202 is a newer PI3K δ inhibitor that appears to have a more favorable

toxicity profile and is being studied in various B-cell malignancies (NCT02006485).

• Ibrutinib

The irreversible Bruton's tyrosine kinase inhibitor, ibrutinib, has demonstrated modest activity in follicular lymphoma. In a Phase I study of eight patients with relapsed and refractory disease, the ORR was 63% and median PFS was 24 months at a dose of 8.3–12.5 mg/kg/day [39]. Less impressive responses were seen in the Phase II setting in 40 heavily pretreated patients: ORR 30%, PFS 9.9 months [40]. The DAWN study was a larger study of 110 patients with chemoimmunotherapy-resistant follicular lymphoma as defined by progression within 1 year of the last dose of chemotherapy [41]. The ORR was 21 and 11% of patients achieved a CR. The median duration of response was 19 months, and the 2-year OS was 63%.

Like idelalisib, it has been added to chemoimmunotherapy and other novel agents. In a Phase I/Ib combination with BR for previously treated NHL, the ORR was 90% and CR was 50% in the ten patient follicular lymphoma cohort [42]. Results of the Phase III trial of ibrutinib with BR or R-CHOP in previously treated follicular lymphoma and marginal zone lymphoma will provide more insight into the role of ibrutinib with chemoimmunotherapy in indolent NHL (NCT01974440). It is also being studied with the BCL-2 inhibitor, venetoclax, which has demonstrated an ORR of 38% (CR: 14%) as a single agent in previously treated follicular lymphoma [43]. The Phase I/II combination study in relapsed and refractory follicular lymphoma includes correlative studies focused on identifying predictive biomarkers, such as next-generation sequencing and evaluation of BCL-2 family member expression (NCT02956382).

Rituximab in combination with ibrutinib in previously untreated follicular lymphoma produced an ORR of 85% with a tolerable safety profile but the CR rate was only 35% [44]. When lenalidomide was added to this doublet in the same setting, the ORR improved to 95% but 82% of patients developed a rash. Thirty-six percent of patients developed a grade 3 rash, which was considered unacceptable, and the triplet was not taken further [45]. These data do not support the use of ibrutinib in the front-line setting for follicular lymphoma, but with the identification of an accurate predictive biomarker, it may have a role in the relapsed/refractory setting.

• Obinutuzumab

Over the past decade several second- and third-generation CD20 monoclonal antibodies have been developed in attempts to surpass rituximab. Antibodies to alternative extracellular targets have also undergone extensive clinical investigation. Ofatumumab was the first monoclonal antibody to be approved after rituximab, initially in refractory CLL. While the fully human anti-CD20 antibody appeared to have comparable activity to the chimeric rituximab in relapsed follicular lymphoma, it showed minimal activity in the rituximab-refractory population (ORR: 11%) [46,47]. Obinutuzumab is a humanized glyco-engineered type II anti-CD20 monoclonal antibody which has demonstrated superiority to rituximab in preclinical models [48]. It utilizes antibody-dependent cellular cytotoxicity and apoptosis as its mechanisms of action. In the Phase II GAUGUIN study, obinutuzumab produced an ORR of 50% and median PFS of 12 months in previously treated follicular lymphoma ($n = 34$) including some patients with rituximab-refractory disease [49]. The randomized Phase II GAUSS trial, which compared obinutuzumab with rituximab in relapsed indolent NHL, reported a higher ORR in the follicular lymphoma cohort of 45 versus 27%; $p = 0.01$. There was no difference in CR/CRu rate or PFS noted though. Most adverse events occurred at a similar incidence in each arm but infusion-related reactions and cough were seen more frequently with obinutuzumab (74 vs 51%; 24 vs 9%) [50].

Based on these data, two randomized Phase III trials were designed. The GADOLIN study was a multicenter, Phase III trial that compared obinutuzumab plus bendamustine with bendamustine monotherapy in rituximab-refractory NHL [51]. Rituximab-refractory NHL was defined as no response or progression within 6 months of rituximab. In the follicular lymphoma cohort ($n = 321$), the addition of the antibody induced a longer median PFS (25 vs 14 months, $p < 0.0001$) and median OS (not reached vs 53.9 months, $p = 0.0061$). There were slightly more grade 3–5 adverse events in the antibody arm (73 vs 66%), however, the incidences of $\geq$ grade 3 infections and secondary malignancies were similar. These data supported the approval of obinutuzumab in rituximab-refractory follicular lymphoma. The GALLIUM study compared rituximab-based chemoimmunotherapy (CHOP, CVP and B) to obinutuzumab-based

chemoimmunotherapy in previously untreated advanced follicular lymphoma [52]. While the CT-derived ORR and CR rates were comparable between the arms, a greater number of patients achieved MRD negativity in the obinutuzumab-based arm (92 vs 85%, $p = 0.0041$). At a median follow-up of 34.5 months, there was a 34% reduction in the risk of PFS event relative to rituximab-based chemoimmunotherapy. There was no difference in the OS at a relatively early analysis of 3 years, but an OS advantage may be noted with longer follow-up, potentially for those who achieved MRD negativity or a PET-derived CR (data pending). These data are encouraging and support approval for obinutuzumab into the front-line setting for follicular lymphoma. Surprisingly, bendamustine induction, regardless of the concomitant antibody, was associated with an increased incidence of fatal adverse events compared with the other chemotherapy arms. Final analysis and publication of these data will hopefully help clarify these findings.

Antibody–drug conjugates

Since the success of brentuximab vedotin in Hodgkin's lymphoma and anaplastic large cell lymphoma, considerable efforts have been placed on developing a B-cell-directed antibody–drug conjugate (ADC). Polatuzumab vedotin is an ADC which targets CD79b, a transmembrane component of the BCR [53]. In a Phase I dose-escalation trial in relapsed and refractory B-cell malignancies, polatuzumab produced responses in 7 out of 16 patients with indolent NHL who were treated at the recommended Phase II dose of 2.4 mg/kg. Three patients achieved a CR and the median PFS was 7.9 months. Polatuzumab was subsequently combined with rituximab in the Phase II relapsed/refractory ROMULUS study [54]. The doublet produced an ORR of 70% and CR of 40% in the follicular lymphoma cohort ($n = 20$). Peripheral neuropathy occurred in 39% of all patients enrolled and was reversible with dose reduction and delayed treatment. Pinatuzumab vedotin, an ADC against CD22, was explored with rituximab in a parallel arm of the study. As less activity was noted in the pinatuzumab arm, only polatuzumab is undergoing further development. When combined with BR or B-obinutuzumab in a Phase Ib/II study of relapsed/refractory follicular lymphoma, the ORR was 100% (CR: 83%) among the six patients enrolled in total [55]. Ongoing studies

include combinations with obinutuzumab and lenalidomide (NCT02600897), and obinutuzumab and venetoclax (NCT02611323).

• Immune checkpoint inhibitors

T-cell exhaustion via overexpression of programmed-death (PD)-1 has been demonstrated to be a key contributing factor in the development of several solid tumors, as well as in follicular lymphoma. Immune checkpoint inhibitors have revolutionized treatment of some malignancies, such as melanoma, lung cancer and refractory Hodgkin's lymphoma, by interrupting the interaction of PD-1 with its ligand, PD-L1, and inducing cell death [56–58]. Pidilizumab is one of the first PD-1 inhibitors to be explored in follicular lymphoma. While it possesses minimal activity as a single agent, it has promising activity in combination with other targeted therapies [59]. In a Phase II study of relapsed follicular lymphoma, combination with rituximab resulted in an ORR of 66% (CR: 52%) with median PFS of 18.8 months [60]. In a more recent Phase I trial of relapsed/refractory hematologic malignancies, nivolumab demonstrated an ORR of 40% (CR: 10%) and a PFS at 24 weeks of 68% in ten patients with follicular lymphoma [61]. Atezolizumab, a humanized IgG1 monoclonal antibody directed against PD-L1, is being studied with obinutuzumab-based chemoimmunotherapy in previously untreated and relapsed and refractory follicular lymphoma (NCT02220842) and obinutuzumab-lenalidomide in relapsed/refractory patients (NCT02631577). By capitalizing on a completely unique mechanism of action, immune checkpoint inhibition has great promise in this disease, but most likely in combination with other agents.

Role of cellular therapy

The appropriate management of patients with multiple relapsed or refractory disease remains a point of discussion. Historically, patients have received autologous or allogeneic stem cell transplantation (SCT) if young and fit enough; however, data regarding its use in the postrituximab era are largely based on subset analyses or retrospective studies [62,63]. Autologous SCT is also considered for patients with histologic transformation; risk factors for which include constitutional symptoms, elevated LDH, change in performance status, high FLIPI and histologic grade 3 disease [64]. Of the 40 patients on the PRIMA

study who developed a histologic transformation after first-line induction, those who received an autologous SCT experienced a notably longer OS (not reached vs 1.7 years) than those who did not. Allogeneic SCT appears to have a role in younger patients who have experienced a relapse of follicular lymphoma after autologous SCT. In a retrospective study of 183 patients who had suffered a relapse after autologous SCT, reduced intensity allogeneic SCT was associated with a 5-year OS of 51% [65]. Allogeneic SCT is also more frequently being considered for patients who are primary refractory or have relapsed within 2 years, as they have a particularly worse prognosis as evident by the National Lymphocare study [28]. In patients who have experienced a remission duration of less than 12 months, retrospective analyses have indicated a significantly higher event-free survival at 3 years for patients who received an allogeneic SCT (80%) than those who had received an autologous SCT (42%, $p < 0.015$) [66]. Patient characteristics that ultimately determine the possibility of transplant include general condition, age, prior treatments, risk factors and disease burden.

In general, chemo-sensitive disease is necessary for either autologous or allogeneic SCT. Patients who are unable to achieve a remission with salvage regimens remain a challenge. Chimeric antigen receptor (CAR) modified T-cell therapy provides a potential solution for those with chemo-refractory disease. CAR T cells are genetically modified autologous T cells which express tumor-specific receptors that allow recognition of cancer cells and induction of cell death. This technology has demonstrated remarkable activity in a number of B-cell malignancies including acute lymphoblastic leukemia and CLL. In a Phase II study of 14 relapsed and refractory CD19 follicular lymphoma patients, at 3 months, 79% ($n = 11$) experienced a response, 50% of which were complete remissions [67]. Complete remission rate was increased to 64% at 6 months as 2 patients with partial response converted to CR. Progression-free survival rate at 11.4 months was found to be 77%. Cytokine release syndrome was seen in 6 patients (2 patients with grade 3 and 4). Although the data are preliminary, CAR T-cell therapy provides an exciting possibility for patients lacking therapeutic options and re-evaluation of the use of SCT in certain populations is warranted.

Conclusion

Achieving durable response with the least amount of toxicity is the most important goal in the management of follicular lymphoma. Despite high response rates of greater than 90% with chemoimmunotherapy, the complete remission rates are considerably lower and patients inevitably relapse. Recent data have identified that patients who are unable to achieve a complete remission with front-line induction, those who relapse within 2 years and those who are unable to maintain a complete remission by 30 months of front-line therapy have a significantly worse long-term outcomes. A better understanding of the pathogenesis of this disease, including the intrinsic pathways and tumor microenvironment, has facilitated targeted therapeutic approaches. Superior antibody-based therapies, small molecule inhibitors and immune-directed agents carry the promise of effective treatment with a potentially more tolerable safety profile than conventional chemotherapy. Combinations of these novel agents, such as rituximab and lenalidomide, may replace current standards and eliminate the initial need for cytotoxic regimens. Incorporation into current regimens will hopefully allow for more lengthy remissions and improved survival rates for patients.

Future perspective

As with most malignancies, the future management of follicular lymphoma relies greatly on innovative yet appropriate clinical trial design.

These biologically based regimens must be studied carefully and in a systematic way as unexpected adverse events have been noted in previous trials. Research investigations should incorporate realistic, yet clinically meaningful end points. As median OS for follicular lymphoma is greater than 15 years and the median PFS after front-line induction can be several years, a primary end point of OS or PFS is not feasible. Considerable advancements can be made during that time, thus newer validated end points, such as response by postinduction PET-CT or progression of disease within 2 years, should be explored. On those same lines, therapeutic trials need to be directed to patients who are deemed to be high-risk through newer prognostic indices including those with MRD. Correlative analyses should be focused on identifying not only prognostic, but predictive biomarkers, in order to improve treatment selection for patients. Achievement of these milestones will enable a personalized approach to each patient and hopefully, the possibility of a cure.

Financial & competing interests disclosure

Dr. Ujjani's disclosures include Genentech, Pharmacyclics, Gilead, and Abbvie. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

- Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992–2001. *Blood* 107(1), 265–276 (2006).
- Shirley MH, Sayeed S, Barnes I, Finlayson A, Ali R. Incidence of haematological malignancies by ethnic group in England, 2001–7. *Br. J. Haematol.* 163(4), 465–477 (2013).
- Goldin LR, Bjorkholm M, Kristinsson SY, Turesson I, Landgren O. Highly increased familial risks for specific lymphoma subtypes. *Br. J. Haematol.* 146(1), 91–94 (2009).
- Limpens J, Stad R, Vos C *et al.* Lymphoma-associated translocation t(14;18) in blood B cells of normal individuals. *Blood* 85(9), 2528–2536 (1995).
- Schuler F, Dolken L, Hirt C *et al.* Prevalence and frequency of circulating t(14;18)-MBR translocation carrying cells in healthy individuals. *Int. J. Cancer* 124(4), 958–963 (2009).
- Kahl BS, Yang DT. Follicular lymphoma: evolving therapeutic strategies. *Blood* 127(17), 2055–2063 (2016).
- Kridel R, Sehn LH, Gascoyne RD. Pathogenesis of follicular lymphoma. *J. Clin. Invest.* 122(10), 3424–3431 (2012).
- Yang ZZ, Grote DM, Ziesmer SC *et al.* IL-12 upregulates TIM-3 expression and induces T cell exhaustion in patients with follicular B cell non-Hodgkin lymphoma. *J. Clin. Invest.* 122(4), 1271–1282 (2012).
- Solal-Céligny P, Roy P, Colombat P *et al.* Follicular lymphoma international prognostic index. *Blood* 104(5), 1258–1265 (2004).
- Federico M, Bellei M, Marcheselli L *et al.* Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. *J. Clin. Oncol.* 27(27), 4555–4562 (2009).
- Pastore A, Jurinovic V, Kridel R *et al.* Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. *Lancet Oncol.* 16(9), 1111–1122 (2015).
- Kridel R, Chan FC, Mottok A *et al.* Histological transformation and progression in follicular lymphoma: a clonal evolution study. *PLoS Med.* 13(12), e1002197 (2016).
- Solal-Céligny P, Lepage E, Brousse N *et al.* Doxorubicin-containing regimen with or without interferon alfa-2b for advanced

- follicular lymphomas: final analysis of survival and toxicity in the Groupe d'Etude des Lymphomes Folliculaires 86 Trial. *J. Clin. Oncol.* 16(7), 2332–2338 (1998).
- 14 Friedberg JW, Byrtek M, Link BK *et al.* Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. *J. Clin. Oncol.* 30(27), 3368–3375 (2012).
- 15 Hiddemann W, Kneba M, Dreyling M *et al.* Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood* 106(12), 3725–3732 (2005).
- 16 Marcus R, Imrie K, Belch A *et al.* CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood* 105(4), 1417–1423 (2005).
- 17 Marcus R, Imrie K, Solal-Celigny P *et al.* Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J. Clin. Oncol.* 26(28), 4579–4586 (2008).
- 18 Bachy E, Houot R, Morschhauser F *et al.* Long-term follow up of the FL2000 study comparing CHVP-interferon to CHVP-interferon plus rituximab in follicular lymphoma. *Hematologica* 98(7), 1107–1114 (2013).
- 19 Federico M, Luminari S, Dondi A *et al.* R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. *J. Clin. Oncol.* 31(12), 1506–1513 (2013).
- **Front-line comparison of chemoimmunotherapy regimens in follicular lymphoma.**
- 20 Rummel MJ, Niederle N, Maschmeyer G *et al.* Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, Phase III non-inferiority trial. *Lancet* 381(9873), 1203–1210 (2013).
- **Front-line comparison of the two more favored chemoimmunotherapy regimens in indolent non-Hodgkin lymphoma.**
- 21 Rummel MJ, Maschmeyer G, Ganser A *et al.* Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent and mantle cell lymphomas (MCL) – 7 year updated results from the StiL NHL1 study. Presented at: *The 56th American Society of Hematology*. San Francisco, CA, USA, 6–9 December 2014.
- 22 Flinn IW, van der Jagt R, Kahl BS *et al.* Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood* 123(19), 2944–2952 (2014).
- 23 Salles G, Seymour JF, Offner F *et al.* Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA), a Phase III, randomised controlled trial. *Lancet* 377(9759), 42–51 (2011).
- 24 Salles G, Seymour JF, Feugier P *et al.* Updated 6-year follow-up of the PRIMA study confirms the benefit of 2-year rituximab maintenance in follicular lymphoma patients responding to frontline immunochemotherapy. Presented at: *The 55th American Society of Hematology (ASH) Annual Meeting*. New Orleans, LA, USA, 7–9 December 2013.
- 25 Bachy E, Brice P, Delarue R *et al.* Long-term follow-up of patients with newly diagnosed follicular lymphoma in the prerituximab era: effect of response quality on survival—A study from the groupe d'étude des lymphomes de l'adulte. *J. Clin. Oncol.* 28(5), 822–829 (2010).
- 26 Trotman J, Luminari S, Boussetta S *et al.* Prognostic value of PET-CT after first-line therapy in patients with follicular lymphoma: a pooled analysis of central scan review in three multicentre studies. *Lancet Haematol.* 1(1), e17–e27 (2014).
- 27 Maurer MJ, Ghesquieres H, Ansell SM *et al.* Event-free survival at 12 months (EFS12) from diagnosis is a robust endpoint for disease-related survival in patients with follicular lymphoma in the immunochemotherapy era. Presented at: *The 56th American Society of Hematology (ASH) Annual Meeting*. San Francisco, CA, USA, 6–9 December 2014.
- 28 Casulo C, Byrtek M, Dawson KL *et al.* Relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. *J. Clin. Oncol.* 33(23), 2516–22 (2015).
- 29 Shi Q, Flowers CR, Hiddemann W *et al.* Thirty-month complete response as a surrogate end point in first-line follicular lymphoma therapy: an individual patient-level analysis of multiple randomized trials. *J. Clin. Oncol.* JCO2016708651 (2016) (Epub ahead of print).
- 30 Pott C, Monitillo L, Genuardi E *et al.* A comparative analysis of next-generation sequencing and real-time quantitative PCR for minimal residual disease detection in follicular lymphomas. *Blood* 122(122), 4293 (2013).
- 31 Luminari S, Galimberti S, Versari A *et al.* Positron emission tomography response and minimal residual disease impact on progression-free survival in patients with follicular lymphoma. A subset analysis from the FOLL05 trial of the Fondazione Italiana Linfomi. *Haematologica* 101(2), e66–e68 (2016).
- 32 Gribben JG, Fowler N, Morschhauser F. Mechanisms of action of lenalidomide in B-cell non-Hodgkin lymphoma. *J. Clin. Oncol.* 33(25), 2803–2811 (2015).
- 33 Fowler NH, Davis RE, Rawal S *et al.* Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, Phase II trial. *Lancet Oncol.* 15(12), 13118 (2014).
- 34 Martin P, Jung SH, Johnson JL *et al.* CALGB 50803 (Alliance), a Phase II trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma. Presented at: *American Society of Clinical Oncology (ASCO) Annual Meeting*. Chicago, IL, USA, 30 May–3 June 2014.
- **Multicenter Phase II data of R2 in previously untreated follicular lymphoma.**
- 35 Kimby E, Rondeau S, Vanazzi A *et al.* Rituximab plus lenalidomide versus rituximab monotherapy in untreated follicular lymphoma patients in need of therapy. First analysis of survival endpoints of the randomized Phase-II trial SAKK 35/10. Presented at: *The 58th American Society of Hematology (ASH) Annual Meeting*. San Diego, CA, USA, 3–6 December 2016.
- 36 Gopal AK, Kahl BS, de Vos S *et al.* PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. *N. Engl. J. Med.* 370(11), 1008–1018 (2014).
- **Basis of US FDA approval of idelalisib in follicular lymphoma.**
- 37 Smith SM, Pitcher B, Jung SH *et al.* Unexpected and serious toxicity observed with combined idelalisib, lenalidomide and

- rituximab in relapsed/refractory B cell lymphomas: alliance A051201 and A051202. Presented at: *The 56th American Society of Hematology (ASH) Annual Meeting*. San Francisco, CA, USA, 6–9 December 2014.
- 38 Cheah CY, Nastoupil LJ, Neelapu SS, Forbes SG, Oki Y, Fowler NH. Lenalidomide, idelalisib, and rituximab are unacceptably toxic in patients with relapsed/refractory indolent lymphoma. *Blood* 125(21), 3357–3359 (2015).
 - 39 Fowler N, Boyd TE, Sharman JP *et al.* Long-Term Follow-up and Analysis of Dose Groups with Ibrutinib in Relapsed Follicular Lymphoma. Presented at: *The 57th American Society of Hematology (ASH) Annual Meeting*. Orlando, FL, USA, 5 December – 8 December 2015.
 - 40 Bartlett NL, LaPlant BR, Qi J *et al.* Ibrutinib monotherapy in relapsed/refractory follicular lymphoma (FL), preliminary results of a Phase II Consortium (P2C) trial. Presented at: *The 56th American Society of Hematology (ASH) Annual Meeting*. San Francisco, CA, USA, 6–9 December 2014.
 - 41 Gopal AK, Schuster SJ, Fowler N *et al.* Ibrutinib as treatment for chemoimmunotherapy-resistant patients with follicular lymphoma: first results from the open-label, multicenter, Phase II DAWN study. Presented at: *The 58th American Society of Hematology (ASH) Annual Meeting*. San Diego, CA, USA, 3–6 December 2016.
 - 42 Maddocks K, Christian B, Jaglowski S *et al.* A Phase I/II study of rituximab, bendamustine, and ibrutinib in patients with untreated and relapsed/refractory non-Hodgkin lymphoma. *Blood* 125(2), 242–248 (2015).
 - 43 Davids MS, Roberts AW, Seymour JF *et al.* Phase I first-in-human study of Venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. *J. Clin. Oncol.* 35(8), 826–833 (2017).
 - 44 Fowler N, Nastoupil L, de Vos S *et al.* Ibrutinib combined with rituximab in treatment-naïve patients with follicular lymphoma: arm 1 + arm 2 results from a multicenter, open-label Phase II study. Presented at: *The 58th American Society of Hematology (ASH) Annual Meeting*. San Diego, CA, USA, 3–6 December 2016.
 - 45 Ujjani CS, Jung SH, Pitcher B *et al.* Phase I trial of rituximab, lenalidomide, and ibrutinib in previously untreated follicular lymphoma: alliance A051103. *Blood* 128(21), 2510–2516 (2016).
 - 46 Hagenbeek A, Gadeberg O, Johnson P *et al.* First clinical use of ofatumumab, a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a Phase I/II trial. *Blood* 111(12), 5486–5495 (2008).
 - 47 Czuczman MS, Fayad L, Delwail V *et al.* Ofatumumab monotherapy in rituximab-refractory follicular lymphoma: results from a multicenter study. *Blood* 119(16), 3698–3704 (2012).
 - 48 Mossner E, Brunker P, Moser S *et al.* Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. *Blood* 115(22), 4393–4402 (2010).
 - 49 Salles GA, Morschhauser F, Solal-Celigny P *et al.* Obinutuzumab (GA101) in patients with relapsed/refractory indolent non-Hodgkin lymphoma: results from the Phase II GAUGUIN study. *J. Clin. Oncol.* 31(23), 2920–2926 (2013).
 - 50 Sehn LH, Goy A, Offner FC *et al.* Randomized Phase II trial comparing Obinutuzumab (GA101) with Rituximab in patients with relapsed CD20+ indolent B-Cell non-Hodgkin lymphoma: final analysis of the GAUSS study. *J. Clin. Oncol.* 33(30), 3467–3474 (2015).
 - 51 Cheson B, Trněný M, Bouabdallah K *et al.* Obinutuzumab plus Bendamustine followed by Obinutuzumab maintenance prolongs overall survival compared with Bendamustine alone in patients with Rituximab-Refractory indolent non-Hodgkin lymphoma: updated results of the GADOLIN study. Presented at: *The 58th American Society of Hematology (ASH) Annual Meeting*. San Diego, CA, USA, 3–6 December 2016.
 - **Basis of FDA approval of obinutuzumab in follicular lymphoma.**
 - 52 Marcus RE, Davies AJ, Ando K *et al.* Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: primary results of the randomized Phase III GALLIUM study. Presented at: *The 58th American Society of Hematology (ASH) Annual Meeting*. San Diego, CA, USA, 3–6 December 2016.
 - 53 Palanca-Wessels MC, Czuczman M, Salles G *et al.* Safety and activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: a Phase I study. *Lancet Oncol.* 16(6), 704–715 (2015).
 - 54 Morschhauser F, Flinn I, Advani RH. Updated results of a Phase II randomized study (ROMULUS) of Polatuzumab vedotin or Pinatuzumab vedotin plus Rituximab in patients with relapsed/refractory non-Hodgkin lymphoma. Presented at: *The 56th American Society of Hematology (ASH) Annual Meeting*. San Francisco, CA, USA, 6–9 December 2014.
 - 55 Herrera A, Matasar M, Assouline S *et al.* Polatuzumab vedotin combined with Bendamustine (B) and Rituximab (R) or Obinutuzumab (G) in patients with relapsed or refractory (R/R) follicular lymphoma (FL) or diffuse large B-cell lymphoma (DLBCL), preliminary results of a Phase Ib/II dose-escalation study. Presented at: *The 58th American Society of Hematology (ASH) Annual Meeting*. San Diego, CA, USA, 3–6 December 2016.
 - 56 Robert C, Long GV, Brady B *et al.* Nivolumab in previously untreated melanoma without BRAF mutation. *N. Engl. J. Med.* 372, 320–330 (2015).
 - 57 Borghaei H, Paz-Ares L, Horn L *et al.* Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N. Engl. J. Med.* 373(17), 1627–1639 (2015).
 - 58 Ansell AM, Lesokhin AM, Borrello I *et al.* PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N. Engl. J. Med.* 372(4), 311–319 (2015).
 - 59 Berger R, Rotem-Yehudar R, Slama G *et al.* Phase I safety and pharmacokinetic study of CT-011, a humanized antibody interacting with PD-1, in patients with advanced hematologic malignancies. *Clin. Cancer Res.* 14, 3044–3051 (2008).
 - 60 Westin J, Chu F, Fayad L *et al.* Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, Phase II trial. *Lancet Oncol.* 15(1), 69–77 (2014).
 - 61 Lesokhin AM, Ansell SM, Armand P *et al.* Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a Phase Ib study. *J. Clin. Oncol.* 34(23), 2698–2704 (2016).
 - 62 Schouten HC, Qian W, Kvaloy S *et al.* High dose therapy improves progression free survival and survival in relapsed follicular non-Hodgkin's lymphoma (NHL), results from the randomized European CUP trial. *J. Clin. Oncol.* 21(21), 3918–3927 (2003).
 - 63 Van Besien K, Loberiza FR Jr, Bajorunaite R *et al.* Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. *Blood* 102(10), 3521–3529 (2003).

- 64 Sarkozy C, Trneny M, Xerri L *et al.* Risk factors and outcomes for patients with follicular lymphoma who had histologic transformation after response to first-line immunochemotherapy in the PRIMA trial. *J. Clin. Oncol.* 34(22), 2575–2582 (2016).
- 65 Robinson SP, Boumendil A, Finel H *et al.* Reduced intensity allogeneic stem cell transplantation for follicular lymphoma relapsing after an autologous transplant achieves durable long term disease control. An analysis from the Lymphoma Working Party of the EBMT. *Ann. Oncol.* pii: mdw124 (2016) (Epub ahead of print).
- 66 Lunning MA, Migliacci JC, Hilden P *et al.* The potential benefit of allogeneic over autologous transplantation in patients with very early relapsed and refractory follicular lymphoma with prior remission duration of ≤ 12 months. *Br. J. Haematol.* 173(2), 260–264 (2016).
- 67 Chong EA, Svoboda J, Nasta SD *et al.* Chimeric Antigen Receptor Modified T Cells Directed Against CD19 (CTL019) in Patients with Poor Prognosis, Relapsed or Refractory CD19+ Follicular Lymphoma: Prolonged Remissions Relative to Antecedent Therapy. Presented at: *The 58th American Society of Hematology (ASH) Annual Meeting*, San Diego, CA, USA, 3–6 December 2016.